



Forward message

Forward to COVID-19 e book:



Dr. Abdullatif Al Khal,

Honorary Chief Editor,
Director of Medical Education at Hamad Medical Corporation

Infectious diseases remain major cause of death worldwide accounting for up to one third of annual deaths despite advances in medicine. This is mainly due globalization, urbanization, emerging pathogens, growing population, over-crowding conditions, human migration driven by wars, economic adversities, and severe weather changes due to global warming. Throughout the recorded history, humanity was afflicted with numerous pandemics due to serious pathogens such as smallpox, cholera, plague, and influenza among other pathogens. These pandemics led to millions of deaths in addition to disruption of social, economic and political disruptions and changed the course of the human history. Many of those pathogens were zoonotic in nature where they jumped from animals to humans to ignite devastating pandemics.

COVID-19 pandemic, caused by SARS-CoV-2, which jumped from bats to humans in late 2019, has caused a global pandemic like no other in the recent human history. An unprecedented pandemic of such scale that could not have been believed to be happening in the 21st century and it defied all expectations. It is yet another proof of the vulnerability of the human race to many hidden viruses and other pathogens in nature that are waiting to cross the animal-human boundary to trigger a pandemic, and it only another warning that heralds more pandemics to follow.

Because of the serious nature of COVID-19, its high level of infectivity and ease of spread, and high rates of hospitalizations and deaths associated with it, the virus became the focus of researchers all over the world in an effort to better understand its behaviour and to come up with the right tools to fight it back. Huge amount of literature was published since the pandemic started and the rates of publications addressing all aspects of COVID-19 has increased exponentially. The amount of knowledge available to us now has helped us greatly in drafting preventive public health policies and treatment protocols which significantly improved the outcomes and helped exert control on the pandemic. However, the clinical information about COVID-19 is mostly scattered in the form of scientific publications and review articles, and it is hard to find one resource that contains all the relevant clinical information, that is up to date, to help doctors and other health professionals find answers to most of their questions. This is the main purpose behind this book.

The book reflects a sincere effort to put as much information that is relevant to the healthcare professional taking care of COVID-19 patients or just interested in learning more about the different aspects of the disease. The idea was originated by Dr. Harman Saman, a leading pulmonologist at Hamad Medical Corporation with extensive experience in caring for patients with severe Covid-19 and a key member in the clinical team that worked on scaling up the healthcare system to be able to accommodate the huge burden of COVID-19 cases and to give them the highest level of care. To ensure the highest level of accuracy of the information that came in the book, Dr Saman communicated thoroughly with all the medical experts who contributed to the different chapters, tried to rely on the latest scientific information that was published in peer-reviewed journals from local and international literature.

One of the main features of this book is the fact that it is published electronically online that can be updated live to reflect progress in science related to this virus in order to keep the data provided in the book updated and readily available to its readers. The editor plans to add more chapters to cover additional aspects of the disease, so it becomes more comprehensive.

I believe that this book will become a major and trustable reference for all healthcare professionals who wish to learn about COVID-19 worldwide. I am certain that you will find it enjoyable and enlightening.

[Home](#)
[Forward message](#)
[Introduction](#)
[Chapters](#)
[Editors team](#)
[Contact us](#)



Copyright © 2022 Ministry of Public Health. All rights reserved.



Introduction



Dr. Harman Saman,

The Editor.
Consultant in pulmonary and general internal medicine
Hazm Mebaireek General Hospital
Hamad Medical Corporation

A- A brief history of pandemics:

Our species' relationship with other organisms has consistently been complex, not always predictable, and at times resulted in an almost near complete wipeout of communities.

Nonetheless, the ecology of human development is dependent on this relationship, and an alternative reality without such interaction of humankind with other organisms is impossible to imagine.

The history of our planet tells us that global scale cataclysms, including pandemics, are recurring events. These events might share a recognisable pattern that gets visible on a closer look.

Therefore, studying and understanding these patterns might lead to predicting the occurrences and their catastrophic outcome. This, in turn, would help the preparedness of governments, communities and individuals.

The records documenting the history of this universe rely heavily on cataclysms. The big bang marks the creation of the universe. Various extinction-level events are linked to the earth's timeline being habitable by various life forms, including the homo sapiens.

Similarly, the pandemics serve as historical markers of the start and end of eras and even dynasties, signifying that humanity's history is documented in calamities.

The very outlook of our future existence as species may well be dependent on researching pandemics with the view of preventing and mitigating the impact of future ones.

Nothing has killed human beings on a scale as large as infectious diseases have. The Justinian plague, caused by Yersinia pestis, killed as many as 50 million people, half the global population in the 6th century.

This relatively simple organism is responsible for at least three human plague pandemics(1).

The "Black Death" killed up to 200 million people in the 14th century(2).

Smallpox has had an immense effect on humankind's very existence, as early as early historical records began well into the dawn of the 20th century. It is estimated that smallpox claimed the lives of 300 million people in the 20th century alone, even though an effective vaccine had been used for a long-time (3).

The city of Athens was struck by a plague in 430BC when the city was under siege by Sparta during the Peloponnesian War (431-404 BC). Approximately two-thirds of the population died during this pandemic that lasted about five years, and it did not spare even the mighty Spartans(4).

As we navigate our way through the current pandemic caused by SARS-CoV-2 infection, it is not difficult to see a resemblance with other pandemics. For example, the "Asiatic flu" or "Russian flu" of 1889–1890, which killed about 1 million people worldwide, out of a population of about 1.5 billion, caused symptoms very similar to SARS-CoV-2 infection, including daily persistent headache(5).

Most scholars consider the Spanish flu (1918-1919) as the most devastating epidemic in modern history, as the infectious disease spread very fast, most likely reached Spain from France, perhaps as the result of the heavy railroad traffic of Spanish and Portuguese migrant workers to and from France(6).

The ease of travel causing the rapid spread of the Spanish flu is also similar to the major challenge in the current pandemic.

B- COVID-19 pandemic:

World Health Organization (WHO) defines a pandemic as "an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people."(7).

On 31 December 2019, the WHO was informed of cases of a cluster of pneumonia cases of unknown aetiology in Wuhan city, Hubei province of China. The causative organism was later identified as SARS-CoV-2, a novel virus belonging to the coronaviridae family(8).

The WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19) in the international classification of diseases (ICD).

The infection spread at an alarming rate, quickly crossed the international borders, resulting in a global pandemic.

On 11 March 2020, WHO characterised COVID-19 as a pandemic. COVID-19 is a rapidly evolving global disease that affects the lungs and can affect any organ during the illness(8). The sheer volume of cases, coupled with atypical disease presentations and unpredictable disease course, created a diagnostic and management challenge even for the best-equipped healthcare systems worldwide(8).

To date, 136,129,987 are affected, and 2,941,267 died from the infection, with no sign of a slowdown of the pandemic.

The pandemic exposed the many vulnerabilities of health systems worldwide in dealing with large scale health crisis. Most health systems including in developed economies showed severe signs of stress and failed to cope with a large number of acute admissions to hospitals, including the much-needed intensive care units. The pandemic provided proof that health systems worldwide learnt little from previous pandemics, as they did not demonstrate any level of preparedness to manage major health crisis.

This is partly because of the chronic underfunding of the health sectors by governments and partly because of the global health leaders ignoring the warning signs of upcoming pandemics flagged by epidemiologists and public health experts.

As a result, the COVID-19 pandemic rapidly turned into a devastating international crisis claiming lives daily since its emergence. As time passed, the realisation of the need for highly coordinated and consorted planning and action at national, regional and international levels grew.

Health and political leaders engaged in a complex and synergistic work of planning and execution with the primary aim of saving lives through protecting the most vulnerable individuals in the society and preparing hospitals and other health facilities to care for the infirm.

Governments, lawmakers, global leaders, and leaders from a wide range of healthcare sectors engaged in damage control and contained the mass hysteria.

A significant challenge has been to strike a balance between the urgent need to contain and slow down the transmission of the virus within communities through reliable intervention on the one hand and to keep the economy and other important and vital aspects of modern life running on the other.

Such a balance requires continuous analysis of vital data about the pandemic. Indeed, one of the main successes that enabled some measure of effective fight against the virus has been live data collection. The accuracy of collection and valid analysis of a massive amount of live data through sophisticated statistical and mathematical simulation software remains one of the major weapons at the disposal of health leaders.

For example, CovidSIM Version 1.0, a pandemic preparedness tool, is a practical and easy-to-use simulation tool to support decision making in public and global health, epidemiology and economy; it is adapted to presumed clinical scenarios.

The primary purpose of CovidSIM is to deliver predictions on the COVID-19 pandemic and illustrate the effects of different control strategies and their combined effects on the trajectories of the viral spread (9).

C- COVID-19 pandemic and the State of Qatar:

With a population of 2,807,805, there has been a total of 136,159,922 diagnosed cases and 331 death thus far; the State of Qatar ranked high on the list of low mortality rate worldwide.

The introduction of nationwide screening, laws to restrict travel to and from the country and rolling out of national vaccination program have been critical elements in the fight against COVID-19 in Qatar.

Different components of the health system in this gulf state came together in a coordinated, pre-emptive, and holistic fashion that promoted public engagement and education with the view of controlling the spread of the virus as much as possible.

There has been consorted effort to maximise the health system's capacity to accommodate the unprecedented large number of acute admissions to medical and intensive care units. The virology lab's capacity increases significantly to deal with ever-rising numbers of viral PCR swabs used for screening and diagnosis.

The Ministry of Public Health created a national committee responsible for communication with the public, other government departments, and international agencies to update the daily development of the COVID-19 situation in the state.

The introduction of the National Health Incident Command Centre (NHICC), previously known as SWICC committee – system-wide incident command committee, made it possible to centralise the services in order to redistribute the manpower and the services and open brand new COVID facilities to adapt and cope with the dynamic changes in the load and pressure on different parts of the health system in the State of Qatar.

Clinicians and scientists in the State of Qatar began to share their experience in the management of this pandemic via publications in peer-reviewed journals and presentations and talk at local, regional and international meetings and conferences.

The clinician-scientists contribution from Qatar to the global research on COVID-19 can be gauged from the sheer number of publications produced from Qatar. A preliminary literature search on Pubmed using the Boolean strategy of "(Qatar) AND (COVID-19 OR SARS-CoV-2 OR pandemic)" during 2020 revealed 266 results.

These include two randomised clinical trials, 14 systematic reviews and meta-analyses, and over 50 review articles. Moreover, more work is expected to be published in the future.

C-Why online COVID-19 Educational Tool?

Despite the large number of studies published since the start of the pandemic, the currently available literature is fragmented and discusses a limited number of aspects of this multisystem disease. Moreover, to the best of our knowledge, there is no unifying, easily accessible reference tool currently available to encompass the multitudes of challenges imposed by COVID-19 infection.

This tool or digital book provides practical and problem-based solutions to clinicians' common and important problems at primary, secondary and tertiary levels. Also, COVID-19 related research and medical practice are progressing at an unprecedented rate, making it hard for clinicians to keep up to date with the latest research, national and international guidelines.

This multiplicity of guidelines has caused and will continue to confuse clinicians and, at times, resulting in inconsistent medical practice. Therefore this digital book aims to form an online education resource easily accessible to clinicians of all backgrounds and grades, working in and outside the state of Qatar.

The tool is an evidence-based reference aiming to support clinicians to find quick answers and solution to different aspects of the COVID-19 pandemic.

The online COVID-19 Educational Tool is the first of its kind, hosted Ministry of Public Health (MoPH) home page. A medical expert committee maintains this tool from a diverse clinical and scientific background working in Qatar.

This ensures the validity and the relevance of the material provided by this tool in the face of an ever-changing pandemic and evolution of the medical literature.

A steering committee of experts regularly updates this tool to maintain its high scientific integrity and reputation as a reliable and valid reference to clinicians and medical scientists worldwide.

D- What is the online COVID-19 Educational Tool made of?

1. This educational tool is a digital book hosted by the MoPH website
2. Currently, the tool comprises 12 chapters covering a wide range of system-based aspects of COVID-19 infection.
3. Each chapter presents a literature review and guidelines and a discussion section in which lessons learned and common pitfalls are explained. Moreover, each chapter contains evidence-based and expert opinion advice to increase the preparedness of health systems to deal with the current and future epidemics/pandemics.
4. All the chapters will be updated regularly by the editorial team. These updates enable the book to be of high quality and contain the latest best evidence practice.
5. It is important to emphasise that this project is not a research enterprise as no new data is generated, and therefore an application for ethics approval is not required.
6. The tool allows readers to access important literature and guidelines available on the internet by clicking hyperlinks. The references literature and guidelines are put in a context that is relevant to a specific clinical problem.
7. The chapters contain a flowchart and other forms of depictions to guide readers to find the relevant information.
8. The references provided in the tool are all validated and confirmed by the editor for their accuracy and quality.

E-Who should read the online COVID-19 Educational Tool?

1. The resource is primarily aimed at clinicians: medical, nursing, allied healthcare personnel and students of all grades and specialities within the primary, secondary and tertiary health settings.
2. This resource will also be a significant source to medical researchers in Qatar and elsewhere who are planning future projects.
3. This tool has the potential to accurately documents important clinical and management aspects of this pandemic in Qatar that can be referred to by future scientists, historians, and documentary makers.

F-How to access the online COVID-19 Educational Tool?

The website to this tool is freely available and is embedded within the MoPH home pages. An index of all the chapters and their contents is provided. With a click, the reader is taken to a chapter or a subheading within a chapter.

A list of keywords is provided to help identify a subject of interest using search engines such as Google.

Each chapter contains hyperlinks to important guidelines, scientific papers, vital data, and flowcharts that promptly help clinicians find validated answers to their clinical questions.

References:

1. Wagner DM, Klunk J, Harbeck M, Devault A, Waglechner N, Sahl JW, et al. Yersinia pestis and the plague of Justinian 541-543 AD: a genomic analysis. *Lancet Infect Dis.* 2014;14(4):319-26.
2. Duncan CJ, Scott S. What caused the Black Death? *Postgrad Med J.* 2005;81(955):315-20.
3. Voigt EA, Kennedy RB, Poland GA. Defending against smallpox: a focus on vaccines. *Expert Rev Vaccines.* 2016;15(9):1197-211.
4. Littman RJ. The plague of Athens: epidemiology and paleopathology. *Mt Sinai J Med.* 2009;76(5):456-67.
5. Rozen TD. Daily persistent headache after a viral illness during a worldwide pandemic may not be a new occurrence: Lessons from the 1890 Russian/Asiatic flu. *Cephalgia.* 2020;40(13):1406-9.
6. Trilla A, Trilla G, Daer C. The 1918 "Spanish flu" in Spain. *Clin Infect Dis.* 2008;47(5):668-73.
7. Grennan D. What Is a Pandemic? *JAMA.* 2019;321(9):910.
8. Li X, Wang L, Yan S, Yang F, Xiang L, Zhu J, et al. Clinical characteristics of 25 death cases with COVID-19: A retrospective review of medical records in a single medical center, Wuhan, China. *Int J Infect Dis.* 2020;94:128-32.
9. Schneider KA, Ngwa GA, Schwerm M, Eichner L, Eichner M. The COVID-19 pandemic preparedness simulation tool: CovidSIM. *BMC Infect Dis.* 2020;20(1):859.

[Home](#)
[Forward message](#)
[Introduction](#)
[Chapters](#)
[Editors team](#)
[Contact us](#)



Copyright © 2022 Ministry of Public Health. All rights reserved.



Search this site



Editors team

Honorary Chief Editor:



Dr. Abdullatif Mohammed Al Khal

Head of Infectious Diseases Division and Senior Consultant, Infectious Diseases at Hamad Medical Corporation

The Editor:



Dr. Harman Saman,

Consultant in pulmonary and general internal medicine

Hazm Mebaireek General Hospital

Hamad Medical Corporation

Editorial Board:

1. Dr. Muna S.AL. MASLAMANI

Consultant Infectious disease,

Communicable Disease Center

Hamad Medical Corporation,

2. Dr. Majid Alabdulla ,

Chairman of Department of Psychiatry

Department of Psychiatry

3. Dr. Mohamed Gaafar Mohamedali

Consultant General Internal Medicine
Hazm Mebaireek General Hospital,
Hamad Medical Corporation

4. Professor Peter Haddad Senior

Consultant Psychiatrist,
Hamad Medical Corporation, Qatar
Honorary Professor, Qatar University.

5. Dr. Kawa Amin

Consultant Geriatrician,
Hamad Medical Corporation.

6. Dr. Yahia Zakaria B. Imam

Consultant Stroke Medicine and Neurology,
Hamad Medical Corporation.

7. Dr. Zohaib Yousaf -Assistant editor

Chief Fellow, Internal Medicine,
Hamad Medical Corporation

[Home](#)
[Forward message](#)
[Introduction](#)
[Chapters](#)
[Editors team](#)
[Contact us](#)



Copyright © 2022 Ministry of Public Health. All rights reserved.



Infectious Disease

Infectious Disease Chapter

Table of content:

- **COVID-19 PATHOGENESIS**
 - Introduction
 - Life cycle of SARS-CoV-2
 - Pathogenesis of COVID-19
- **COVID-19 CLINICAL MANIFESTATIONS**
 - Introduction
 - Spectrum of the disease
 - Asymptomatic COVID-19
 - Incubation period
 - Symptoms at time of diagnosis
 - Respiratory failure manifestation
 - Gastrointestinal manifestations
 - Hematologic manifestations
 - Dermatologic manifestations
 - Neurologic manifestations
 - Endocrine manifestations
 - Cardiovascular manifestations
 - Long term sequelae of COVID-19
 - Neurologic manifestations
 - Neurologic manifestations
- **COVID19 MANAGEMENT & TREATMENT**
 - General Management Issues
 - Empiric treatment for influenza during influenza season
 - Empiric treatment for bacterial pneumonia in select patients
 - Prevention of and evaluation for venous thromboembolism
 - NSAID use
 - Nebulized medications
 - Managing chronic medications
 - ACE inhibitors/ARBs:
 - Statins
 - Immunomodulatory agents
- **Covid-19-Specific Therapy**
 - Antiviral treatment
 - Remdesivir
 - Hydroxychloroquine/chloroquine
 - Favipiravir
 - Lopinavir-ritonavir
 - Ivermectin
 - Steroids
 - Dexamethasone
 - Blood-Derived Products Under Evaluation for the Treatment of COVID-19
- **Convalescent plasma for COVID-19**
 - Immune-Based Therapy
 - Monoclonal antibodies
 - IL-6 pathway inhibitors
 - IL-1 pathway inhibitors
 - Janus kinase inhibitor
 - Complement inhibitors
 - Interferons
 - Adjunctive Therapy

- Venous Thromboembolism Prophylaxis and Screening
- Vitamin C
- Vitamin D
- Zinc Supplementation

- **VACCINES AGAINST SARS-COV-2**

- Introduction
- SARS-CoV-2 Vaccines
- Inactivated vaccines and live-attenuated vaccines
- Nucleic acid vaccines
- Vector vaccines
- Subunit vaccines and virus-like particles vaccines

- **REFERENCES**

Keywords: COVID-19, pathogenesis of COVID-19, severity of COVID-19, manifestations of COVID-19, management of COVID-19 infection, treatment of COVID-19 infection.

Authors:

- Dr. MUNA A.RAHMAN S.AL.MASLAMANI, Senior Consultant and Medical Director of CDC
- Dr. Mohd. Abdullah Juma Abu Khatab, Senior Consultant
- Dr. Hussam Abdel Rahman S. Al Soub, Senior Consultant
- Dr. Alaaeldin Abdelmajid Basheer Abdelmajid, Associate Consultant

COVID-19 VIROLOGY AND PATHOGENESIS:

INTRODUCTION

In December 2019, numerous cases of “pneumonia of unknown origin” were reported throughout Wuhan, China. By January 7, 2020, sequencing revealed that the pathogen was a new coronavirus (2019-nCoV), within the Betacoronavirus genus.

Further analysis revealed that this 2019-nCoV had similarities in its receptor-binding domain (RBD) and conserved replicase sequence with SARS-CoV-1, suggesting that they were in the same subgenera (Sarbecovirus) (1, 2).

These similarities in structure were used to classify the 2019 nCoV as SARS-CoV-2.

The coronavirus structural proteins that form the viral particle are the spike (S) glycoprotein, envelope (E) protein, membrane (M) protein, and the nucleocapsid (N) protein (Figure 1).

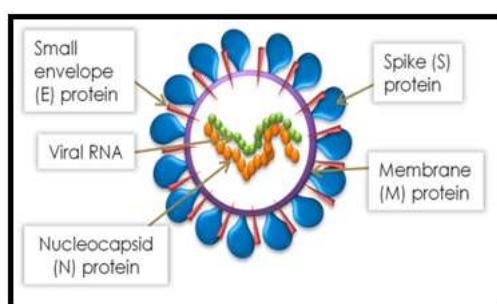


Figure 1: Schematic representation of SARS-CoV-2 and its structural proteins, (3).

These proteins are less conserved than non-structural proteins, playing important functions in the viral life cycle.

Spike (S) protein has an important role in the virus pathogenesis and organ tropism, being responsible for the viral entry through receptor recognition and membrane fusion (4).

The envelope (E) protein is the smallest of the structural proteins but has a crucial role in assembly, budding, envelope formation, and virulence (5).

The main function of the membrane (M) protein is to promote viral assembly due to its membrane-bending properties (6).

The nucleocapsid (N) protein is a multifunctional protein that packages the viral RNA genome into a ribonucleoprotein complex called nucleocapsid to protect the genome (7).

Life cycle of SARS-CoV-2

The SARS-CoV-2 infection process starts with the viral entry mediated by the interaction of the spike (S) glycoprotein with the host angiotensin-converting enzyme 2 (ACE2) receptor, and cleavage of the S protein by the host transmembrane serine protease 2 (TMPRSS2) prior to the fusion to the host cell membrane. Following their entry, the viral genome is unveiled with ORF1a and ORF1ab being translated to the two polyproteins pp1a and ab, that further undergo proteolysis by papain-like (PLpro) and chymotrypsin-like proteases to yield 16 nonstructural proteins (16 nsps).

These protein elements constitute the RNA replicase-transcriptase protein complex and controls single stranded RNA genome (sgRNA) production, replication, and transcription.

The positive-sense RNA genome (+gRNA) is produced by replication and a set of nested 7-9 sgRNA are formed through discontinuous transcription. The sgRNAs are translated into structural and nonstructural proteins from the transcription of the first ORF close to 5' end.

Subsequently, +gRNA and nucleocapsids are assembled in the host cytosol and bud into the lumen of Endoplasmic reticulum-Golgi intermediate compartment (ERGIC).

Mature viral particles are then released from the host cell via its internal membrane through exocytosis (Figure 2).

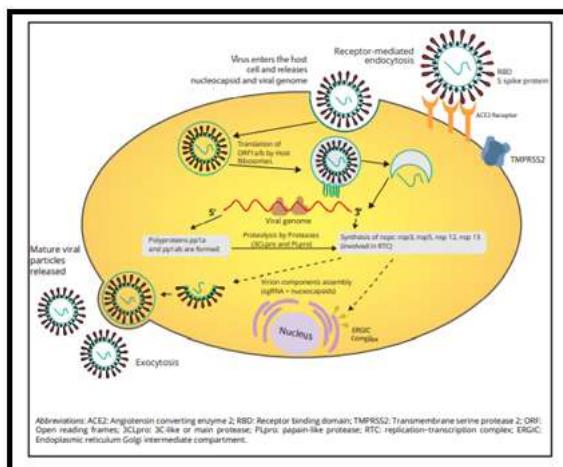


Figure 2: Lifecycle of SARS-CoV-2, (3).

Pathogenesis of COVID-19

Coronaviruses primarily target epithelial cells and are generally associated with respiratory and gastrointestinal infections (8). These viruses attach to target cell receptors and release their genomes into target cells through fusion of the viral envelope with the host plasma membrane.

They utilize the spike (S) protein, which is crucial for determining tropism and transmissibility of the virus. The S protein is divided into an S1 domain and an S2 domain, which are responsible for receptor binding and cell membrane fusion, respectively (2) (Figure 3).

The S1 domain is what contains the RBD, which has specific receptor affinity. In prior coronavirus outbreaks, SARS-CoV-1 targeted the angiotensin-converting enzyme 2 (ACE2) receptor, whereas MERS-CoV utilized the dipeptidyl peptidase 4 (DPP4) receptor (1).

Similarly, SARS-CoV-2 also targets ACE2 receptors on human respiratory epithelial cells, suggesting a similar RBD structure to SARS-CoV-1.

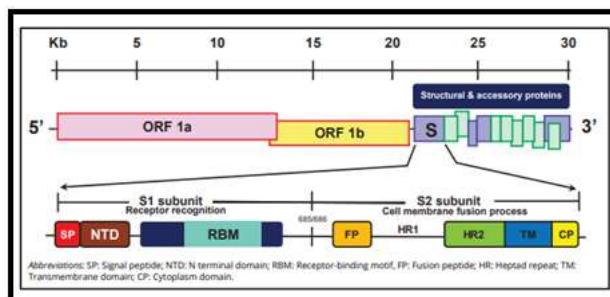


Figure 3: Genomic organization of S protein, (9).

In addition, various human secretory proteases, such as transmembrane protease/serine subfamily member 2 (TMPRSS2) and furin, have been implicated in the pathogenesis of coronaviruses.

Human secretory proteases are responsible for the cleavage "priming" of various viral surface receptors and adhesion molecules and thereby enhancing viral fusion with host cell membranes. In both SARS-CoV-1 and SARS-CoV-2 infected patients, TMPRSS2 has the ability to localize to viral-targeted cells and enhance entry through the proteolysis of both the S1 and ACE2 proteins, which enhances membrane fusion and viral uptake (S1 priming and ACE2 downregulation) [8]. The proteolysis of ACE2 not only promotes viral entry but also seems to be a key mechanism for the severity of lung disease (10). The renin-angiotensin system has a crucial role in acute lung injury; in that the ACE2 receptor has a protective role against acute lung failure [8].

ACE2 is therefore a key negative regulatory factor for severity of lung disease and thus its down-regulation contributes to the severity of illness (11). Like TMPRSS2, furin is also responsible for the cleavage "priming" of SARS-CoV-2 surface receptors.

Researchers have identified a furin cleavage site in the S2 domain of SARS-CoV-2, thus suggesting that S2 priming serves a role in the pathogenesis (11). Interestingly, this furin cleavage site has not been observed among other viruses within its subgenera (i.e. SARS-CoV1).

However, it is present among more genetically distant coronaviruses, such as MERS-CoV, suggesting a possible convergent evolutionary pathway between the two. Furthermore, the high expression of furin in human lungs may help to explain why SARS-CoV-2 has more efficiently spread throughout the population in comparison to SARS-CoV-1 (11).

Infection leads to increased levels of cytokines (interferon γ , interleukin-1, and interleukin-6), chemokines (CXCL10 and CCL2), and inflammatory markers (C-reactive protein, procalcitonin, and ferritin) (12).

This dysregulates the host immune response to SARS-CoV-2 lung infection leading to exuberant cytokine release (cytokine storm) and a resultant immune-mediated tissue injury.

This has been postulated as a critical pathogenic factor in the progression to acute respiratory distress syndrome (ARDS) and other end-organ complications (13).

ARDS is the most common medical complication seen with SARS-CoV-2, and it contributes to a significant amount of the morbidity and mortality associated with the illness.

Therefore, it is considered to be the hallmark immune-mediated clinical consequence (13). Other complications include shock, acute kidney injury, acute cardiac injury, liver dysfunction, coagulopathy, infection, and even thrombotic disease in otherwise low-risk patients (12).

These complications are seen in greater frequency among severe SARS-CoV-2 cases and therefore serve as major contributors to both intensive care unit (ICU) admission and overall mortality (12).

Pediatric patients are at a lower risk of severe complications and more likely to be asymptomatic or have milder symptoms (14). When compared to adults, children reported symptoms such as fever and cough at lower frequencies and were much less likely to have severe/critical disease (5.9% vs. 18.5%) (14). However, when stratified among age groups, 10.6% of children aged less than 1 year were severe/critical, indicating that although children manifest a milder form overall presence of severe disease depends on the age group (14). It is hypothesized that children have these milder pulmonary disease manifestations due to decreased gene expression of ACE2 receptors on respiratory epithelial cells.

However, a newly described post-infectious complication of SARS-CoV-2, known as multisystem inflammatory syndrome in children (MIS-C), is being reported.

This is a Kawasaki-like syndrome that presents as fever, prominent gastrointestinal upset, rash, conjunctivitis, and neurological findings.

In comparison to conventional Kawasaki's, children with MIS-C are less likely to have coronary involvement (15).

Although causality between SARS-CoV-2 and MIS-C has not been proven, reports of an increased incidence of Kawasaki-like syndrome in areas heavily affected by the pandemic shows a possible epidemiological link (16).

COVID-19 CLINICAL MANIFESTATIONS

Spectrum of the disease

A wide range of the disease severity is reported ranging from asymptomatic / mild symptoms to severe symptoms, acute respiratory distress syndrome and death. The difference in severity and demographics has led to the presence of varying mortality rates by region and demographics (16-18)

The Chinese Center for Disease Control and Prevention report looked at 44,500 COVID-19 confirmed cases and found: 80 % has mild disease. 15% had severe disease (hypoxia or involvement of 50% of lungs within 24-48 hours) and 5% were critical. The case fatality rate was 2.3% (19).

Asymptomatic COVID-19

Asymptomatic presentation and mild symptoms in many studies were used interchangeably and it is estimated that 20-40% of patients labeled as asymptomatic at time of diagnosis, developed symptoms later. The potential infectiousness is a concerning feature in asymptomatic patients (19). Additionally, being asymptomatic does not equate to being free of infection signs; in 44 asymptomatic patients, 40% had ground glass opacity on CT studies (20).

Incubation period

The incubation period of the virus is known to be up to 14 days, however median incubation ranged from 2 to 7 days in different studies (21, 22)

Symptoms at time of diagnosis

Cough fever and myalgia where the most common symptoms, in 40 to 60% of cases in different studies. Although anosmia and dysgeusia were publicly described as distinctive features for COVID-19 in a review of 32 studies; 35% -40 % patients developed it. It is worth mentioning that anosmia and dysgeusia are not unique to COVID and are also described in other viral infections (22), in a Systematic Review and Meta-Analysis of 25 studies, anosmia was associated with a milder COVID-19 disease course of (23).

Patients with severe disease with ARDS usually develop dyspnea after a median 6.5 days from onset of symptoms. Among critically ill patients, some will develop ARDS. Patients with COVID-19 pneumonia have a median 2 weeks length of stay. Critically ill patients who needed extra corporeal membrane oxygenation, had low survival rates (5 -15%) (24)

Gastrointestinal manifestations:

Gastrointestinal manifestations (GI) symptoms such as nausea, vomiting, abdominal pain and diarrhea were reported in 10 - 70% of COVID-19 patients (25). COVID-19 presenting with isolated GI symptoms was reported which have acute abdomen investigation and management. Counterintuitively, having GI symptoms as the initial presentation increased the likelihood of detecting COVID-19(26). Transient transaminitis was seen 20 -40% of patients, with some case reports describing severe liver injury in patients with pre-existing liver disease (27).

Hematologic manifestations:

Different hematological disorders had been described. Lymphopenia was observed in majority of patients (60- 90%), thrombocytopenia in 5% - 35%, neutropenia, and some case reports reported hemophagocytic syndrome (25).

However, the most feared hematologic complications are the thrombotic syndromes.

It is estimated that in ICU's patients; venous thromboembolism (VTE) developed in 24-40% of patients, despite prophylactic anticoagulation (25). In contrast, in the non-ICU settings, only 3-8% of VTE incidents were observed (28).

In the outpatient setting it is difficult have accurate estimates, however in one study of 77 of COVID-19 pneumonia patients being seen in emergency department then discharged home; 13 (16.9%) patient developed pulmonary embolism (29).

Dermatologic manifestations:

Dermatologic manifestations were observed in about 10-13% of COVID-19 patients. The most common lesions include chilblains/pernio-like lesion (51.5%), erythematous maculopapular rashes (13.3%), and viral exanthem (7.7%). Postulated mechanisms include autoimmune reaction and vasculitis. It is important not to ignore other common etiologies when evaluating skin manifestations in COVID-19 receiving Tocilizumab, hydroxychloroquine, antibiotics, and Remdesivir such as medication induced lesions (30, 31)

Neurologic manifestations:

Some nonspecific neurological symptoms as headache (40%), delirium, confusion and impaired consciousness were reported in variable estimates. similar to what is seen in SARS and MERS (25).

Case reports of acute inflammatory demyelinating polyneuropathy, meningoencephalitis, hemorrhagic posterior reversible encephalopathy syndrome, and acute necrotizing encephalopathy, including the brainstem and basal ganglia, were described (25, 32)

Endocrine manifestations:

COVID-19 similar to any infection or acute inflammatory condition; may cause acute endocrine dysfunction such hypo-hyperglycemia, ketosis or adrenal crisis in patients with relevant pre-existing endocrine conditions (25).

Cardiovascular manifestations:

A wide spectrum of cardiovascular complication is caused by COVID-19 and is usually associated with severe COVID-19 disease and confers a worse outcome.

The spectrum of cardiac manifestations ranges from myocardial ischemia, myocardial infarction, cardiomyopathy, arrhythmias and myocarditis.

The pathophysiology is diverse and include exiting coronary heart disease, dysregulated cytokine release, vasculopathy and high levels of ACE inhibitors (25).

Long term sequelae of COVID-19

It was observed that mild courses of COVID-19 were associated with short term duration of symptoms up to two weeks.

More sever courses required hospitalization are more likely to suffer long term symptoms which persisted for two months (13% to 60%).

Symptoms described were fatigue (most common symptom up to 80% of cases suffered prolonged symptoms).

Dyspnea also was reported in 70%.

Chest pain and cough were less commonly reported as 40%).

myalgia, persistent anosmia and dysgeusia were also described" as long haul" complications

The psychological impact of COVID-19 is evident in many reports.

These include ;post-traumatic stress disorder, worsened memory and worsened concentration(33, 34).

MANAGEMENT OF COVID-19 INFECTION:

General Management Issues

Empiric treatment for influenza during influenza season:

The clinical features of seasonal flu and COVID-19 infection can overlap and difficult to distinguish.

Therefore, during seasonal flu outbreaks patients can be treated with Oseltamivir, if COVID-19 PCR is negative.

Empiric treatment for bacterial pneumonia in select patients

Routine empiric treatment with antibiotics for mild cases of COVID-19 infection is.

Not indicated.

we recommend empiric treatment for community-acquired pneumonia in severe cases requiring ICU admission and in patients with clinical suspicion of secondary bacterial pneumonia (e.g., new fever after defervescence with new consolidation on chest imaging or high CRP, PCT).

Prevention of and evaluation for venous thromboembolism

Pharmacologic prophylaxis of venous thromboembolism for all hospitalized patients with COVID-19 is recommended and many guidelines have adopted a D-Dimer based strategy.

Non-steroidal anti-inflammatory drugs (NSAID) use

There is minimal data informing the risks of non-steroidal anti-inflammatory drugs (NSAIDs) in the setting of COVID-19. Using Paracetamol as the preferred antipyretic agent, if possible, is preferred. If NSAIDs are needed, use the lowest effective dose (35).

Nebulized medications:

Inhaled medications should be administered by metered dose inhaler, whenever possible, rather than through a nebulizer, to avoid the risk of aerosolization of SARS-CoV-2 through nebulization. If a nebulizer must be used, appropriate infection control precautions should be taken.

Managing chronic medical conditions:

- **ACE inhibitors/ARBs:** Patients receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should continue treatment with these agents if there is no other reason for discontinuation (e.g., hypotension, acute kidney injury) (10, 36)
- **Statins:** To be continued in hospitalized patients with COVID-19 who are already taking them (10).

Covid-19-Specific Therapy

Antiviral treatment

1. Remdesivir

Remdesivir for hospitalized patients with severe COVID-19 pneumonia (requiring supplemental oxygen) is recommended (36). The suggested adult dose is 200 mg intravenously on day 1 followed by 100 mg daily for 5 days total (with extension to 10 days if there is no clinical improvement and in patients requires mechanical ventilation or Extracorporeal Membrane Oxygenation ECMO).

Remdesivir should not be used with hydroxychloroquine or chloroquine because of the potential drug-drug interaction.

2. Hydroxychloroquine/chloroquine

In the initial stages of the pandemic hydroxychloroquine or chloroquine was recommended for the treatment of COVID-19 in hospitalized patients. Later on, with more evidence emerging regarding its effectiveness in hospitalized patients, The IDSA and the NIH guidelines recommended against the use of hydroxychloroquine/ Chloroquine alone or in combination with azithromycin. additionally, the NIH recommends the same for non-hospitalized patients except in the setting of clinical trials (37-39).

3. Favipiravir

Favipiravir is a purine analogue that inhibits the RNA dependent RNA polymerase of influenza and other RNA viruses. It has in vitro activity against SARS-CoV-2. In our local protocol, it is used for treatment of mild- moderate COVID-19 pneumonia (40).

4. Lopinavir-ritonavir

The IDSA and NIH panels recommend against using lopinavir/ritonavir or other HIV protease inhibitors to treat COVID-19 (39, 41, 42)

5. Ivermectin

It is recommended in the case of treatment of strongyloidiasis; either confirmed or suspected in patients who may require steroids. Pre-emptive treatment of Strongyloides prior to glucocorticoid administration is reasonable for patients from endemic areas (ie, tropical and subtropical regions).

In our guideline, we adopt an algorithm of treatment of Strongyloides infections.

Ivermectin has been shown to inhibit the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell cultures (43)

Steroids

Dexamethasone

Low-dose dexamethasone is recommended for hospitalized patients with severe COVID-19 who are receiving supplemental oxygen (including those who are on high-flow oxygen and noninvasive ventilation). Dexamethasone is given at a dose of 6 mg oral or 8 mg IV daily for 10 days or until discharge, whichever is shorter (44, 45). If dexamethasone is not available, it is reasonable to use other glucocorticoids at equivalent doses (e.g., total daily doses of hydrocortisone 150 mg, methylprednisolone 32 mg, or prednisone 40 mg).

Blood-Derived Products Under Evaluation for the Treatment of COVID-19

Convalescent plasma for COVID-19

- Convalescent plasma with high titer neutralizing antibodies to SARS-CoV-2 is an investigational therapy for reducing the likelihood or severity of COVID-19. Based on observational and unpublished trial data, convalescent plasma may improve outcomes if administered earlier in the course of infection, and additional trials are ongoing (46, 47). However, randomized trials do not demonstrate a clear clinical benefit of convalescent plasma in hospitalized patients with severe COVID-19.
- The IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial.
- NIH stated that there are insufficient data to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19:
 1. COVID-19 convalescent plasma
 2. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins
- The Panel also recommends against the use of the following blood-derived products except in a clinical trial:
 1. Mesenchymal stem cells (All)
 2. Non-SARS-CoV-2-specific intravenous immunoglobulin (IVIG) (All). This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.
- Thus, we suggest that convalescent plasma not routinely be used outside clinical trial scope In Qatar we have established our own local protocols to use convalescent plasma which is updated regularly based on going research and as new evidence or data arise.

Immune-Based Therapy

1. Monoclonal antibodies

- Trials of monoclonal antibodies that have been developed to neutralize SARS-CoV-2 by targeting the SARS-CoV-2 spike protein and preventing viral cell entry are also underway. Currently in Qatar those are not available, and they are not included in our local treatment protocol [69].
- Combination of Casirivimab (previously REGN10933) and Imdevimab (previously REGN10987) are two recombinant human monoclonal antibodies blocks the binding of the RBD to the host cell and are being evaluated for the treatment of COVID-19.
- On November 21, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to make the Casirivimab plus Imdevimab combination available for the treatment of non-hospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization.
- Bamlanivimab Plus Etesevimab This anti-SARS-CoV-2 mAb combination has demonstrated a clinical benefit in people with mild to moderate COVID-19 who are at high risk for progression to severe disease and/or hospitalization.
- Sotrovimab This anti-SARS-CoV-2 mAb combination has demonstrated a clinical benefit in people with mild to moderate COVID-19 who are at high risk for progression to severe disease and/or hospitalization
- The FDA has also issued an EUA for Bamlanivimab monotherapy is not recommended
- The field of monoclonal antibodies is rapidly evolving new drugs may be available soon for better coverage and results

2. IL-6 pathway inhibitors

In our protocol, we recommend the use of IL-6 receptor blockers Tocilizumab in treatment of covid pneumonia cytokine release storm (CRS) with evidence of a pro-inflammatory state (with elevations in C-reactive protein [CRP], ferritin, D-dimer, or lactate dehydrogenase and IL 6 level with confirmed pneumonia and or worsening oxygen requirements) (48).

While the IDSA guideline panel recommends against the routine use of tocilizumab.

3. IL-1 pathway inhibitors

- Anakinra is used in Qatar in the context of a clinical trial in some studies Anakinra was found to reduce both the need for invasive mechanical ventilation in the ICU and the mortality rate among patients with severe forms of COVID-19, without serious side-effects. Confirmation of efficacy will require controlled trials
- Canakinumab is another IL-1-beta antagonist with limited human data for COVID-19 that is being studied in a phase III clinical trial (48)

4. Janus kinase inhibitor:

Baricitinib to be used in combination with Remdesivir in patients with COVID-19 who require oxygen or ventilatory support (48). Due to non-availability of the drug in Qatar we did not include it in our protocol. Adding baricitinib to Remdesivir appears to modestly improve the time to recovery, but effects on other endpoints are uncertain and interactions with glucocorticoid use are unknown.

5. Complement inhibitors:

In the mouse models of both SARS-CoV and MERS-CoV, complement activation has been shown to play a role in the pathogenesis of ARDS. Eculizumab is currently being studied for the treatment of COVID-19 (48). Ravulizumab, another complement inhibitor, is also being investigated in randomized trials for COVID-19.

6. Interferons:

In our protocol we recommend using interferons in combination with Ritonavir/Lopinavir (Kaletra) and ribavirin for severe pneumonia in the ICU setting as a second option. In one open-label trial from Hong Kong, 127 adults hospitalized with primarily non severe COVID-19 were randomly assigned 2:1 to a combination intervention (subcutaneous interferon beta, oral ribavirin, plus lopinavir-ritonavir if symptom onset was within 7 days or ribavirin plus lopinavir-ritonavir if symptom onset was between 7 to 14 days) versus control (lopinavir-ritonavir alone). Patients in the intervention group had more rapid times to a negative SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test on a nasopharyngeal swab (median 7 versus 12 days), clinical improvement (median 4 versus 8 days), and hospital discharge (median 9 versus 15 days); in a subgroup analysis, the differences were only observed among patients with symptom onset within 7 days who thus received interferon beta as part of the intervention.

NIH: There are insufficient data for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19:

- Interleukin (IL)-1 inhibitors (e.g., anakinra).
- Interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19. The Panel recommends against the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial:
 - Anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) or anti-IL-6 monoclonal antibody (siltuximab) (BII).
 - Interferons (alfa or beta) for the treatment of severely or critically ill patients with COVID-19 (AIII).
 - Bruton's tyrosine kinase inhibitors (e.g., acalabrutinib, ibrutinib, zanubrutinib) and Janus kinase inhibitors (e.g., baricitinib, ruxolitinib, tofacitinib) (AIII).

Adjunctive Therapy

Adjunctive therapies are frequently used in patients with COVID-19 to prevent and/or treat the infection or its complications. Some of these agents are being studied in clinical trials.

1. Venous Thromboembolism Prophylaxis and Screening

- For non-hospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy.
- Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation,
- There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.
- In our local protocol we recommend pharmacologic prophylaxis of venous thromboembolism for all hospitalized patients with COVID-19 based on D-Dimer,

2. Vitamin C

- The potential role of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19 is being studied (49)
- There are insufficient data for the COVID-19 either for or against the use of vitamin C for the treatment of COVID-19 in critically or noncritically ill patients.

3. Vitamin D

- Vitamin D supplements may increase the levels of T regulatory cells in healthy individuals and patients with autoimmune diseases; vitamin D supplements may also increase T regulatory cell activity.
- The rationale for using vitamin D is based largely on immunomodulatory effects that could potentially protect against COVID-19 infection or decrease the severity of illness (49).
- There are insufficient data to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19.
- In vit D deficient patients, vit D replacement is recommended.

4. Zinc Supplementation

- There are insufficient data to recommend either for or against the use of zinc for the treatment of COVID-19 (50)

- Increased intracellular zinc concentrations efficiently impair replication in a number of RNA viruses.
- If it is used it should not exceed the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial (for elemental zinc 11 mg daily for men and 8 mg for nonpregnant women is the recommended daily allowance)(50)

VACCINES AGAINST SARS-COV-2

Introduction

Since there is no effective antiviral drug that works in all patient groups, vaccination will likely be the most effective way to control the pandemic. Development of a safe and effective COVID-19 vaccine is not easy but manufacturing, distribution, and administering the vaccine could be potentially challenging as well.

A number of COVID-19 vaccines are being developed. As of November 2021, there are More than 60 vaccines are currently listed for stage 1 or stage 1,2 trials, while a whopping 184 candidates in pre-clinical trials are registered with the WHO.

The development of immune memory by the vaccines is what will protect the person against subsequent COVID-19 infection.

SARS-CoV-2 Vaccines

Several SARS-CoV-2 vaccine types are currently under development, including inactivated vaccines, live attenuated vaccines, nucleic acid vaccines, adenovirus-based vector vaccines, and recombinant subunits vaccines (Table 1). Each approach has advantages and disadvantages (51, 52)(Figure 4).

Vaccine Category	Sponsor	Vaccine Candidate	Ref/registration number	Preclinical	Phase I	Phase II	Phase III/IV
mRNA	Moderna/NIH	mRNA-1273	NCT04283461				
mRNA	Pfizer/BioNTech	BNT162	EudraCT 2020-001038-36, NCT04380701				
Adenovirus-based	CarSino Biologics/Academy of Military Medical Sciences	Ad5-nCoV	ChiCTR2000031781, ChiCTR2000030906				
Inactivated	Wuhan Institute of Biological Products	COVID-19 vaccine (Vero cells)	ChiCTR2000031809				
Inactivated	Sinovac Biotech	PiCoVacc	NCT04352608				
Adenovirus vector	Oxford/University/AstraZeneca	ChAdOx1 nCoV-19	NCT04324606				
Inactivated	Beijing Institute of Biological Products	Inactivated SARS-CoV-2 vaccine (Vero cells)	ChiCTR2000032459				
Lentivirus vector	Shenzhen Genoimmune Medical Institute	Covid-19/sAPC	NCT04299724				
Lentivirus vector	Shenzhen Genoimmune Medical Institute	LV-SMENP-DC	NCT04276896				
DNA plasmid	Inovio/Beijing Advecience/Ology	INO-4800	NCT04336410				
Recombinant protein	Novavax	NVX-CoV2373	NCT04368988				
bacterial vector	Symvivo Corporation	baeTRI-Spike	NCT04334980				
Trained Immunity-Based	Merck	Bacille Calmette-Guerin (BCG)	NCT04326441, NCT04362124, NCT04379336, NCT04350931, NCT04327206, NCT04369794, NCT04373291, NCT04348370				

Table I: Landscape of COVID-19 Vaccine Development, (53).

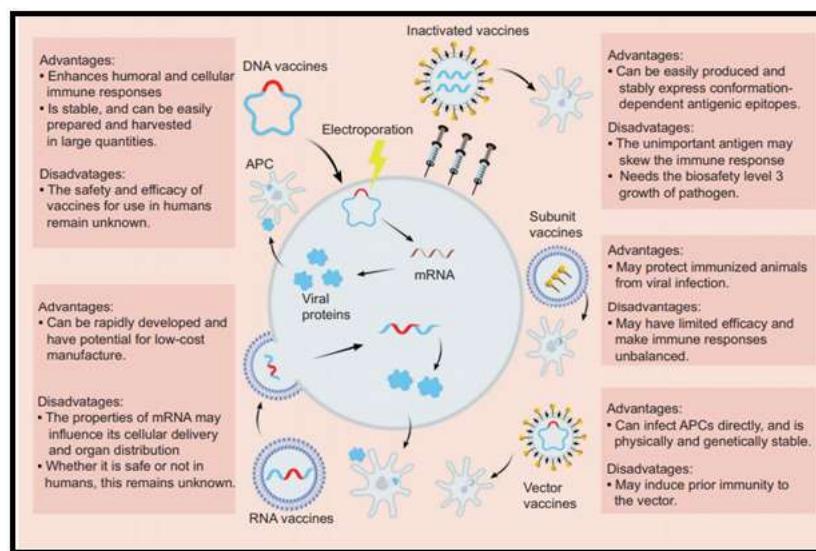


Figure 4: Overview of the diverse types of vaccines, and their potential advantages and disadvantages, (54).

Inactivated vaccines and live-attenuated vaccines

Inactivated vaccines are produced by growing SARS-CoV-2 in cell culture then inactivating it chemically, heat or radiation, usually it is combined with other adjuvant like aluminum hydroxide to enhance the immune response.

They have stable expression of conformation-dependent antigenic epitopes and can be easily produced in large quantities which require safety level 3 [55].

Two inactivated whole virus SARS-CoV-2 vaccines are currently available and in use.

1. Sinovac:

- Two doses are required. (0.5 ml) given intramuscularly 2–4 weeks apart.
- Approved from 18 years old and above
- No enough data to recommend using it in pregnant ladies, WHO recommends the use of the Sinovac-CoronaVac (COVID-19) vaccine in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks
- Up to date no recommendation for third or booster dose
- Had an efficacy of 83.5 percent (95% CI 65.4–92.1) in study done in Turkey [56]. However lower efficacy was reported from other studies done in other countries.[57]

2. WIV04 and HB02 (Sinopharm):

- Two doses are required. (0.5 ml) given intramuscularly 3–4 weeks apart.
- Approved from 18 years old and above
- No enough data to recommend using it in pregnant ladies, WHO recommends the use of the Sinovac-CoronaVac (COVID-19) vaccine in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks
- Up to date no recommendation for third or booster dose
- vaccine efficacy starting 14 days after full vaccination was estimated as 73 percent (95% CI 58–82) for WIV04 and 78 percent (95% CI 65–86) for HB02, each compared with an alum-only placebo [58].

Live-attenuated vaccines:

- live-attenuated vaccines are genetically weakened versions of the wild-type virus
- A live attenuated COVID-19 vaccine would stimulate both humoral and cellular immunity and can be administered intranasally
- Currently no available vaccine in this category

Nucleic acid vaccines

Nucleic acid vaccines, such as mRNA vaccines and DNA vaccines, are other popular vaccine forms. These vaccines are delivered into human cells, where they will then be transcribed into viral proteins.

mRNA vaccines represent a promising alternative compared to conventional vaccines due to their high potency, ability for rapid development, and cost-efficient production.

Two mRNA SARS-CoV-2 vaccines are currently available and in use.

1- Pfizer-BioNTech

- 2 doses, 0.3 ml intramuscular are required with 3 weeks apart
- Approved from age for 12 years and above
- Recently approved in some countries to be used from 5-11 years old with dose of 0.1 ml
- Third dose was approved in certain categories 4 weeks after the second dose
- Booster dose was approved in certain categories after 6 months from
- Efficacy 94.1 percent vaccine efficacy in preventing symptomatic COVID-19 infection [5]
- Can be used in pregnant and lactating women

2- Moderna

- 2 doses, 0.5 ml intramuscular are required with 4 weeks apart
- The Moderna vaccine is recommended for people aged 18 years and older
- Third dose was approved in certain categories 4 weeks after the second dose
- Booster dose was approved in certain categories after 6 months from
- Efficacy 95% in preventing symptomatic COVID-19 second dose [60]
- Can be used in pregnant and lactating women.

Vector vaccines

Vector vaccines are generally constructed from a carrier virus, such as an adeno or pox virus, and are engineered to carry a relevant gene from the virus, usually the S gene.

Three Non-replicating viral vector SARS-CoV-2 vaccines are currently available and in use.

1- Janssen/Johnson & Johnson

- This vaccine is based on a replication-incompetent adenovirus 26 vector that expresses a stabilized spike protein
- Single dose vaccine 0.5 ml given intramuscularly
- Recommended for people 18 years and older
- Booster Shot: At least 2 months after receiving your vaccine.
- The J&J/Janssen COVID-19 Vaccine was 66.3% effective in clinical trials [61]

2- Oxford-AstraZeneca,

- This vaccine is based on a replication-incompetent chimpanzee adenovirus vector that expresses the spike protein
- Two doses regimen vaccine 0.5 ml given intramuscularly given 4 -12 weeks apart
- Approved from 18 years old and above
- Up to date no recommendation for third or booster dose
- Vaccine had 70.4 percent efficacy in preventing symptomatic COVID-19 at or after 14 days following the second dose [62]

3- Sputnik V (Gamaleya Research Institute)

- Sputnik V is the world's first registered vaccine based on a well-studied human adenovirus vector platform
- Two doses regimen vaccine 0.5 ml given intramuscularly given 3 weeks apart
- Approved from 18 years old and above
- Vaccine had 91.6 percent efficacy in preventing symptomatic COVID-19 starting at 21 days following the first dose (at the time of the second dose).[63]

Subunit vaccines and virus-like particles vaccines

One PROTEIN SUBUNIT SARS-CoV-2 vaccine. But it is not yet available for use

1. Novavax

This is a recombinant protein nanoparticle vaccine composed of trimeric spike glycoproteins and a potent Matrix-M1 adjuvant

Two doses regimen vaccine 0.5 ml given intramuscularly given 3 weeks apart

To be used from 18 years old and above

Had 90.4 percent (95% CI 82.9-94.6) efficacy in preventing symptomatic COVID-19 starting at or after seven days following the second dose [64]

In conclusion, the field of SARS-CoV-2 vaccinology is very active with a new data released every day, however, much remains to be learned regarding SARS-CoV-2 immunity, including the protective immunity induced by vaccines and the maintenance of immunity against this virus.

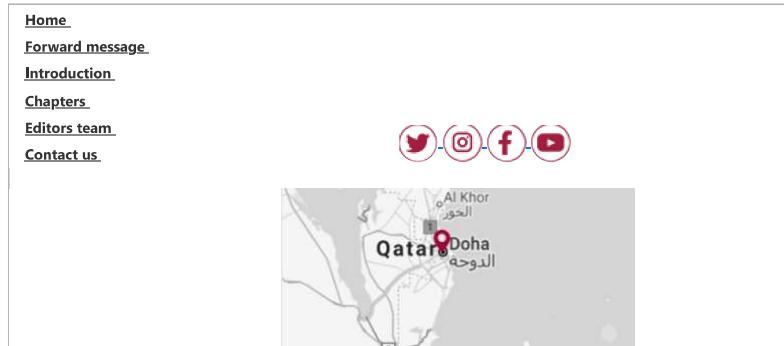
Furthermore, multiple vaccine types will probably be needed across different populations such as immature infants, children, pregnant women, immunocompromised individuals, and immunosenescent individuals aged ≥65 years.

Reference:

1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-74.
2. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3.
3. Gil C, Ginex T, Maestro I, Nozal V, Barrado-Gil L, Cuesta-Geijo MA, et al. COVID-19: Drug Targets and Potential Treatments. J Med Chem. 2020;63(21):12359-86.
4. Gallagher TM, Buchmeier MJ. Coronavirus spike proteins in viral entry and pathogenesis. Virology. 2001;279(2):371-4.
5. Castano-Rodriguez C, Honrubia JM, Gutierrez-Alvarez J, DeDiego ML, Nieto-Torres JL, Jimenez-Guardeno JM, et al. Role of Severe Acute Respiratory Syndrome Coronavirus Viroropins E, 3a, and 8a in Replication and Pathogenesis. mBio. 2018;9(3).
6. Neuman BW, Kiss G, Kunding AH, Bhella D, Baksh MF, Connelly S, et al. A structural analysis of M protein in coronavirus assembly and morphology. J Struct Biol. 2011;174(1):11-22.
7. McBride R, van Zyl M, Fielding BC. The coronavirus nucleocapsid is a multifunctional protein. Viruses. 2014;6(8):2991-3018.
8. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019;17(3):181-92.
9. Berekaa MM. Insights into the COVID-19 pandemic: Origin, pathogenesis, diagnosis, and therapeutic interventions. Front Biosci (Elite Ed). 2021;13:117-39.
10. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11(8):875-9.
11. Coutard B, Valle C, de Lamballerie X, Canard B, Seidah NG, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res. 2020;176:104742.
12. Xu J, Yang X, Yang L, Zou X, Wang Y, Wu Y, et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. Crit Care. 2020;24(1):394.
13. Coperchini F, Chiavato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 2020;53:25-32.
14. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020;145(6).
15. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-System Inflammatory Syndrome in Children (MIS-C) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed Management. Children (Basel). 2020;7(7).

16. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771-8.
17. Stokes EK, Zambrano LD, Anderson KN, Milder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(24):759-65.
18. Lewnard JA, Liu VX, Jackson ML, Schmidt MA, Jewell BL, Flores JP, et al. Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study. *BMJ*. 2020;369:m1923.
19. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill*. 2020;25(10).
20. Wang Y, Liu Y, Liu L, Wang X, Luo N, Li L. Clinical Outcomes in 55 Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Who Were Asymptomatic at Hospital Admission in Shenzhen, China. *J Infect Dis*. 2020;221(11):1770-4.
21. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. *N Engl J Med*. 2020;382(22):2081-90.
22. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. *N Engl J Med*. 2020;382(22):2163-4.
23. Aziz M, Goyal H, Haghbin H, Lee-Smith WM, Gajendran M, Perisetti A. The Association of "Loss of Smell" to COVID-19: A Systematic Review and Meta-Analysis. *Am J Med Sci*. 2021;361(2):216-25.
24. Horwitz LI, Jones SA, Cerfolio RJ, Francois F, Greco J, Rudy B, et al. Trends in COVID-19 Risk-Adjusted Mortality Rates. *J Hosp Med*. 2021;16(2):90-2.
25. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020;26(7):1017-32.
26. Khader M, Al Bishawi A, Kambal A, Abdelmajid A. SARS-CoV-2 infection presenting as colitis with chest and abdomen CT findings. *Radiol Case Rep*. 2020;15(11):2427-32.
27. Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, et al. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. *Circulation*. 2020;142(2):184-6.
28. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA*. 2020;324(8):799-801.
29. Gervaise A, Bouzad C, Peroux E, Helissey C. Acute pulmonary embolism in non-hospitalized COVID-19 patients referred to CTPA by emergency department. *Eur Radiol*. 2020;30(11):6170-7.
30. Gianotti R, Veraldi S, Recalcati S, Cusini M, Ghislanzoni M, Boggio F, et al. Cutaneous Clinico-Pathological Findings in three COVID-19-Positive Patients Observed in the Metropolitan Area of Milan, Italy. *Acta Derm Venereol*. 2020;100(8):adv00124.
31. Diaz-Guimaraens B, Dominguez-Santas M, Suarez-Valle A, Pindado-Ortega C, Seldia-Enriquez G, Bea-Ardebol S, et al. Petechial Skin Rash Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *JAMA Dermatol*. 2020;156(7):820-2.
32. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol*. 2020;19(5):383-4.
33. Carfi A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent Symptoms in Patients After Acute COVID-19. *JAMA*. 2020;324(6):603-5.
34. Goertz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ Open Res*. 2020;6(4).
35. Little P. Non-steroidal anti-inflammatory drugs and covid-19. *BMJ*. 2020;368:m1185.
36. Zhang XJ, Qin JJ, Cheng X, Shen L, Zhao YC, Yuan Y, et al. In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19. *Cell Metab*. 2020;32(2):176-87 e4.
37. Group RC, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 2020;383(21):2030-40.
38. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med*. 2020;383(21):2041-52.
39. Consortium WHOST, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyanamoorthy V, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021;384(6):497-511.
40. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering (Beijing)*. 2020;6(10):1192-8.
41. Group RC. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2020.
42. Yang P, Tekwani S, Martin GS. In COVID-19, adding lopinavir-ritonavir to usual care did not shorten time to clinical improvement. *Ann Intern Med*. 2020;172(12):JC63.
43. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res*. 2020;178:104787.
44. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704.
45. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. *JAMA*. 2020;324(13):1307-16.
46. Brown BL, McCullough J. Treatment for emerging viruses: Convalescent plasma and COVID-19. *Transfus Apher Sci*. 2020;59(3):102790.
47. Kulkarni S, Fisk M, Kostapanos M, Banham-Hall E, Bond S, Hernan-Sancho E, et al. Repurposed immunomodulatory drugs for Covid-19 in pre-ICU patients - multi-Arm Therapeutic study in pre-ICU patients admitted with Covid-19 - Repurposed Drugs (TACTIC-R): A structured summary of a study protocol for a randomised controlled trial. *Trials*. 2020;21(1):626.
48. Tonati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. *Autoimmun Rev*. 2020;19(7):102568.
49. Wei XB, Wang ZH, Liao XL, Guo WX, Wen JY, Qin TH, et al. Efficacy of vitamin C in patients with sepsis: An updated meta-analysis. *Eur J Pharmacol*. 2020;868:172889.
50. Kumar A, Kubota Y, Chernov M, Kasuya H. Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. *Med Hypotheses*. 2020;144:109848.
51. Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. *Virus Res*. 2020;288:198114.
52. Amaran F, Krammer F. SARS-CoV-2 Vaccines: Status Report. *Immunity*. 2020;52(4):583-9.
53. Wang J, Peng Y, Xu H, Cui Z, Williams RO, 3rd. The COVID-19 Vaccine Race: Challenges and Opportunities in Vaccine Formulation. *AAPS PharmSciTech*. 2020;21(6):225.
54. Dong Y, Dai T, Wei Y, Zhang L, Zheng M, Zhou F. A systematic review of SARS-CoV-2 vaccine candidates. *Signal Transduct Target Ther*. 2020;5(1):237.

55. Plotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S ,The complexity and cost of vaccine manufacturing - An overview. *Vaccine*. 2017;35(33):4064. Epub 2017 Jun 21
56. Tanrıover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, KöseŞ, ErdinçFŞ, Akalın EH, TabakÖF, Pullukçu H, BatumÖ,Şimşek Yavuz S, TurhanÖ, Yıldırım MT, Köksalı, Taşova Y, Korten V, Yılmaz G,Çelen MK, Altın S,Çelikli, Bayındır Y, Karaoğlani, Yılmaz A,Özkul A, Gür H, Unal S, CoronaVac Study Group Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet*. 2021;398(10296):213. Epub 2021 Jul 8.
57. Baraniuk C ,What do we know about China's covid-19 vaccines? .*BMJ*. 2021;373:n912. Epub 2021 Apr 9.
58. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, Al Nusair M, Hassany M, Jawad JS, Abdalla J, Hussein SE, Al Mazrouei SK, Al Karam M, Li X, Yang X, Wang W, Lai B, Chen W, Huang S, Wang Q, Yang T, Liu Y, Ma R, Hussain ZM, Khan T, Saifuddin Fasihuddin M, You W, Xie Z, Zhao Y, Jiang Z, Zhao G, Zhang Y, Mahmoud S, ElTantawy I, Xiao P, Koshy A, Zaher WA, Wang H, Duan K, Pan A, Yang X ,Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial.*JAMA*. 2021;326(1):35.
59. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, French RW Jr, Hammitt LL, TüreciÖ, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC, C4591001 Clinical Trial Group , Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine.*N Engl J Med*. 2020;383(27):2603. Epub 2020 Dec 10.
60. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T, COVE Study Group . Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403. Epub 2020 Dec 30.
61. Sara E. Oliver, Julia W. Gargano, Heather Scobie, Megan Wallace, Stephen C. Hadler, Jessica Leung, Amy E. Blain, Nancy McClung, Doug Campos-Outcalt, Rebecca L. Morgan, Sarah Mbaeyi, Jessica MacNeil; José R. Romero, H. Keipp Talbot, Grace M. Lee; Beth P. Bell, ; Kathleen Dooling, The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Janssen COVID-19 Vaccine — United States, February 2021 Weekly / March 5, 2021 / 70(9);329–332On March 2, 2021, this report was posted online as an MMWR Early Release.
62. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, Baillie VL, Barnabas SL, Bhorat QE, Bibi S, Briner C, Cicconi P, Collins AM, Colin-Jones R, Cutland CL, Darton TC, Dheda K, Duncan CJA, Emery KRW, Ewer KJ, Fairlie L, Faust SN, Feng S, Ferreira DM, Finn A, Goodman AL, Green CM, Green CA, Heath PT, Hill C, Hill H, Hirsch I, Hodgson SHC, Izu A, Jackson S, Jenkin D, Joe CCD, Kerridge S, Koen A, Kwatra G, Lazarus R, Lawrie AM, Lelliott A, Libri V, Lilie PJ, Mallory R, Mendes AVA, Milan EP, Minassian AM, McGregor A, Morrison H, Mujadidi YF, Nana A, O'Reilly PJ, Padayachee SD, Pittella A, Plested E, Pollock KM, Ramasamy MN, Rhead S, Schwarzbold AV, Singh N, Smith A, Song R, Snape MD, Sprinz E, Sutherland RK, Tarrant R, Thomson EC, Török ME, Toshner M, Turner DPJ, Vekemans J, Villafana TL, Watson MEE, Williams CJ, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Pollard AJ, Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK.*Lancet*. 2021;397(10269):99. Epub 2020 Dec 8.
63. Logunov DY, Dolzhikova IV, Zubkova OV, Tukhvatulin AI, Shcheplyakov DV, Dzharullaeva AS, Grousova DM, Erokhova AS, Kovyrshina AV, Botikov AG, Izhaeva FM, Popova O, Ozharovskaya TA, Esmagambetov IB, Favorskaya IA, Zrelkin DI, Voronina DV, Shcherbinin DN, Semikhin AS, Simakova YY, Tokarskaya EA, Lubenets NL, Egorova DA, Shmarov MM, Nikitenko NA, Morozova LF, Smolyarchuk EA, Kryukov EV, Babira VF, Borisevich SV, Naroditsky BS, Gintzburg AL . Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. *Lancet*. 2020;396(10255):887. Epub 2020 Sep 4.
64. Novavax. Novavax COVID-19 Vaccine Demonstrates 90% Overall Efficacy and 100% Protection Against Moderate and Severe Disease in PREVENT-19 Phase 3 Trial. <https://ir.novavax.com/2021-06-14-Novavax-COVID-19-Vaccine-Demonstrates-90-Overall-Efficacy-and-100-Protection-Against-Moderate-and-Severe-Disease-in-PREVENT-19-Phase-3-Trial> (Accessed on June 25, 2021).





Mental Health

CHAPTER: The Psychiatric Impact of the COVID-19 pandemic

Majid Alabdulla , Iain Tulley , Sazgar Hamad, Zerak Al-Salihy, Peter M. Haddad

Key words: Psychiatry, Qatar, COVID-19, Depression, Anxiety, Psychosis, Mental Health Services, Quarantine

1. Review of literature

1.1 Introduction

The changing nature of the COVID-19 pandemic across time and geography makes a brief synthesis of the psychiatric literature challenging. In addition, the long-term psychological effects of the pandemic remain unknown.

Research from previous epidemics and natural disasters indicates survivors can experience long term mental health problems including post-traumatic stress disorder, depressive and anxiety disorders and substance misuse (1, 2).

The economic recession that will follow the COVID pandemic also makes long-term mental health consequences inevitable. Constraints on length mean that the focus is largely on adult populations.

1.2 The pandemic and risk factors for psychiatric disorder

The COVID-19 pandemic is associated with psychosocial and organic risk factors for developing psychiatric disorder.

Psychosocial factors can affect those with and without COVID-19. They stem from SARS-CoV-2 being highly transmissible and associated with high morbidity and mortality. To minimize contagion, governments have imposed lockdowns, quarantine and travel restrictions.

Individuals face anxiety related to fear of infection, the wellbeing of others, social isolation, security of finances and employment and many have experienced bereavement (3).

The demands of the pandemic may make parents less able to address their children's needs. Children and adolescents may worry about their parents' health and disrupted schooling.

Increased proximity within the home, and other pandemic-related stressors, can precipitate or exacerbate family violence. Social distancing may reduce the ability of victims of abuse to support and help.

Many countries have seen increased reports of domestic violence during the pandemic (4).

Quarantine has negative psychological effects in adults including post-traumatic stress symptoms, confusion, and anger (3). A pre-COVID-19 study, investigated the psychosocial responses of children and their parents to quarantine (5).

Mean post-traumatic stress scores were four times higher in children who had been quarantined than in those who were not quarantined.

The proportion of parents meeting criteria for a trauma-related mental health disorder was 28% among those subject to quarantine versus 6% of those not quarantined.

Increased exposure to COVID-19 social media use has been associated with worse mental health (6). The pandemic has provided opportunity for rumour and misinformation about COVID-19.

This highlights the importance of the media, health care workers (HCW) and governments providing balanced and accurate information (7).

Organic risk factors encompass the bodily changes seen during COVID-19 and include inflammation, hypoxia, organ failure, and the iatrogenic effects of medical treatment, for example corticosteroids.

SARS-CoV-2 primarily affects the respiratory system but affects other bodily systems. Coronaviruses known to be neurotropic (replicating in neurons) include SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV)(8).

To what extent SARS-CoV-2 is neurotropic remains uncertain. Viral RNA has been detected in the cerebrospinal fluid of patients with COVID-19 encephalitis and meningitis but such cases appear rare (9, 10).

1.3 Impact of the pandemic on the mental health of the general population

Early research assessing the psychiatric impact of COVID-19 in the general population consisted of cross-sectional studies with convenience samples. A meta-analysis of 17 cross-sectional observational studies conducted in general adult population during the COVID-19 pandemic reported the following prevalence rates: stress = 29.6%, anxiety = 31.9% and depression = 33.7% (11).

The pandemic has also impacted on the mental health of young people, especially in terms of depression and anxiety in adolescents (12).

Cross sectional studies cannot determine whether levels of morbidity differ to that before the pandemic and convenience samples mean that results may not be generalizable. Longitudinal studies using representative samples overcome these problems.

Longitudinal studies show that the pandemic's impact on population mental health varies between countries. Studies in the UK(13, 14) and USA (15) during the early stages of the pandemic showed an increased prevalence of population mental health problems versus pre-pandemic levels.

Data from the nationally representative United Kingdom Household Longitudinal Study (UKHLS) showed that the prevalence of population mental health problems, defined as a (GHQ-12 score ≥ 3 , increased from 24.3% in 2017-2019 to 37.8% in April 2020, soon after the first UK national lockdown started (14).

Subsequently the prevalence of mental health problems decreased (May, 34.7%; June, 31.9%) but remained significantly higher than pre-COVID-19 levels. The increase was most marked in younger people (age 18-34 year), females and high-income and education groups.

A nationally representative survey in the USA found that prevalence of depression symptoms increased from 8.5% before COVID-19 to 27.8% during COVID-19, a more than 3 fold increase (see figure 1) (16).

In this study depressive symptoms were defined as a Patient Health Questionnaire-9 cutoff of 10 or higher. Those with lower incomes, less savings and greater exposure to stressors (e.g. job loss, death of someone close due to COVID-19) reported a greater burden of depression symptoms.

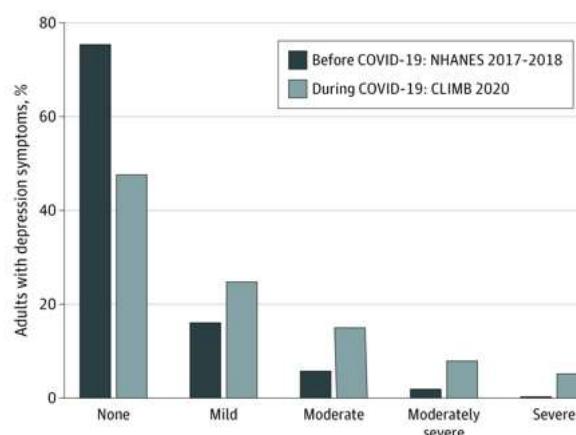


Figure 1: Depression Symptoms in US Adults Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic
(reproduced from Ettman et al 2020, JAMA Network Open)

Before COVID-19 estimates from the National Health and Nutrition Examination Survey (NHANES) from 2017-2018. During COVID-19 estimates from the COVID-19 and Life Stressors Impact on Mental Health and Well-being (CLIMB) study collected from March 31 to April 13, 2020.

Depression symptoms categories calculated using the Patient Health Questionnaire-9: none (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20). Percentages weighted to the population of noninstitutionalized US adults aged 18 years or older.

several European countries experienced second waves of infection and re-entered national lockdown in late 2020 and this would be expected to affect population mental health.

1.4 Impact of the pandemic on the mental health of health care workers (HCWs)

Preti et al (2020) reported a systematic review of 44 studies assessing the psychological impact of epidemics/pandemics on the mental health of HCWs (physicians, nurses, and auxiliary staff) (2). Most studies related to SARS (27 studies) but five studies related to COVID-19. Across these studies, insomnia was reported by 34% to 36.1% of HCWs and severe anxiety symptoms by 45%.

The prevalence of post-traumatic stress disorder (PTSD) symptoms ranged 11% to 73.4%, with the highest prevalence in COVID-19 studies. PTSD and depressive symptoms, as well as general psychological distress, were reported after periods ranging from 6 months up to 3 years after the infective outbreak.

Working on a unit with a high risk of infection was associated with worse mental health outcomes. Perceived organizational support, adequacy of training and confidence in equipment and infection control measures were protective factors for one or more mental health outcomes.

Pappa et al examined the effects of the COVID-19 pandemic on the mental health of HCWs (18). The meta-analysis includes 13 cross-sectional studies (33,062 participants) and all but one were conducted in China.

Pooled prevalence rates were 23.2% for anxiety, 22.8% for depression and 38.9% for insomnia. Most participants reporting affective symptoms had mild symptoms. Female gender and being a nurse were associated with higher rates of affective symptoms.

The occupational finding may reflect most nurses being female. Methodological differences hinder comparisons with other studies.

Nevertheless, the prevalence rates for anxiety and depression among HCWs in this meta-analysis are similar to those reported for the general population in China during the same period.

The prevalence rates were at the lower end of rates reported among HCWs during the MERS and SARS epidemics.

This may reflect COVID-19 having a lower mortality than MERS and SARS and health care services in China becoming more proficient in managing epidemics and supporting HCWs in the interim.

It is clear that the COVID-19 pandemic can impact on the mental health of HCWs. Extrapolating from previous epidemics suggests that HCW are also at risk of persisting morbidity (2). Health care services need to implement strategies to mitigate mental health risks and provide intervention for those affected.

1.5 Impact of the pandemic on people with a prior psychiatric history

In this section, we examine two separate questions; whether those with a psychiatric history, compared to those without, are (i) more prone to develop COVID-19 and (ii) more prone to experience psychiatric morbidity during the pandemic.

Three large cohort studies, one from the UK (19) and two from the USA, (20),(21) found that a past diagnosis of psychiatric disorder, compared to no diagnosis, was associated with an

increased risk of COVID-19.

A Korean study found no such association but was smaller than the previous studies and employed the least matching (22). On balance, current evidence suggests that a history of psychiatric illness is an independent risk factor for COVID-19. This is consistent with studies showing an association between psychiatric disorder and other severe infections (23).

Possible explanations include a weakened immune system and/or a pro-inflammatory state in those with psychiatric disorder which increases the risk of infection/ progression to severe disease, behavioural factors (for example less adherence to social distancing recommendations), residual lifestyle factors that are not adequately controlled for in the analyses and psychotropic medication increasing vulnerability/severity of COVID-19.

Irrespective of the explanation, these results highlight the need for additional health education and support care for those with psychiatric histories during the COVID-19 pandemic.

A further study showed that patients with a history of substance use disorder in the last year, compared to those without, had an increased risk for COVID-19 and adverse outcomes (24).

These effects were especially marked for opiate use disorder.

Those with a prior mental health disorder may be a vulnerable group to experience psychiatric complications in the pandemic.

They are likely to be less financially secure and have smaller social networks making the pandemic more stressful, while lockdowns and staff illness may interrupt access to mental health care.

Several cross-sectional studies have reported higher levels of psychiatric symptoms during the pandemic in those with prior psychiatric histories versus those with no such history (25), (26).

However, the cross-sectional design prevents a comparison with morbidity prior to the pandemic. Achieving this, requires a longitudinal design with data from before as well as during the pandemic.

A Dutch study employed existing psychiatry case-control cohorts to assess the impact of the pandemic on people with and without prior mental health disorders (depressive, anxiety, or obsessive-compulsive disorders). The pre-pandemic data reflected mean assessments gathered over several preceding years.

The pandemic data was gathered during the first few weeks of the Dutch national lockdown (27). The key findings were:

1. Individuals with a higher number, or more chronic mental health disorders reported a greater impact of the pandemic on their mental health, more fear of COVID-19, and less positive coping with the pandemic. A graded dose-response relation was evident.
2. The severity of symptom of depression, anxiety, worry, and loneliness, both before and during the pandemic, were higher in people with more severe and more chronic mental health disorders (i.e. depressive, anxiety, or OCD) compared to those with no history of psychiatric disorder.
3. In terms of change from before to during the pandemic, people without severe or chronic mental health disorders tended to show an increase in all four symptom scores (depression, anxiety, OCD, loneliness) but the increase was modest. In contrast, people with the highest number or chronicity of mental health disorders either showed no increase in symptom severity or a significant decrease in symptom severity.

In summary, in the Netherlands, the mental health of people with a prior psychiatric history was worse during the early phase of the pandemic compared to those with no psychiatric history. However, this represented persistence or recurrence of long standing morbidity.

One cannot assume that similar results will be seen in other countries.

Further work is needed to determine the impact of the pandemic in other countries and the trajectories over time.

1.6 Psychiatric morbidity in COVID-19 patients

Taquet et al (2020) conducted an electronic health record network cohort study, with data from 69 million individuals, to assess the risk of a psychiatric disorder being diagnosed in the 14 to 90 days following either a diagnosis of COVID-19 or one of six acute health events (i.e. controls) (19).

The latter were influenza, another respiratory tract infection, cholelithiasis, urolithiasis, skin infection, and fracture of a large bone. Propensity score matching controlled for confounders.

The study assessed the incidence of a first psychiatric diagnosis well as all psychiatric diagnoses (i.e. relapses and new diagnoses combined). We will discuss the findings for first onset and all psychiatric disorder separately.

An increased incidence of a first psychiatric diagnosis was seen in the 3-month following COVID-19 compared to all six control health conditions (5.8% versus 2.5% to 3.4%) i.e. a first psychiatric diagnosis was approximately twice as likely to follow COVID-19 than other acute health event(19). A significantly increased risk of first onset disorder was seen for anxiety disorder (4.9%), mood disorder (2.0%), insomnia (1.9%), and dementia (restricted to those >65 years) (1.6%) but not for psychotic disorders (0.1%).

This is despite case reports noting new onset psychosis associated with the pandemic (28).

The researchers excluded psychiatric diagnoses made in the first 14 days after COVID-19 which makes it less likely that dementia cases represent misdiagnosis of delirium.

Turning to total diagnoses (new onset disorders and relapses combined), the incidence of any psychiatric diagnosis in the 3-month follow-up period was 18.1% (19).

This was significantly higher than following each of the 6 control conditions where the total rate of psychiatric diagnosis ranged from 12.7% to 15.1%. With regard to specific diagnoses, the rates following COVID-19 for first or relapsed disorder were: anxiety disorder = 12.8%, mood disorders = 9.9%, and psychotic disorder = 0.90%.

The incidence rates in this study are likely to underestimate the true incidence for several reasons, including the fact that the pandemic reduced presentation rates for a wide range of health disorders.

Given that observational studies have access to limited data, as recorded in medical records, the findings of this study (19) need to be confirmed/refuted by prospective cohort studies. Several such studies are ongoing across the world.

A wide range of neuropsychiatric presentations occur with COVID (29). Delirium is especially common in older patients (30) and those who have required intensive care (31).

Other acute syndromes include psychosis, mood disorders, catatonia, encephalopathy, encephalitis, and cerebral hemorrhages and infarcts. Long-COVID involves a wide range of disabling symptoms, including fatigue and cognitive impairment, that can persist for month after acute infection (32).

1.7 Provision of mental health care during the pandemic

The early stages of the pandemic led to widespread disruption to psychiatric services across the globe.

This included appointments being cancelled and medication supply changes being interrupted. In addition, patients may avoid booking face to face appointments for fear of infection.

Similar factors may reduce blood monitoring, especially pertinent to those prescribed lithium and clozapine.

Reduced access to care is a particular concern in first episode psychosis as increased duration of untreated psychosis is associated with a poorer outcome (33).

Psychiatric services have undergone radical changes to adapt to the pandemic. This has included switching from face to face appointments to remote consultations. Fortunately, psychiatry can adapt to telemedicine more easily than most medical specialties as it is less reliant on physical examinations and investigations.

Telepsychiatry may be more acceptable to some patients as it is perceived as less stigmatizing but it can also present challenges.

It is unclear how the use of telepsychiatry will alter when the pandemic ends/ is brought under control. Its effectiveness and acceptability require further assessment.

Psychiatric wards are prone to COVID-19 outbreaks in the way that prisons and nursing homes are .

Fortunately, widespread COVID-19 outbreaks in psychiatric units appear to have been uncommon with only isolated cases reported (34), (35). Changes in practice on psychiatric wards to reduce infection risk have included reduced visiting, reduced leave, protocols for managing COVID-19 and in the United Kingdom remote, rather than face to face, mental health tribunals.

The long term psychiatric effects of the pandemic are as yet unknown. However, it is likely that there will be an increased prevalence of morbidity in the general population for months if not years to come, partly reflecting the economic recession that will inevitably follow.

Across the world psychiatric services are underfunded compared to services in other specialties. As such there is likely to be marked pressure on psychiatric services and there has been a call for increased funding to mitigate this.

Strategies are needed at national levels to mitigate the expected increase in morbidity and establish effective services.

2. Experience in Qatar

2.1 Introduction

The pandemic in Qatar has been well managed.

The first COVID-19 case was reported in Qatar in late February 2020.

The following month the government introduced a lockdown that included strict control on entry to the country from abroad, mandatory quarantine, a policy of working from home where possible and the closure of mosques, schools and

universities, non-essential shops, parks and public beaches. A contact tracing app for smart phones and the wearing of facemasks in public were made mandatory.

These polices proved effective with the daily rate of infection peaking at the end of May 2020 and falling to under 300 new cases per day by the end of July.

A four-phase easing of the lockdown commenced in mid-June 2020 with phase 4 starting on September 1st.

The COVID-19 pandemic posed a major challenge to mental health services in Qatar.

Services needed to continue to meet the mental health needs of the population yet follow the national lockdown and social distancing regulations introduced by the Ministry of Public Health.

The Hamad Medical Corporation (HMC) Mental Health Service closed most community services, switched from face to face to remote clinics and set up a series of new and innovative services.

In parallel many staff became involved in research, audit and quality improvement projects to better understand the impact of the pandemic and the effectiveness of the new services.

In part 2 of this chapter we focus on the service changes introduced by the HMC Mental Health Service in response to the pandemic and provides a brief overview of the Service's COVID-19 psychiatric research.

We have focused on HMC as this reflects the experience of the authors and because HMC is the main provider of secondary care mental health services in Qatar.

However, it is important to acknowledge that the Primary Health Care Corporation (PHCC), Qatar Red Crescent and specialist secondary mental health providers, most notably Naufar and Sidra, all played an essential part in providing psychiatric services in Qatar during the pandemic.

2.2 Mental health Services response to COVID-19 in Qatar

2.2.1 National Mental Health Helpline:

In March 2020, only a few weeks of the first COVID-19 case was reported in Qatar, HMC introduced a national mental health helpline.

This provides support for people experiencing psychological distress, including the young and elderly, the quarantined, those with pre-existing mental health conditions and front-line healthcare professionals.

One of the aims of the helpline was to reach out to patients who would otherwise be reluctant to engage with mental health services due to the associated stigma.

The helpline offers a wide range of services including assessment by mental health nurses and psychiatrists and interventions that range from basic psychological support to structured psychological interventions.

All calls are received by the tier 1 triage team who conduct an initial assessment and offer basic psychological aid.

Calls that require structured psychological interventions are passed on to the tier 2 team, which is comprised of clinical psychologists. Complicated calls that may require assessment or intervention from a psychiatrist are forwarded to a tier 3 team. This service, being culturally more acceptable, has been well accepted as people with psychological issues are often reluctant to seek help from mental health services in this Middle East due to stigma.

The helpline offers the following services:

- Child and adolescent (parents) support helpline for patients and the public.
- Adult mental health support helpline for patients and the public.
- Older adult and carer support helpline for patients and the public.
- Frontline responders and national helpline to all healthcare professionals.

During 2020 the Mental Health Service contacted tens of thousands of craft and manual worker through text messages in several languages, with Mental Health messaging and information on how to reach the helpline. A quality improvement project assessing patients experience of the mental health help-line was exceptionally positive.

2.2.2 Virtual Women's mental health service:

The virtual women's mental health service (vWMHS) offers a range of specialized mental health services for the adult (18-64 years) female population of Qatar. The service works in close collaboration with the other mental health virtual services and is based at Barwa tower 3.

The vWMHS has three service streams namely bereavement support, peri-natal mental health service and psychological wellbeing early intervention service. The service offers a fully confidential service by experienced, multi-lingual mental health professionals.

Its aims include:

- providing timely, targeted and brief multidisciplinary team (MDT) support at difficult times and so avoid escalation of mental health problems and their impact on quality of life.
- empowering women to manage their own mental health and daily challenges in positive and constructive ways
- Providing guidance and signposting to other health services as needed

The service is sensitive to the challenges facing the female population.

Individual members of MDT act as the point of contact for the caller throughout their care at the vWMHS.

There is easy access to and structuring within the vWMHS (see figure 2) enabling the service to reach a large number of female patients within a short period of time.

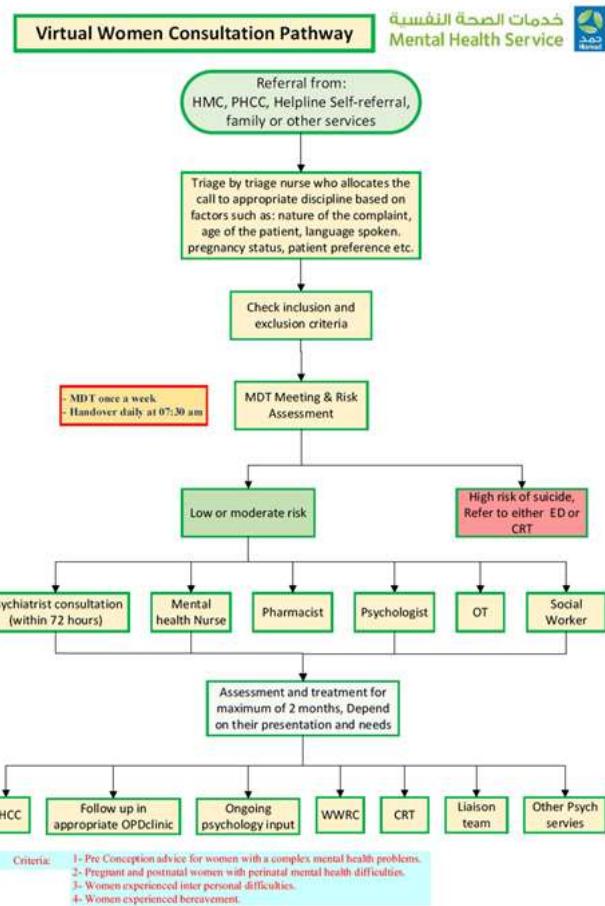


Figure 2: vWMS service consultation pathway

subgroup that the vWMHS cares for is pregnant women and those in the puerperium.

These women are a high risk group for experiencing psychiatric disorder.

This is likely to be even more so during the pandemic given the additional stressors facing people.

A cross-sectional survey of women accessing maternity services in Qatar assessed depression and anxiety symptomatology using the Patient Health Questionnaire Anxiety and Depression Scale (PHQ-ADS).

The result showed a high prevalence of anxiety and depression, 34.4 and 39.2% respectively (36).

2.2.3 Consultation liaison service in general hospitals:

Qatar has a well-established consultation liaison (CL) psychiatry service.

The rapid increase in the number of patients with COVID-19 being admitted to acute hospitals throughout spring 2020, and newly opened field hospitals and quarantine sites, led the CL service to develop outreach to these sites to provide assessment and management of patients with comorbid mental health difficulties.

The expansion of the CL service was successful but was not without its challenges. It involved deploying 5 psychiatric residents and 6 fellows to work in new CL services in COVID-19 sites.

In turn, this led to a shortage in junior doctors in existing mental health facilities and created an extra burden on the remaining trainees to provide coverage during working hours and on-call duties. However, staff were generally flexible and pleased to help manage a global crisis.

Iqbal et al (2020) provided a retrospective review of 50 consecutive referrals, who were COVID-19 positive (confirmed by real-time polymerase chain reaction), seen by the CL service in Qatar in the early part of the pandemic (37).

Most patients who were seen were male and the median age was 39.5 years. Most (66%) had no past psychiatric history.

The principal psychiatric diagnoses made by the CL team were delirium (n = 13), psychosis (n = 9), acute stress reaction (n = 8), anxiety disorder (n = 8), depression (n = 8) and mania (n = 8).

Other than delirium, these diagnoses were seen in both symptomatic and asymptomatic COVID patients. Approximately half the patients with mania and psychosis had no past psychiatric history suggesting that COVID-19 could trigger new first episodes of both disorders. As discussed in section one of this chapter, this could reflect psychosocial distress and /or organic factors. The CL service is providing follow up to those with more severe psychiatric disorders that arise during the pandemic.

2.2.4. Home delivery of psychiatric medications:

During their national lockdown, and subsequently when community services were restricted to reduce transmission of the virus, the psychiatric service introduced service to deliver medication to patients in their homes. Patients with a high risks of non-compliance and those prescribed medications that required regular monitoring, such as lithium and clozapine, were prioritised and put on a virtual system that monitored their drug levels and relevant blood investigations.

2.2.5 Psychological support for people in isolation and quarantine centres:

During the pandemic the State of Qatar opened 51 nationwide quarantine sites across the country that have cared for around 26,000 individuals to date. Due to the high prevalence of mental health disorders, especially anxiety, depression and post-traumatic stress disorders, in individuals isolated in quarantine sites (3), the psychiatric services offered psychological support and counselling to these vulnerable group of individuals. The HMC Mental Health Services delivered, with meals, information leaflets to all people in quarantine, again informing of how to seek help. Psychological support and counselling are also provided to healthcare workers who are managing quarantine sites.

2.2.6 Introduction of clinics and confidential helplines to frontline healthcare workers:

The HMC Mental Health Service recognized the risk of mental disorders affecting frontline health care workers. Therefore, a specialized clinic service was introduced for frontline healthcare workers and sited within COVID-19 facilities. Furthermore, a confidential helpline was also set up to provide a remote counselling service and psychological input on individual basis taking into consideration the sensitivities surrounding protection of personal data and psychiatric histories.

2.2.7. Other Mental Health Services

Unlike general hospital wards, patients on psychiatric wards are more mobile and usually eat communal meals and participate in group therapeutic activities. As such psychiatric wards are prone to COVID-19 outbreaks in the same way that other institutions are. Most of Qatar's acute psychiatric beds are located at the HMC Psychiatry Hospital in Doha. From the start of the pandemic the importance of keeping the psychiatric hospital free of COVID-19 was recognized. An outbreak in the Psychiatric Hospital would have been particularly serious as there are few other inpatient mental health beds. Strategies adopted to reduce the risk of a COVID-19 outbreak in the Psychiatric Hospital included reduced visiting, reduced patient leave and protocols for managing COVID-19 cases.

The limited number of in-patient psychiatric beds in Qatar was a major challenge during the early months of the pandemic when an increased number of emergency mental health cases were being seen. To reduce pressures, a new 13-bedded psychiatric unit was opened in Al-Wakra hospital to admit patients who were released from COVID-19 hospital sites and quarantine and who required inpatient psychiatric care. The mental health services also ensured that a psychiatric ward in Rumailah Hospital was available to support the Communicable Disease Center in the fight against COVID.

2.2.8 Information management and public education

A campaign used many media to carry positive mental health messages. It built on the theme 'it's ok not to be ok' and in October 2020, as part of World Mental Health Day, relaunched under the banner 'Are you OK'. Key aims were to increase awareness of mental health problems, reduce associated stigma and encourage people to seek help if they experienced psychological upset. In conjunction with the MoPH, the HMC Mental Health Service sent regular reassuring text messages to the public to pro-actively reduce the risk of anxiety and panic. Clinicians in the Mental Health Service, including the Chairman, Dr Majid Al Abdulla, made appearances on local TV channels and through social media to increase people's mental health awareness and advise the general public on how to access mental health services during the pandemic.

More than 7000 frontline healthcare workers were trained in identifying psychological distress in order to check in with and support colleagues affected by COVID. Partnership working between the HMC Mental Health Service, MoPH, Primary Health Care Corporation, Qatar Airways, Sidra and Naufar was instrumental in ensuring a coherent and far reaching program of communication and awareness.

The mental health and awareness campaign occurred alongside a HMC- MoPH public education campaign to provide accurate information on COVID-19. This operated through national and social media. It included accurate and evidence-based information on COVID-19 that aimed to demystify the disease and challenge false beliefs and ideas about COVID-19. Myths and misinformation remain global problems in the pandemic and this was particularly so during its early months in spring and summer 2020.

Overall, the pandemic raised the profile of mental health in Qatar as the public recognised its impact on their mental health and those close to them and the importance of high quality mental health services.

2.3 COVID-19 related mental health research in Qatar

Qatar has a strong track record for mental health research in the Gulf region. The onset of the pandemic led to a series of new research projects being set up to investigate the mental health consequences of the pandemic. This work involved a range of organizations in Qatar including HMC, Sidra and Qatar University. Some studies have been completed and published in the academic literature and referred to in previous sections. However, most projects are ongoing at the time of writing (Feb. 2021). This section does not aim to review all COVID-19 related mental health research from Qatar, rather it aims to give examples to illustrate the breadth of work being undertaken with the emphasis on research involving HMC. It is hoped that the results of research will help provide a greater understanding of the pandemic on mental health with findings specific to Qatar.

The HMC Child and Adolescent mental health service is involved in a series of research projects. This includes exploration the relationship between pandemic fears and obsessive-compulsive symptoms (OCD) in adolescents (aged 14-18 years) with pre-existing mental and behavioural disorders. Preliminary results suggest that this group can exhibit significant pandemic fears which in turn may predict obsessive-compulsive symptoms and vice versa. Khan's group are also assessing the impact of the COVID-19 pandemic on individuals with autistic spectrum disorders (ASD) and their caregivers. People with ASD find it difficult to adjust to new routines and as such may find the pandemic and lockdowns particularly stressful. Preliminary results show no worsening in the behaviour of individuals with ASD during the pandemic in Qatar but an increased burden among their caregivers.

The psychological effect of quarantine in Qatar has been investigated. Reagu et al (2021) used a questionnaire to assess individuals in quarantine during June and July 2020 (38). The median age of respondents was 36 years. 37.4% of respondents reported depressive symptoms and 25.9% reported anxiety symptoms. Scores were higher for migrants from poor socioeconomic group and this group reported that lack of family contact was a major stressor. The results highlight the importance of helping migrant workers maintain their channels of social support during quarantine. Ouanes et al. are conducting a study to assess the impact of quarantine in those aged over 60 years. Preliminary results indicate that the elderly had relatively good coping and resilience. It appeared that they were able to draw on their greater life experience to help them adapt. Wadoo et al (2020) conducted a survey of health care professionals working in quarantine sites (39). They concluded that the psychological impact of working in quarantine centres on healthcare workers was less than that seen in several other countries and that nurses were the most vulnerable group.

Nurse led patient education on COVID-19 has been provided to inpatients at the HMC Psychiatric Hospital throughout the pandemic. It involves regular small group sessions for patients as well as individual education provided by primary nurses. A research project is assessing the knowledge and beliefs of patients at admission and the effectiveness of ward based education. Another research project is comparing the knowledge, beliefs and attitudes to COVID-19 among patients with mental health problems compared to the general population.

The success of COVID-19 research at HMC, not just in psychiatry but in other medical fields, partly reflected HMC establishing a fast tract approval for COVID-19 research initiatives early in the pandemic. The work of the Institutional Review Board and its reviewers was instrumental to success of this endeavor.

One of the most difficult challenges that Qatar has faced during the pandemic is the reluctance of people to accept the vaccine. It seems that 70 to 80% of the population need to possess immunity to COVID-19, either through natural infection or vaccination, to achieve herd immunity.

Vaccine hesitancy was also more common among the elderly and in women. COVID-19 vaccine hesitancy has been identified as a problem in Europe (40) and the United States (41). Researchers from the HMC Mental Health Service are working closely with the MoPH, the communication department of Hamad Medical Corporation, and the Tactical Command Group on a strategic level to better understand the scale of the problem and the underlying reasons. They are also working together to utilize the media to provide education about the benefits of vaccination and to target those group most likely to have reservations about vaccination.

3. Discussion and future challenges

COVID-19 pandemic has enormous health, economic, social and political implications. Its impact on mental health is no less than its impact on physical health. Qatar responded swiftly and effectively to manage the pandemic at all levels. Central to this was government establishment of the System Wide Incident Command Committee (SWICC) to manage the pandemic with the appointment of a senior health leader to oversee the process.

The HMC Mental Health Service established a series of new mental health services to meet the needs of existing service users and the increased demand on mental health services from those not currently known to the service. Implementing these changes tested the service's ability to adapt quickly and show resilience. Many valuable lessons were learnt during this process. Overall, the HMC Mental Health Service changes have been a great success. Despite the lockdown, HMC Mental Health Services saw more patients between March and December 2020 than in the same period in the previous year.

Services, in parallel with other services, started to open the gates for new patients to attend psychiatry out-patient appointments face to face rather than remotely if they wished. In addition, home visits were re-initiated but strict rules of full personal protection were applied with staff conducting a COVID-19 screening tool before visiting any patient at home.

It remains unclear what proportion of patients prefer a traditional face to face outpatient appointment with their clinician and what proportion prefer an online consultation. In February 2021, HMC moved all appointments back to a remote format in response to a recent rise in the daily infection rate. The pandemic is not a single discrete episode, rather its impact fluctuates partly reflecting the success of public health measures to suppress infection.

At the time of writing (Feb 2021) the daily infection rate in Qatar still remains relatively low and the country has not experienced a second wave as have many European countries. However, vigilance is required as new more infectious strains of the virus have appeared in different parts of the world risking future wave. The approval of the first COVID-19 vaccines in December 2020 was an incredible scientific achievement. However, rolling out vaccines to the world's population is a huge challenge and it remains unclear how long immunity will last, whether boosters will be needed and whether new mutations will arise that are resistant to the vaccine. Qatar was one of the first countries in the world to start vaccinations.

Over the last year, knowledge has been gained regarding the short-term mental health impact of the pandemic. In particular, an increased incidence of mental disorders, including anxiety, depression, and insomnia, has been documented in the general

population in countries hard-hit by the pandemic. However, the long term psychiatric impact of COVID-19 remains unknown. Future patterns of psychiatric morbidity will partly reflect the pandemic's future social impact. On balance it seems likely that COVID-19 will have a profound impact on society for years, if not decades, to come.

An economic recession seems inevitable. Unemployment, financial pressures, limitations on travel, concern about family and friends and increased domestic violence are expected to contribute to high levels of future psychiatric morbidity. Future social changes may have a particular impact on children and adolescents whose formative years will be shaped by the pandemic and its aftermath.

It is unclear if utero exposure to SARS-CoV-2 is a factor for the future development of psychiatric disorder. In-utero exposure to viral illnesses has been suggested as a possible aetiological factor in the development of schizophrenia. Supportive evidence includes an observational study demonstrating an increased rate of schizophrenia in children born five months after the peak of the 1957 influenza pandemic in 1957 (42).

Qatar has an active program of COVID-19 mental health research which should contribute to an evidence based approach to managing the mental health consequences of the pandemic in the years to come.

However, implementing service change was not without its challenges. For example, during the early months of the pandemic more patients presented to the mental health triage clinics and there was a greater pressure for urgent admissions to the HMC Psychiatric Hospital, perhaps due to a reduction in community services and increased stress and anxiety due to the pandemic and the lockdown.

On a positive note, the opportunity for learning and training of junior doctors, and other health care professionals, was increased through exposure to challenging cases often requiring crisis interventions.

Many members of the public in Qatar are grieving for the losses they have experienced during the pandemic. COVID-19 continues to have a high global death toll.

The COVID-19 death rate in Qatar, per million population, has been one of the lowest in the world. However, approximately 90% of the population are expatriate workers who will be affected by the greater impact of COVID-19 in their native countries.

A proportion will require ongoing interventions including counselling, trauma focused therapy, pharmacotherapy and the availability of crisis interventions.

People with mental health problems seem more vulnerable to suffer from COVID-19 than those without a history of such problems (19), (20). The HMC mental health campaign, accompanied by education sessions online and in the media, helped to encourage service users and their families to adhere to the Ministry of Public Health's COVID-19 guidance and to engage with the new remote psychiatric services including the helpline. In January 2021 HMC Mental Health.

Reference:

1. Esterwood E, Saeed SA. Past Epidemics, Natural Disasters, COVID19, and Mental Health: Learning from History as we Deal with the Present and Prepare for the Future. *Psychiatr Q.* 2020;91(4):1121-33.
2. Preti E, Di Mattei V, Perego G, Ferrari F, Mazzetti M, Taranto P, et al. The Psychological Impact of Epidemic and Pandemic Outbreaks on Healthcare Workers: Rapid Review of the Evidence. *Curr Psychiatry Rep.* 2020;22(8):43.
3. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet.* 2020;395(10227):912-20.
4. Usher K, Bhullar N, Durkin J, Gyamfi N, Jackson D. Family violence and COVID-19: Increased vulnerability and reduced options for support. *Int J Ment Health Nurs.* 2020;29(4):549-52.
5. Sprang G, Silman M. Posttraumatic stress disorder in parents and youth after health-related disasters. *Disaster Med Public Health Prep.* 2013;7(1):105-10.
6. Zhao N, Zhou G. Social Media Use and Mental Health during the COVID-19 Pandemic: Moderator Role of Disaster Stressor and Mediator Role of Negative Affect. *Appl Psychol Health Well Being.* 2020;12(4):1019-38.
7. Erku DA, Belachew SA, Abhra S, Sinnolareddy M, Thomas J, Steadman KJ, et al. When fear and misinformation go viral: Pharmacists' role in deterring medication misinformation during the 'infodemic' surrounding COVID-19. *Res Social Adm Pharm.* 2021;17(1):1954-63.
8. Jarrahi A, Ahluwalia M, Khodadadi H, da Silva Lopes Salles E, Kolhe R, Hess DC, et al. Neurological consequences of COVID-19: what have we learned and where do we go from here? *J Neuroinflammation.* 2020;17(1):286.
9. Yeh EA, Collins A, Cohen ME, Duffner PK, Faden H. Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. *Pediatrics.* 2004;113(1 Pt 1):e73-6.
10. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-CoV-2. *Int J Infect Dis.* 2020;94:55-8.
11. Salari N, Hosseiniyan-Far A, Jalali R, Vaisi-Raygani A, Rasoulopoor S, Mohammadi M, et al. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. *Global Health.* 2020;16(1):57.
12. Nearchou F, Flinn C, Niland R, Subramanian SS, Hennessy E. Exploring the Impact of COVID-19 on Mental Health Outcomes in Children and Adolescents: A Systematic Review. *Int J Environ Res Public Health.* 2020;17(22).
13. Pierce M, Hope H, Ford T, Hatch S, Hotopf M, John A, et al. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. *Lancet Psychiatry.* 2020;7(10):883-92.
14. Daly M, Sutin AR, Robinson E. Longitudinal changes in mental health and the COVID-19 pandemic: evidence from the UK Household Longitudinal Study. *Psychol Med.* 2020;1-10.
15. Twenge JM, Joiner TE. U.S. Census Bureau-assessed prevalence of anxiety and depressive symptoms in 2019 and during the 2020 COVID-19 pandemic. *Depress Anxiety.* 2020;37(10):954-6.

16. Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S. Prevalence of Depression Symptoms in US Adults Before and During the COVID-19 Pandemic. *JAMA Netw Open*. 2020;3(9):e2019686.
17. van der Velden PG, Contino C, Das M, van Loon P, Bosmans MWG. Anxiety and depression symptoms, and lack of emotional support among the general population before and during the COVID-19 pandemic. A prospective national study on prevalence and risk factors. *J Affect Disord*. 2020;277:540-8.
18. Pappa S, Ntella V, Giannakas T, Giannakouli VG, Papoutsis E, Katsounou P. Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: A systematic review and meta-analysis. *Brain Behav Immun*. 2020;88:901-7.
19. Yang H, Chen W, Hu Y, Chen Y, Zeng Y, Sun Y, et al. Pre-pandemic psychiatric disorders and risk of COVID-19: a UK Biobank cohort analysis. *Lancet Healthy Longev*. 2020;1(2):e69-e79.
20. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry*. 2021;8(2):130-40.
21. Wang Q, Xu R, Volkow ND. Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. *World Psychiatry*. 2021;20(1):124-30.
22. Lee SW, Yang JM, Moon SY, Yoo IK, Ha EK, Kim SY, et al. Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study. *Lancet Psychiatry*. 2020;7(12):1025-31.
23. Song H, Fall K, Fang F, Erlendsdottir H, Lu D, Mataix-Cols D, et al. Stress related disorders and subsequent risk of life threatening infections: population based sibling controlled cohort study. *BMJ*. 2019;367:I5784.
24. Wang QQ, Kaelber DC, Xu R, Volkow ND. COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States. *Mol Psychiatry*. 2021;26(1):30-9.
25. Hao F, Tan W, Jiang L, Zhang L, Zhao X, Zou Y, et al. Do psychiatric patients experience more psychiatric symptoms during COVID-19 pandemic and lockdown? A case-control study with service and research implications for immunopsychiatry. *Brain Behav Immun*. 2020;87:100-6.
26. Van Rheenen TE, Meyer D, Neill E, Phillipou A, Tan EJ, Toh WL, et al. Mental health status of individuals with a mood-disorder during the COVID-19 pandemic in Australia: Initial results from the COLLATE project. *J Affect Disord*. 2020;275:69-77.
27. Pan KY, Kok AAL, Eikelenboom M, Horsfall M, Jorg F, Luteijn RA, et al. The mental health impact of the COVID-19 pandemic on people with and without depressive, anxiety, or obsessive-compulsive disorders: a longitudinal study of three Dutch case-control cohorts. *Lancet Psychiatry*. 2021;8(2):121-9.
28. Haddad PM, Al Abdulla M, Latoo J, Iqbal Y. Brief psychotic disorder associated with quarantine and mild COVID-19. *BMJ Case Rep*. 2020;13(12).
29. Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry*. 2020;7(10):875-82.
30. Mattace-Raso F, Polinder-Bos H, Oosterwijk B, van Bruchem-Visser R, Goudzwaard J, Oudshoorn C, et al. Delirium: A Frequent Manifestation in COVID-19 Older Patients. *Clin Interv Aging*. 2020;15:2245-7.
31. Kotfis K, Williams Roberson S, Wilson J, Pun B, Ely EW, Jezowska I, et al. COVID-19: What do we need to know about ICU delirium during the SARS-CoV-2 pandemic? *Anaesthetist Intensive Ther*. 2020;52(2):132-8.
32. Raveendran AV. Long COVID-19: Challenges in the diagnosis and proposed diagnostic criteria. *Diabetes Metab Syndr*. 2020;15(1):145-6.
33. Qin H, Zhang J, Wang Z, Min H, Yan C, Chen F, et al. Duration of untreated psychosis and clinical outcomes of first-episode schizophrenia: a 4-year follow-up study. *Shanghai Arch Psychiatry*. 2014;26(1):42-8.
34. Rovers JE, van de Linde LS, Kenters N, Bissering EM, Nieuwenhuijse DF, Oude Munnink BB, et al. Why psychiatry is different - challenges and difficulties in managing a nosocomial outbreak of coronavirus disease (COVID-19) in hospital care. *Antimicrob Resist Infect Control*. 2020;9(1):190.
35. Xiang YT, Zhao YJ, Liu ZH, Li XH, Zhao N, Cheung T, et al. The COVID-19 outbreak and psychiatric hospitals in China: managing challenges through mental health service reform. *Int J Biol Sci*. 2020;16(10):1741-4.
36. Farrell T, Reagu S, Mohan S, Elmidanay R, Qaddoura F, Ahmed EE, et al. The impact of the COVID-19 pandemic on the perinatal mental health of women. *J Perinat Med*. 2020;48(9):971-6.
37. Iqbal Y, Al Abdulla MA, Albrahim S, Latoo J, Kumar R, Haddad PM. Psychiatric presentation of patients with acute SARS-CoV-2 infection: a retrospective review of 50 consecutive patients seen by a consultation-liaison psychiatry team. *BJPsych Open*. 2020;6(5):e109.
38. Reagu S, Wadoo O, Latoo J, Nelson D, Ouane S, Masoodi N, et al. Psychological impact of the COVID-19 pandemic within institutional quarantine and isolation centres and its sociodemographic correlates in Qatar: a cross-sectional study. *BMJ Open*. 2021;11(1):e045794.
39. Wadoo O, Latoo J, Iqbal Y, Kudlur Chandrappa NS, Chandra P, Masoodi NA, et al. Mental wellbeing of healthcare workers working in quarantine centers during the COVID-19 pandemic in Qatar. *Qatar Med J*. 2020;2020(3):39.
40. Neumann-Bohme S, Varghese NE, Sabat I, Barros PP, Brouwer W, van Exel J, et al. Once we have it, will we use it? A European survey on willingness to be vaccinated against COVID-19. *Eur J Health Econ*. 2020;21(7):977-82.
41. Malik AA, McFadden SM, Elharake J, Omer SB. Determinants of COVID-19 vaccine acceptance in the US. *EClinicalMedicine*. 2020;26:100495.
42. O'Callaghan E, Sham P, Takei N, Glover G, Murray RM. Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet*. 1991;337(8752):1248-50.



Copyright © 2022 Ministry of Public Health. All rights reserved.



Critical Care and Respiratory

Chapter: Critical Care and Respiratory Medicine, Acute complications of COVID-19 infection, By Dr Harman Saman, Dr Hatem Mabrouk Taher Abusriwil and Dr Mohamad Yahya Khatib

Table of content:

- [**COVID-19 pneumonia**](#)
 - COVID-19 pneumonia incidence rate and implications of disease severity
 - COVID-19 pneumonia in immunocompromised
 - COVID-19 and superadded bacterial infection
 - COVID-19 and inflammatory pneumonia
 - COVID-19 and fungal coinfection
 - COVID-19 and tuberculosis (TB)
 - COVID-19 pneumonia and non-tuberculous mycobacterial (NTM) infections
 - COVID-19 and Bacillus Calmette–Guérin (BCG) vaccine
- [**COVID-19 and Pulmonary Embolism \(PE\)/Venous thromboembolism \(VTE\)**](#)
 - Pathogenesis of VTE/PE in COVID-19 infection
 - Incidence rate of VTE/PE in COVID-19 infection
 - Diagnosis of VTE/PE in COVID-19 infection
 - Service set up and treatment of VTE/PE during the pandemic
- [**COVID-19 and Pneumothorax/pneumomediastinum**](#)
- [**COVID-19 and pleural effusion and empyema**](#)
- [**COVID-19 diagnostic Chest Imaging**](#)
 - Chest x-rays
 - Chest Computed tomography
 - Lung and pleural ultrasound
- [**Critical Care Medicine and COVID-19 infection**](#)
 - Epidemiology
 - Risk factors for critical and rapid progression of disease
 - Clinical features of critically unwell patients
 - Adult Respiratory Distress Syndrome (ARDS)
 - Special consideration of Invasive Mechanical Ventilation (IMV) in ARDS
 - Sedation and analgesia
 - Nutrition and bowel care
 - Daily monitoring
 - Management of hospital acquired or ventilation associated infection/pneumonia (HAP and VAP respectively) and other comorbidities

I. COVID-19 pneumonia:

Keywords: pneumonia, inflammatory pneumonia, cytokine storm/hyperinflammation, immunocompromised, superadded bacterial infection, tuberculosis, non-tuberculum mycobacterium, BCG, fungal infection, silent hypoxia, respiratory failure, high resolution CT scan, Tocilizumab, corticosteroids, antibiotics.

a) COVID-19 pneumonia incidence rate and implications of disease severity:

On 31 December 2019, a cluster of pneumonia cases of unknown aetiology were detected in Wuhan City, Hubei Province of China and were reported to World Health Organisation (WHO)(1). The causative organism was later identified as SARS-CoV-2, a novel virus belonging to the coronaviridae family(1).

The majority (about 81%) of individuals with COVID-19 infections have only mild disease (2). Patients who develop **pneumonia**, however, are more likely to suffer from severe illness, which represent about 14% of the cases(1) Important indications of severe disease are dyspnoea, hypoxia (with SpO₂ <94%), and/or >50 percent lung involvement on imaging (3). Around 5% of individuals with COVID-19 pneumonia are expected to develop critical disease with features of respiratory failure, shock, and/or multiorgan dysfunction(3). In the state of Qatar, a large epidemiological study showed, 2.3% of patients had mild illness with pneumonia and 2% were severe or critically ill(4). In Qatar, during the pandemic, the majority of patients with pneumonia treated in hospital including those who required no oxygen supplementation(4).

As the commonest serious complication of COVID-19 infection, pneumonia causes fever, cough, dyspnoea, and **bilateral infiltrates on chest x-rays**(5, 6). Several cohorts showed that dyspnoea approximately one week after the onset of initial symptoms of COVID-19 infection might heralds the development of pneumonia which often led to further clinical deterioration(5-7). Moreover, there are several studies, showing that patients might be asymptomatic even in the presence of hypoxia and evidence of **ground glass changes on chest CT scan** (8, 9). In some cases lack of breathless in the presence of severe hypoxia (sometimes referred to as silent hypoxia) appears to proceed a rapidly issuing severe **type 1 respiratory failure** which is a medical emergency that requires prompt medical intervention(10). Besides the clinical features and chest imaging, raised inflammatory markers, such as white cell count, C reactive protein, ferritin and D-dimmer, aid the diagnosis of pneumonia. Normal serum procalcitonin levels are noted in majority of patients admitted to general wards, but procalcitonin levels are commonly raised in patients requiring ICU care and elevated procalcitonin levels usually indicates serious superimposed bacterial infection(6).

b) COVID-19 pneumonia in immunocompromised:

In immunosuppressed patients, as in the case of HIV coinfection or patients receiving cytotoxic or other immunosuppressing drugs, persistent pneumonia several weeks after the onset of the disease, has been reported. Such patients responded poorly to standard antimicrobial treatment(11). Therefore, patients with COVID-10 pneumonia who are immune deficient are better treated jointly by members of multidisciplinary teams (MDT), that include infectious diseases specialists, respiratory physicians and microbiologists. Members of MDT thoroughly investigate to detect and treat opportunistic microorganisms using extended culture and sensitivity tests to antibiotics, this to avoid misdiagnosis and inappropriate choice and prolonged use of antimicrobial drugs (9).

c) COVID-19 and superadded bacterial infection:

Similar to other common viral respiratory infections, such as influenza, infection with COVID-19 virus commonly leads to secondary bacterial superinfection due to disturbance to the physical barrier served by the respiratory epithelium and disruption to host antibacterial innate and adaptive defences(12). Superadded infection with Streptococcus pneumoniae, Staphylococcus aureus and Acinetobacter baumannii, is shown to be associated with severe disease and increased mortality in ICU(12, 13). The choice of antibiotic treatment should be guided by local antibiotic protocol(s) that usually take into account the incidence and prevalence of specific organisms and their sensitivity profile in local communities.

d) COVID-19 and inflammatory pneumonia:

In addition to bacterial coinfection, there's histological evidence of infiltration of the lungs with inflammatory cells and proinflammatory cytokines, ranging from oedema, proteinaceous exudate, vascular congestion, inflammatory clusters with multinucleated giant cells, interstitial fibroblastic proliferation, and reactive hyperplasia of pneumocytes in mild to moderate disease to diffuse alveolar damage with lymphocytic infiltrate, small thrombotic vessels, and foci of alveolar haemorrhage, in the critically unwell patients(14-16). Therefore, an important component of the ground glass changes that are seen on chest CT scans, is caused by inflammation of the lung interstitium. To tackle inflammatory pneumonia, corticosteroids and anti-interleukin 6 (Tocilizumab) in case of cytokine storm/hyperinflammation, are deployed and recommended in in several **international guidelines** and national guidelines (17, 18).

e) COVID-19 and fungal coinfection:

Autopsy studies of lung tissue obtained from patients deceased as the result of COVID-19 pneumonia, suggest predominance of coinfection with fungal species, such as Cryptococcus spp., Cladosporium spp., Alternaria spp., Aspergillus spp., and Candida spp(19). Diagnosing and treating fungal coinfection can be very challenging, especially in intubated patients with severe COVID-19 pneumonia(20). We, however, do not recommend routine treatment with antifungal therapies. Fungal coinfection should be suspected in immunocompromised and invasively ventilated patients, who continue to show signs of infection, such as ongoing fever and high inflammatory makers and persistence of lung infiltrates on chest imaging, despite adequate treatment with parenteral broad-spectrum antibiotics. Such patients, therefore, should be considered for antifungal treatment, after sending appropriate samples, such as respiratory aspirates, including samples obtained by bronchoscopy, to fungal culture and fungal DNA analysis.

f) COVID-19 and tuberculosis (TB):

Infection with **mycobacterium tuberculosis** remains a leading cause of death in low and middle income countries (21). There's a resurgence in the number of new TB cases in the developed economies. For example, in the UK there are 4500 new cases reported every year. These patients are predominantly located in large metropolitan cities with high immigrant and homeless population, such as London(22). In Qatar, the prevalence of both pulmonary and extra-pulmonary TB, is high, especially among male workers that immigrated from low income countries(23, 24) Therefore, clinicians need to be aware of the interaction between COVID-19 and TB infections, especially as diagnosis of such co-infection can be challenging due to

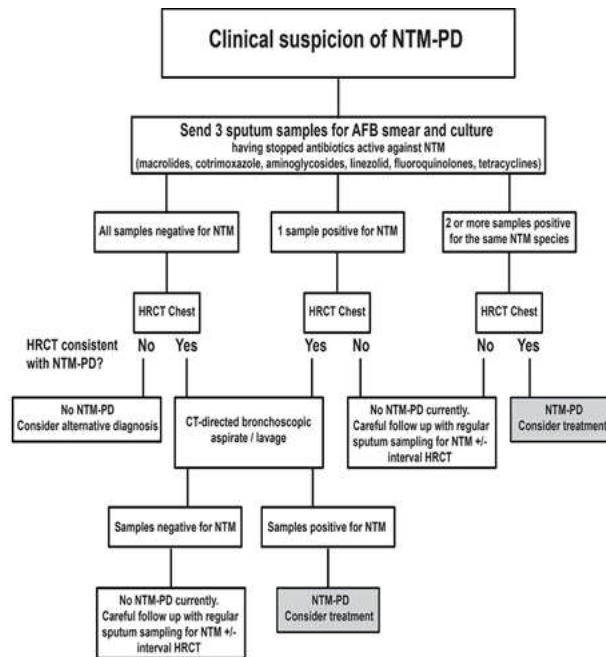
shared common symptoms such as cough, malaise and fever as well as common risk factors for transmission like crowded living conditions such as in hostels and prisons. In addition, patients with both conditions can suffer stigmatisation, which in itself can hinder early presentation for medical care which in-turn delays diagnosis and treatment. In a cohort of 49 patients with COVID-19 and TB coinfection, treatment of TB appeared to have offered no protection against infection with COVID-19. Patients with severe COVID-19 and TB coinfection were more likely to be older, with cavitating lung lesions and to suffer from comorbidities namely COPD, hypertension, HIV and kidney disease(25).

g) COVID-19 pneumonia and non-tuberculous mycobacterial (NTM) infections:

There is a global rise in the numbers of patients with chronic lung diseases diagnosed with NTM infection. NTM pulmonary infection is notoriously difficult to diagnose and its treatment is complicated by resistance to common antibiotics, prolonged duration of treatment (on average 2 years), patients' treatment adherence and treatment toxicity profile (26). It is expected that an important proportion of individuals recovered from acute COVID-19 pneumonia but ended up with chronic lung destruction such as chronic cavities and interstitial lung disease, to be infected with NTM in the future. Clinically infection with NTM often presents with insidious onset but a prolonged (weeks to months) history of cough productive of mucopurulent sputum, weight loss, breathlessness and fatigue. These symptoms often do not or partially respond to antibacterial antibiotics. The Canadian Provincial Infectious Diseases Advisory Committee on Infection Prevention and Control (PIDAC-IPC) provides a set of comprehensive review and guidelines of managing NTB infection. The authors of this chapter recommend utilising algorithm 1 to aid in making a diagnosis of infection with NTM.

h) COVID-19 and Bacillus Calmette–Guérin (BCG) vaccine:

In the middle of the pandemic, a debate regarding the potential protective effect of BCG vaccination against sever COVID-19 pneumonia, through the stimulation of innate immune system, drew the attention of the public and scientific communities alike. This debate was largely triggered by the findings of a few ecological studies that showed lower incidence and mortality rates of COVID-19 infection in countries that mandated vaccination with BCG(27, 28). But such association is hard to prove due to presence of a number of important confounding factors that affected these ecological studies and the lack of high quality randomised controlled trials to investigate the protective effect of BCG(27).



Charles S Haworth et al. Thorax 2017;72:ii1-ii64

Algorithm 1: An algorithm for the investigation of individuals with clinical suspicion of NTM-pulmonary disease (AFB, acid-fast bacilli; HRCT, high-resolution CT; NTM-PD, non-tuberculous mycobacterial pulmonary disease).

2- COVID-19 and Pulmonary Embolism/Venous thromboembolism (VTE):

Keywords: pulmonary embolism, PE, hypercoagulable state, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, Venous thromboembolism (VTE), Adult Respiratory Distress Syndrome (ARDS), D-dimmer, platelet activation, CT Pulmonary Angiogram (CTPA), Hamad General Hospital Anticoagulation Clinic, Thromboembolic Pulmonary Hypertension (CTEPH), Cor pulmonale, Qatar's Communicable Diseases Centre (CDC) Treatment Protocol for confirmed COVID-19 Infection, right ventricular strain, right ventricular strain, massive PE, thrombolysis.

i) Pathogenesis of VTE/PE in COVID-19 infection:

The exact pathogenesis of COVID-19 associated hypercoagulable state is poorly understood. There is evidence that the following changes are likely to contribute significantly to the prothrombotic state of COVID-19 infected patients(29-31):

- I. Elevated fibrinogen

- II. Elevated factor VIII
- III. Hyperviscosity
- IV. Neutrophil extracellular traps (NETs)
- V. Circulating prothrombotic microparticles

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus directly invading endothelial cells, is another potential risk factor to develop Venous thromboembolism (VTE). Such endothelial injury that causes microvascular inflammation, endothelial exocytosis, and/or endotheliitis, is likely to be a critical step in the pathogenesis of Adult Respiratory Distress Syndrome (ARDS) (32-34).

Elevation of D-dimmer, a degradation product of cross-linked fibrin, appears to correlate well with disease severity (35). Although, D-dimmer is a nonspecific indicator often raised in a wide range of infective and inflammatory conditions. In addition, some data suggest that platelet activation might be another causal factor to COVID-19 associated VTE(36, 37).

COVID-19 associated VTE (sometimes referred to as COVID-19-associated coagulopathy (CAC)) is distinct from disseminated intravascular coagulation (DIC)(37).

j) Incidence rate of VTE/PE in COVID-19 infection:

PE appears to be a common complication in patients with moderate to severe COVID-19 pneumonia. A metanalysis of 23 studies that included 7178 COVID-19 patients [mean age 60.4 years] of hospitalized in general wards and ICU; the incidence of PE was 14.7% of cases (95% CI: 9.9-21.3%, I²=95.0%, p<0.0001) and 23.4% (95% CI:16.7-31.8%, I²=88.7%, p<0.0001) respectively.

Segmental/sub-segmental pulmonary arteries were more frequently involved compared to main/lobar arteries (6.8% vs18.8%, p<0.001)(38).

A large French retrospective multicentre observational study of 1240 patients (58.1% men, mean age 64 ± 17 years), 103 (8.3%) patients had PE confirmed by **CT Pulmonary Angiogram (CTPA)**. The same study concluded that PE risk factors in the COVID-19 context do not include traditional thrombo-embolic risk factors but rather independent clinical and biological findings at admission, including a major contribution to inflammation(39).

In a single-center study evaluated 62 COVID-19 patients who underwent CTPA, 37.1% had PE, of those who had PE, 40% receiving prophylactic anticoagulation. This study noted that D-dimer can be used to stratify patients regarding PE risk and severity(40).

The thrombotic complications in ICU patients with COVID-19 is particularly high. In a retrospective observational study of 184 ICU patients with COVID-19 pneumonia all of whom received at least one form VTE prophylaxis; 31% (95%CI 20-41) developed a thrombotic event. Of which CTPA and/or ultrasonography confirmed VTE in 27% (95%CI 17-37%) and arterial thrombotic events in 3.7% (95%CI 0-8.2%). PE was the most frequent thrombotic complication (n = 25, 81%)(41).

In another retrospective analysis of >6500 non-ICU hospitalised patients with COVID-19 found a VTE rate of approximately 3 percent (42). The data regarding the rate of PE in COVID-19 pneumonia treated as outpatient is more limited. One study of 72 outpatients with COVID-19 pneumonia showed a rate of 18% as confirmed by CTPA(43).

K) Diagnosis of VTE/PE in COVID-19 infection:

Clinically patients with COVID-19 pneumonia who complicated by PE may have no additional symptoms. Indicators that might point towards PE in such patients include increased respiratory and heart rate and hypoxia out of proportion to the severity of pneumonia or development of pleuritic chest pain or less commonly new pleural effusion incongruent to the location of the consolidation on chest imaging.

Biochemical evaluation should include: Complete blood count (CBC) including platelet count

Coagulation studies (prothrombin time [PT] and activated partial thromboplastin time [aPTT]), Fibrinogen and D-dimer. A daily measurement of these blood tests can aid in making a diagnosis of PE. Of note mild thrombocytopenia or thrombocytosis, or normal platelet count are all documented in COVID-19 associated PE. Some of these values, especially D-dimmer have prognostic value and may impact decision-making about the escalation of the level of care. A study of 343 patients enrolled from Wuhan Asia General Hospital showed D-dimer on admission greater than 2.0µg/mL (fourfold increase) could effectively predict in-hospital mortality in patients with Covid-19, and that D-dimmer could be an early and helpful marker to improve management of Covid-19 patients(44).

Electrocardiogram (ECG), albeit none sensitive test and may be normal, can be of value in making a diagnosis of PE especially in the presence of **ECG signs of right ventricular strain in patients suspected of PE**.

CTPA, and in special situations **V/Q scan**, are gold standard image modalities of choice to diagnose of PE. In patients with high pretest probability of PE with elevated D-dimmer in whom CTPA or V/Q scan are not feasible, treatment with anticoagulation is recommended without delay, unless there are absolute contraindications for anticoagulation such as life threatening or intracranial bleeding. Echocardiogram is another alternative none radiation emitting scan to look for evidence of **right ventricular strain** and/or blood clots in pulmonary trunk right or left pulmonary arteries. Although, echocardiogram has lower sensitivity for detecting segmental and none segmental blood clots.

I) Service set up and treatment of VTE/PE during the pandemic:

During the pandemic in the state of Qatar, Hamad Medical Corporation launched Hamad General Hospital Anticoagulation Virtual Clinic for patients diagnosed PE and discharged from hospital to minimize the exposure of patients and healthcare providers to and to promote social distancing(45). This service promotes early and regular follow up of discharged patients and with the view of managing any complications from anticoagulation and early detection of chronic complications such **Chronic Thromboembolic Pulmonary Hypertension (CTEPH)** and **Cor pulmonale**.

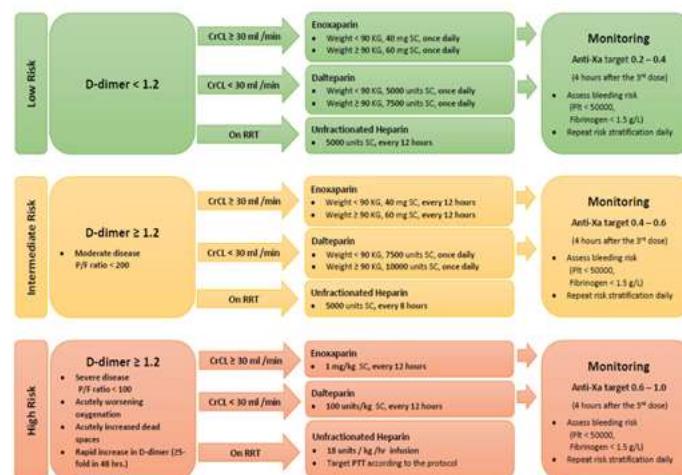
We recommend the use of **European Society of Cardiology Guideline of management of Acute PE** for a comprehensive assessment of patients with PE. A special attention needs to be paid risk stratification of PE (table 1) for early detection and prompt treatment of massive PE, as the latter is a life-threatening medical emergency that require urgent intervention.

In acute and hospital settings Qatar's Communicable Diseases Centre (CDC) version 11 Treatment Protocol for confirmed COVID-19 Infection, table 2, recommends routine VTE prophylaxis via anticoagulation, mechanical compression and early mobilisation. The protocol advises adjustment in the dose of anticoagulation according the level of rise in D-dimmer. Emergency resuscitation including thrombolysis by using tissue **plasminogen activator (tPA)**, table 3, is indicated in massive PE (PE with haemodynamic instability) Thrombolysis can also be used, albeit more controversially, for intermediate-high risk PE (Abnormal RV function AND elevated BNP or troponin)

Early mortality risk		Indicators of risk			
		Haemodynamic instability ^a	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥ 1	RV dysfunction on TTE or CTPA ^b	Elevated cardiac troponin levels ^c
High	+	(+) ^d	(+)	+	(+)
Intermediate	Intermediate–high	-	++ ^e	+	+
	Intermediate–low	-	++ ^e	One (or none) positive	
Low	-	-	-	-	Assessment optional; if assessed, negative

©ESC 2019

Table 1: classification and risk stratification of acute PE as per European Society of Cardiology Guideline



- Adopted from HMGH local protocol for Management of Anticoagulation in COVID19 pneumonia patients admitted to Intensive Care Unit May 2020
- All patients should be routinely placed on routine standard LMWH prophylaxis, with the exception of pregnant women $>= 20$ weeks gestation who should receive unfractionated heparin.

❖ Suggested oral anticoagulation for severely ill patient with COVID19 Pneumonia and high-risk patients for VTE :

Drug	Dose	Frequency	Note
Rivaroxaban	10 mg	once daily	
Dabigatran	220 mg	once daily	Preferred in patients with chronic liver disease
Apixaban	2.5 mg	twice daily	Preferred in patients with renal impairment

✓ For severely ill patient's oral anticoagulation is advised for 35±4 days as VTE prophylaxis unless there is contraindication

Table 2: Qatar's Communicable Diseases Centre (CDC) version 11 recommendation of prophylaxis against VTE and dose adjustment of anticoagulation according to D-dimmer level.

Massive PE – Initial resuscitation

- Fluid-conservative strategy**
 - Rarely helpful (venous pressure generally already excessively high)
 - Don't give fluid unless evidence of low filling pressure (e.g. small IVC or collapsed jugular veins)
- Pressor-aggressive strategy**
 - Epinephrine good front-line agent, titrate for MAP > 65 mm
 - Vasopressin as second-line agent
- Inhaled pulmonary vasodilators**
 - Epoprostanol or nitric oxide – whatever you can get fastest.
 - If refractory may consider combination of nitric oxide plus epoprostanol.
- Thrombolysis**
 - No contraindication: 100 mg alteplase.
 - Relative contraindication & actively dying: 100 mg alteplase.
 - Relative contraindication & stabilized: may start with 50 mg alteplase.
- Other PE-directed therapies (tPA failure/contraindication)**
 - Interventional radiology clot extraction (e.g. FlowTriever)
 - Cardiothoracic surgical extraction
 - VA ECMO

Table 3: emergency resuscitation of massive PE, as defined by the presence of haemodynamic instability: hypotension is defined as a systolic blood pressure (BP) <90 mmHg for a period >15 minutes or a drop in systolic blood pressure substantially below baseline (generally a drop of >40 mmHg)

3- COVID-19 and Pneumothorax/pneumomediastinum:

Keywords: Pneumothorax, barotrauma, pneumomediastinum, positive end expiratory pressure, subcutaneous emphysema, tension pneumothorax.

Pneumothorax can be the presenting complication of COVID-19 infection or develop in hospital in patients on room air or receiving oxygen therapy via O₂ mask, non invasive or invasive positive pressure ventilation (46). Nonetheless, the majority cases of pneumomediastinum and pneumothorax complications occur as the result of barotrauma caused by invasive mechanical ventilation (47).

Spontaneous pneumothorax commonly presents with sudden onset pleuritic chest pain, tachypnoea and/or dry cough and are occasionally detected incidentally on chest x-rays, figure 1 (48). Iatrogenic pneumothorax related to mechanical ventilation is more common in patients with pre-existing lung disease(49). The mechanism of ventilation related alveolar rapture is poorly understood.

High positive end expiratory pressure (PEEP) used for maximum alveolar recruitment to improve oxygenation in adult respiratory distress syndrome is associated with higher rate of pneumothorax (50). However several studies failed to confirm this correlation (51). Human and animal studies suggested deployment of low tidal volume lung protective ventilation might reduce the risk of barotrauma and consequent development of pneumothorax, pneumomediastinum and surgical emphysema(52-54). Other studies showed that low lung compliance, as a surrogate for lung damage, not ventilator settings, are more accurate predictor of barotrauma(55-57).

In majority of patients, severe mediastinal emphysema, pneumothorax are self-limiting and require no invasive intervention. Subcutaneous emphysema usually tracks superiorly and in extremely severe cases may constrict the main airway and impede blood flow in head and neck vessels. **The British Thoracic Society Guidelines of management of pneumothorax** provides important practical advice, figure 2, depending the size of the air leak as well as how to manage acute medical emergencies such as **tension pneumothorax**.

This guideline describes different interventions such as needle aspiration, portable chest drains, Seldinger technique to more invasive surgical chest drain insertion in cases of large air leak.

The impact of barotrauma on mortality rate and ICU stay is controversial. A case series of 71 patients from 16 centres, of whom 60 had pneumothoraces (6 with pneumomediastinum in addition); showed 28 days survival was not significantly different following pneumothorax ($63.1 \pm 6.5\%$) or isolated pneumomediastinum ($53.0 \pm 18.7\%$; $p=0.854$).

Therefore, this study suggested that a diagnosis of pneumothorax/pneumomediastinum did not signify as a marker of poor prognosis(46). However, a prospective cohort of 361 intensive care units from 20 countries showed that barotrauma was associated with a significant increase in the ICU length of stay and mortality(58).

4- COVID-19 and pleural effusion and empyema:

Keywords: pleural thickening, pleural effusion, empyema, thoracocentesis, chest drain

Pleural effusion and empyema caused directly by COVID-19 infection is rare. Pleural effusion is more likely to be secondary to superadded bacterial infection and/or pleural inflammation. Therefore, the same principles of managing parapneumonic

effusion and empyema must be applied in patients with COVID-19 and pleural effusion.

In an observational study, high-resolution CT features of 42 patients (26–75 years, 25 males) with COVID-19 were examined. 5/42 (12%) scans showed pleural effusion.

In follow up HRCT performed to monitor glass ground changes a higher rate of pleural effusion was detected (16/42, 38%) (59). Management of parapneumonic pleural effusion has changed significantly in the past few years as indications for pleural fluid drainage are becoming more specific and guideline based.

The distinction between transudative and exudative based on the [Light's criteria](#) remains an important step in deciding whether pleural intervention is required or not. [The British Thoracic Society](#) provides a practical diagnostic and therapeutic algorithm to manage suspected infected pleural effusion.



Figure 1: Spontaneous right pneumothorax with small pleural effusion (red arrows). The patient had COVID-19 but no respiratory symptoms at presentation. The pneumothorax was an incidental finding on the chest x-rays.

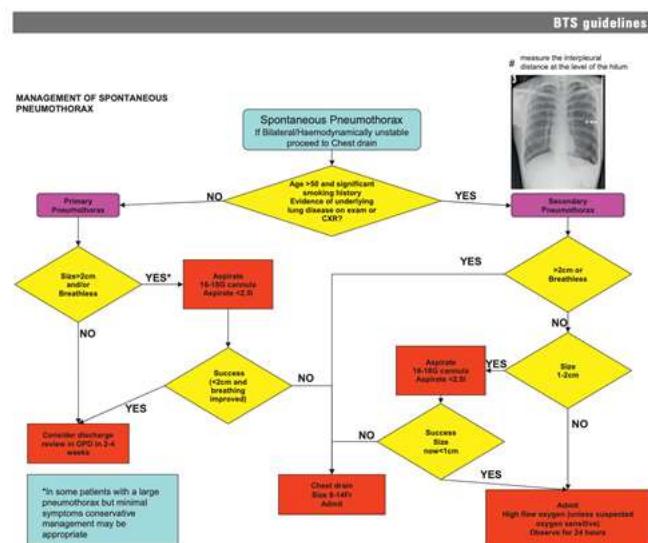
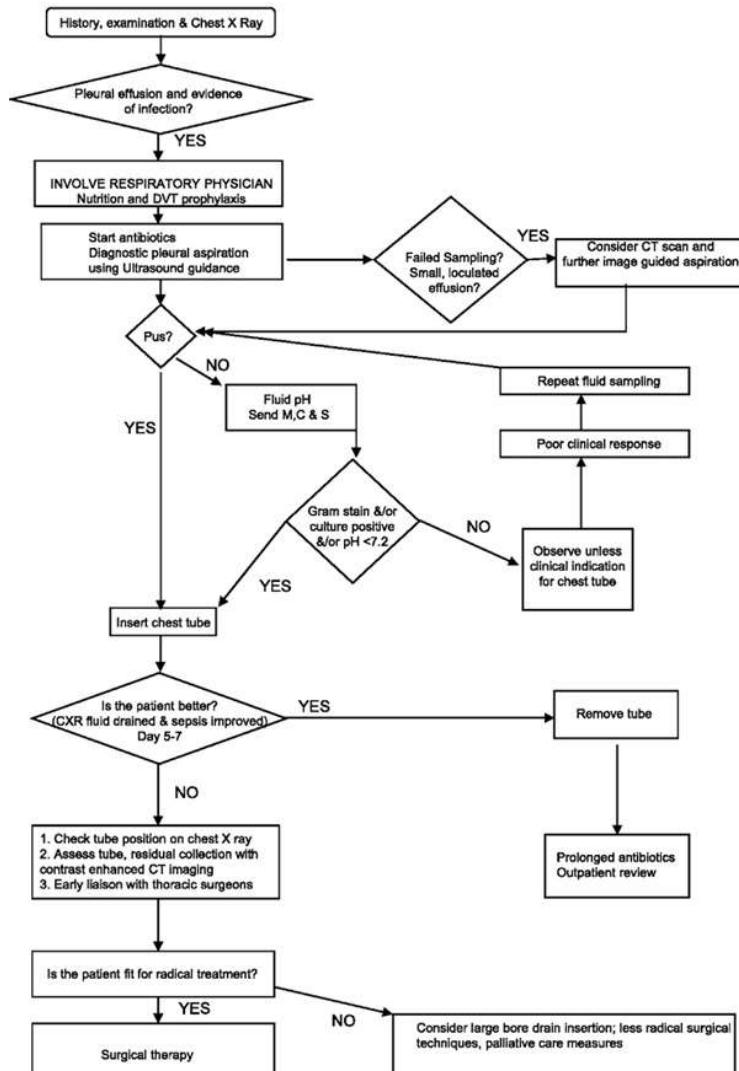


Figure 2: British Thoracic Society flowchart of managing spontaneous pneumothorax.

Diagnostic algorithm for the management of patients with pleural infection



Algorithm: BTS diagnostic and management of infected pleural effusion

Reference:

- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395(10223):507-13.
- Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet.* 2020;395(10223):514-23.
- Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA.* 2020;323(13):1239-42.
- Al Kuwari HM, Abdul Rahim HF, Abu-Raddad LJ, Abou-Samra AB, Al Kanaani Z, Al Khal A, et al. Epidemiological investigation of the first 5685 cases of SARS-CoV-2 infection in Qatar, 28 February-18 April 2020. *BMJ Open.* 2020;10(10):e040428.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA.* 2020;323(11):1061-9.
- Struyf T, Deeks JJ, Takwoingi Y, Davenport C, Leeflang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. *Cochrane Database Syst Rev.* 2020;7:CD013665.
- Wang Y, Liu Y, Liu L, Wang X, Luo N, Li L. Clinical Outcomes in 55 Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Who Were Asymptomatic at Hospital Admission in Shenzhen, China. *J Infect Dis.* 2020;221(11):1770-4.
- Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci.* 2020;63(5):706-11.
- Wilkerson RG, Adler JD, Shah NG, Brown R. Silent hypoxia: A harbinger of clinical deterioration in patients with COVID-19. *Am J Emerg Med.* 2020;38(10):2243 e5- e6.
- Helleberg M, Niemann CU, Moestrup KS, Kirk O, Lebech AM, Lane C, et al. Persistent COVID-19 in an Immunocompromised Patient Temporarily Responsive to Two Courses of Remdesivir Therapy. *J Infect Dis.* 2020;222(7):1103-7.
- Ginsburg AS, Klugman KP. COVID-19 pneumonia and the appropriate use of antibiotics. *Lancet Glob Health.* 2020;8(12):e1453-e4.

13. Sharifipour E, Shams S, Esmkhani M, Khodadadi J, Fotouhi-Ardakani R, Koohpaei A, et al. Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. *BMC Infect Dis.* 2020;20(1):646.
14. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *J Thorac Oncol.* 2020;15(5):700-4.
15. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 Autopsies, Oklahoma, USA. *Am J Clin Pathol.* 2020;153(6):725-33.
16. Wichmann D, Sperhake JP, Lutgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med.* 2020;173(4):268-77.
17. Alattar R, Ibrahim TBH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol.* 2020;92(10):2042-9.
18. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med.* 2020.
19. Fan J, Li X, Gao Y, Zhou J, Wang S, Huang B, et al. The lung tissue microbiota features of 20 deceased patients with COVID-19. *J Infect.* 2020;81(3):e64-e7.
20. Fekkar A, Poignon C, Blaize M, Lampros A. Fungal Infection during COVID-19: Does Aspergillus Mean Secondary Invasive Aspergillosis? *Am J Respir Crit Care Med.* 2020;202(6):902-3.
21. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. *Lancet.* 2015;385(9979):1799-801.
22. Togun T, Kampmann B, Stoker NG, Lipman M. Anticipating the impact of the COVID-19 pandemic on TB patients and TB control programmes. *Ann Clin Microbiol Antimicrob.* 2020;19(1):21-.
23. Al-Khal AL, Bener A, Enarson DA. Tuberculosis among garment workers in an Arabian developing country: State of Qatar. *Arch Environ Occup Health.* 2005;60(6):295-8.
24. Al-Rifai RH, Pearson F, Critchley JA, Abu-Raddad LJ. Association between diabetes mellitus and active tuberculosis: A systematic review and meta-analysis. *PLoS One.* 2017;12(11):e0187967.
25. Tadolini M, Codecasa LR, Garcia-Garcia JM, Blanc FX, Borisov S, Alffenaar JW, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. *Eur Respir J.* 2020;56(1).
26. Johansen MD, Herrmann JL, Kremer L. Non-tuberculous mycobacteria and the rise of *Mycobacterium abscessus*. *Nat Rev Microbiol.* 2020;18(7):392-407.
27. O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? *Nat Rev Immunol.* 2020;20(6):335-7.
28. Miyasaka M. Is BCG vaccination causally related to reduced COVID-19 mortality? *EMBO Mol Med.* 2020;12(6):e12661.
29. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantrangkul V, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost.* 2020;18(7):1738-42.
30. Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost.* 2020;18(7):1747-51.
31. Maier CL, Truong AD, Auld SC, Polly DM, Tanksley CL, Duncan A. COVID-19-associated hyperviscosity: a link between inflammation and thrombophilia? *Lancet.* 2020;395(10239):1758-9.
32. Libby P, Luscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J.* 2020;41(32):3038-44.
33. Lowenstein CJ, Solomon SD. Severe COVID-19 Is a Microvascular Disease. *Circulation.* 2020;142(17):1609-11.
34. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol.* 2020;20(7):389-91.
35. Medcalf RL, Keragala CB, Myles PS. Fibrinolysis and COVID-19: A plasmin paradox. *J Thromb Haemost.* 2020;18(9):2118-22.
36. Allegra A, Innao V, Allegra AG, Musolino C. Coagulopathy and thromboembolic events in patients with SARS-CoV-2 infection: pathogenesis and management strategies. *Ann Hematol.* 2020;99(9):1953-65.
37. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, Teixeira L, Barreto EA, Pao CRR, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. *Blood.* 2020;136(11):1330-41.
38. Roncon L, Zuin M, Barco S, Valerio L, Zuliani G, Zoncini P, et al. Incidence of acute pulmonary embolism in COVID-19 patients: Systematic review and meta-analysis. *Eur J Intern Med.* 2020;82:29-37.
39. Fauvel C, Weizman O, Trimaille A, Mika D, Pommier T, Pace N, et al. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J.* 2020;41(32):3058-68.
40. Kamenetzky M, Moore W, Fanslawa K, Babb JS, Kamenetzky D, Horwitz LI, et al. Pulmonary Embolism on CTPA in COVID-19 Patients. *Radiology: Cardiothoracic Imaging.* 2020;2(4):e200308.
41. Klok FA, Kruij M, van der Meer NJM, Arbous MS, Gomers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145-7.
42. Hill JB, Garcia D, Crowther M, Savage B, Peress S, Chang K, et al. Frequency of venous thromboembolism in 6513 patients with COVID-19: a retrospective study. *Blood Adv.* 2020;4(21):5373-7.
43. Gervaise A, Bouzad C, Peroux E, Helissey C. Acute pulmonary embolism in non-hospitalized COVID-19 patients referred to CTPA by emergency department. *Eur Radiol.* 2020;30(11):6170-7.
44. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost.* 2020;18(6):1324-9.
45. Abdallah I, Eltahir A, Fernyhough L, El-Bardissi A, Ahmed R, Abdulgellel M, et al. The experience of Hamad General Hospital collaborative anticoagulation clinic in Qatar during the COVID-19 pandemic. *J Thromb Thrombolysis.* 2020.
46. Martinelli AW, Ingle T, Newman J, Nadeem I, Jackson K, Lane ND, et al. COVID-19 and pneumothorax: a multicentre retrospective case series. *Eur Respir J.* 2020;56(5).
47. Tucker L, Patel S, Vatsis C, Poma A, Ammar A, Nasser W, et al. Pneumothorax and Pneumomediastinum Secondary to COVID-19 Disease Unrelated to Mechanical Ventilation. *Case Rep Crit Care.* 2020;2020:6655428.
48. Porcel JM. Improving the management of spontaneous pneumothorax. *Eur Respir J.* 2018;52(6).
49. Hsu CW, Sun SF. Iatrogenic pneumothorax related to mechanical ventilation. *World J Crit Care Med.* 2014;3(1):8-14.
50. Gammon RB, Shin MS, Buchalter SE. Pulmonary barotrauma in mechanical ventilation. Patterns and risk factors. *Chest.* 1992;102(2):568-72.
51. Woodring JH. Pulmonary interstitial emphysema in the adult respiratory distress syndrome. *Crit Care Med.* 1985;13(10):786-91.
52. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med.* 1998;157(1):294-323.
53. Dreyfuss D, Saumon G. Barotrauma is volutrauma, but which volume is the one responsible? *Intensive Care Med.* 1992;18(3):139-41.
54. Miller MP, Sagy M. Pressure characteristics of mechanical ventilation and incidence of pneumothorax before and after the implementation of protective lung strategies in the management of pediatric patients with severe ARDS. *Chest.* 2008;134(5):969-73.
55. Boussarsar M, Thierry G, Jaber S, Roudot-Thoraval F, Lemaire F, Brochard L. Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. *Intensive Care Med.* 2002;28(4):406-13.

56. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med.* 1998;158(6):1831-8.
57. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF, Jr., Weaver LK, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO₂ removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1994;149(2 Pt 1):295-305.
58. Anzueto A, Frutos-Vivar F, Esteban A, Alia I, Brochard L, Stewart T, et al. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. *Intensive Care Med.* 2004;30(4):612-9.
59. Xiong Y, Sun D, Liu Y, Fan Y, Zhao L, Li X, et al. Clinical and High-Resolution CT Features of the COVID-19 Infection: Comparison of the Initial and Follow-up Changes. *Invest Radiol.* 2020;55(6):332-9.
60. Wong HYF, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, et al. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology.* 2020;296(2):E72-E8.
61. Yoon SH, Lee KH, Kim JV, Lee YK, Ko H, Kim KH, et al. Chest Radiographic and CT Findings of the 2019 Novel Coronavirus Disease (COVID-19): Analysis of Nine Patients Treated in Korea. *Korean J Radiol.* 2020;21(4):494-500.
62. Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, et al. The Role of Chest Imaging in Patient Management During the COVID-19 Pandemic: A Multinational Consensus Statement From the Fleischner Society. *Chest.* 2020;158(1):106-16.
63. Jacobi A, Chung M, Bernheim A, Eber C. Portable chest X-ray in coronavirus disease-19 (COVID-19): A pictorial review. *Clin Imaging.* 2020;64:35-42.
64. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, Villamizar-Pena R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis.* 2020;34:101623.
65. Li Y, Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. *AJR Am J Roentgenol.* 2020;214(6):1280-6.
66. Miro O, Llorens P, Jimenez S, Pinera P, Burillo-Putze G, Martin A, et al. Frequency, risk factors, clinical characteristics and outcomes of spontaneous pneumothorax in patients with Covid-19: A case-control, emergency medicine-based multicenter study. *Chest.* 2020.
67. Alhakeem A, Khan MM, Al Soub H, Yousaf Z. Case Report: COVID-19-Associated Bilateral Spontaneous Pneumothorax-A Literature Review. *Am J Trop Med Hyg.* 2020;103(3):1162-5.
68. Elaziz MA, Hosny KM, Salah A, Darwish MM, Lu S, Sahlol AT. New machine learning method for image-based diagnosis of COVID-19. *PLoS One.* 2020;15(6):e0235187.
69. Kang H, Xia L, Yan F, Wan Z, Shi F, Yuan H, et al. Diagnosis of Coronavirus Disease 2019 (COVID-19) With Structured Latent Multi-View Representation Learning. *IEEE Trans Med Imaging.* 2020;39(8):2606-14.
70. Mahmud T, Rahman MA, Fattah SA. CovXNet: A multi-dilation convolutional neural network for automatic COVID-19 and other pneumonia detection from chest X-ray images with transferable multi-receptive feature optimization. *Comput Biol Med.* 2020;122:103869.
71. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical Coronavirus Disease 2019 (COVID-19) Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology.* 2020;296(2):E41-E5.
72. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis.* 2020;20(4):425-34.
73. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology.* 2020;296(2):E115-E7.
74. Ojha V, Mani A, Pandey NN, Sharma S, Kumar S. CT in coronavirus disease 2019 (COVID-19): a systematic review of chest CT findings in 4410 adult patients. *Eur Radiol.* 2020;30(11):6129-38.
75. Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. *AJR Am J Roentgenol.* 2020;214(5):1072-7.
76. Bao C, Liu X, Zhang H, Li Y, Liu J. Coronavirus Disease 2019 (COVID-19) CT Findings: A Systematic Review and Meta-analysis. *J Am Coll Radiol.* 2020;17(6):701-9.
77. Peng QY, Wang XT, Zhang LN, Chinese Critical Care Ultrasound Study G. Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. *Intensive Care Med.* 2020;46(5):849-50.
78. Abrams ER, Rose G, Fields JM, Esener D. Point-of-Care Ultrasound in the Evaluation of COVID-19. *J Emerg Med.* 2020;59(3):403-8.
79. Bar S, Lecourtois A, Diouf M, Goldberg E, Bourbon C, Arnaud E, et al. The association of lung ultrasound images with COVID-19 infection in an emergency room cohort. *Anaesthesia.* 2020;75(12):1620-5.
80. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. *J Thorac Imaging.* 2020;35(4):219-27.

Reference:

- Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet.* 2020;395(10223):514-23.
- Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA.* 2020;323(13):1239-42.
- Al Kuwari HM, Abdul Rahim HF, Abu-Raddad LJ, Abou-Samra AB, Al Kanaani Z, Al Khal A, et al. Epidemiological investigation of the first 5685 cases of SARS-CoV-2 infection in Qatar, 28 February-18 April 2020. *BMJ Open.* 2020;10(10):e040428.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA.* 2020;323(11):1061-9.
- Struyf T, Deeks JJ, Dinnis J, Takwoingi Y, Davenport C, Leeflang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. *Cochrane Database Syst Rev.* 2020;7:CD013665.
- Wang Y, Liu Y, Liu L, Wang X, Luo N, Li L. Clinical Outcomes in 55 Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Who Were Asymptomatic at Hospital Admission in Shenzhen, China. *J Infect Dis.* 2020;221(11):1770-4.
- Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci.* 2020;63(5):706-11.

9. Wilkerson RG, Adler JD, Shah NG, Brown R. Silent hypoxia: A harbinger of clinical deterioration in patients with COVID-19. *Am J Emerg Med.* 2020;38(10):2243 e5- e6.
10. Helleberg M, Niemann CU, Moestrup KS, Kirk O, Lebech AM, Lane C, et al. Persistent COVID-19 in an Immunocompromised Patient Temporarily Responsive to Two Courses of Remdesivir Therapy. *J Infect Dis.* 2020;222(7):1103-7.
11. Ginsburg AS, Klugman KP. COVID-19 pneumonia and the appropriate use of antibiotics. *Lancet Glob Health.* 2020;8(12):e1453-e4.
12. Sharifipour E, Shams S, Esmkhani M, Khodadadi J, Fotouhi-Ardakani R, Koohpaei A, et al. Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. *BMC Infect Dis.* 2020;20(1):646.
13. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *J Thorac Oncol.* 2020;15(5):700-4.
14. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 Autopsies, Oklahoma, USA. *Am J Clin Pathol.* 2020;153(6):725-33.
15. Wichmann D, Sperhake JP, Lutgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med.* 2020;173(4):268-77.
16. Alattar R, Ibrahim TBH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol.* 2020;92(10):2042-9.
17. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med.* 2020.
18. Fan J, Li X, Gao Y, Zhou J, Wang S, Huang B, et al. The lung tissue microbiota features of 20 deceased patients with COVID-19. *J Infect.* 2020;81(3):e64-e7.
19. Fekkar A, Poignon C, Blaize M, Lampros A. Fungal Infection during COVID-19: Does Aspergillus Mean Secondary Invasive Aspergillosis? *Am J Respir Crit Care Med.* 2020;202(6):902-3.
20. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. *Lancet.* 2015;385(9979):1799-801.
21. Togun T, Kampmann B, Stoker NG, Lipman M. Anticipating the impact of the COVID-19 pandemic on TB patients and TB control programmes. *Ann Clin Microbiol Antimicrob.* 2020;19(1):21-.
22. Al-Khal AL, Bener A, Enarson DA. Tuberculosis among garment workers in an Arabian developing country: State of Qatar. *Arch Environ Occup Health.* 2005;60(6):295-8.
23. Al-Rifai RH, Pearson F, Critchley JA, Abu-Raddad LJ. Association between diabetes mellitus and active tuberculosis: A systematic review and meta-analysis. *PLoS One.* 2017;12(11):e0187967.
24. Tadolini M, Codecasa LR, Garcia-Garcia JM, Blanc FX, Borisov S, Alffenaar JW, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. *Eur Respir J.* 2020;56(1).
25. Johansen MD, Herrmann JL, Kremer L. Non-tuberculous mycobacteria and the rise of *Mycobacterium abscessus*. *Nat Rev Microbiol.* 2020;18(7):392-407.
26. O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? *Nat Rev Immunol.* 2020;20(6):335-7.
27. Miyasaka M. Is BCG vaccination causally related to reduced COVID-19 mortality? *EMBO Mol Med.* 2020;12(6):e12661.
28. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantangkul V, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost.* 2020;18(7):1738-42.
29. Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost.* 2020;18(7):1747-51.
30. Maier CL, Truong AD, Auld SC, Polly DM, Tanksley CL, Duncan A. COVID-19-associated hyperviscosity: a link between inflammation and thrombophilia? *Lancet.* 2020;395(10239):1758-9.
31. Libby P, Luscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J.* 2020;41(32):3038-44.
32. Lowenstein CJ, Solomon SD. Severe COVID-19 Is a Microvascular Disease. *Circulation.* 2020;142(17):1609-11.
33. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol.* 2020;20(7):389-91.
34. Medcalf RL, Keragala CB, Myles PS. Fibrinolysis and COVID-19: A plasmin paradox. *J Thromb Haemost.* 2020;18(9):2118-22.
35. Allegra A, Innao V, Allegra AG, Musolino C. Coagulopathy and thromboembolic events in patients with SARS-CoV-2 infection: pathogenesis and management strategies. *Ann Hematol.* 2020;99(9):1953-65.
36. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, Teixeira L, Barreto EA, Pao CRR, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. *Blood.* 2020;136(11):1330-41.
37. Roncon L, Zuin M, Barco S, Valerio L, Zuliani G, Zoncini P, et al. Incidence of acute pulmonary embolism in COVID-19 patients: Systematic review and meta-analysis. *Eur J Intern Med.* 2020;82:29-37.
38. Fauvel C, Weizman O, Trimaille A, Mika D, Pommier T, Pace N, et al. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J.* 2020;41(32):3058-68.
39. Kaminetzky M, Moore W, Fansiwala K, Babb JS, Kaminetzky D, Horwitz LI, et al. Pulmonary Embolism on CTPA in COVID-19 Patients. *Radiology: Cardiothoracic Imaging.* 2020;2(4):e200308.
40. Klok FA, Kruij M, van der Meer NJM, Arbois MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145-7.
41. Hill JB, Garcia D, Crowther M, Savage B, Peress S, Chang K, et al. Frequency of venous thromboembolism in 6513 patients with COVID-19: a retrospective study. *Blood Adv.* 2020;4(21):5373-7.
42. Gervaise A, Bouzad C, Peroux E, Helissey C. Acute pulmonary embolism in non-hospitalized COVID-19 patients referred to CTPA by emergency department. *Eur Radiol.* 2020;30(11):6170-7.
43. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost.* 2020;18(6):1324-9.
44. Abdallah I, Eltahir A, Fernyhough L, El-Bardissi A, Ahmed R, Abdulgelil M, et al. The experience of Hamad General Hospital collaborative anticoagulation clinic in Qatar during the COVID-19 pandemic. *J Thromb Thrombolysis.* 2020.
45. Martinelli AW, Ingle T, Newman J, Nadeem I, Jackson K, Lane ND, et al. COVID-19 and pneumothorax: a multicentre retrospective case series. *Eur Respir J.* 2020;56(5).
46. Tucker L, Patel S, Vatsis C, Poma A, Ammar A, Nasser W, et al. Pneumothorax and Pneumomediastinum Secondary to COVID-19 Disease Unrelated to Mechanical Ventilation. *Case Rep Crit Care.* 2020;2020:6655428.
47. Porcel JM. Improving the management of spontaneous pneumothorax. *Eur Respir J.* 2018;52(6).
48. Hsu CW, Sun SF. Iatrogenic pneumothorax related to mechanical ventilation. *World J Crit Care Med.* 2014;3(1):8-14.
49. Gammon RB, Shin MS, Buchalter SE. Pulmonary barotrauma in mechanical ventilation. Patterns and risk factors. *Chest.* 1992;102(2):568-72.
50. Woodring JH. Pulmonary interstitial emphysema in the adult respiratory distress syndrome. *Crit Care Med.* 1985;13(10):786-91.
51. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med.* 1998;157(1):294-323.
52. Dreyfuss D, Saumon G. Barotrauma is volutrauma, but which volume is the one responsible? *Intensive Care Med.* 1992;18(3):139-41.

53. Miller MP, Sagy M. Pressure characteristics of mechanical ventilation and incidence of pneumothorax before and after the implementation of protective lung strategies in the management of pediatric patients with severe ARDS. *Chest*. 2008;134(5):969-73.
54. Boussarsar M, Thierry G, Jaber S, Roudot-Thoraval F, Lemaire F, Brochard L. Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. *Intensive Care Med*. 2002;28(4):406-13.
55. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med*. 1998;158(6):1831-8.
56. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF, Jr., Weaver LK, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO₂ removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;149(2 Pt 1):295-305.
57. Anzueto A, Frutos-Vivar F, Esteban A, Alia I, Brochard L, Stewart T, et al. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. *Intensive Care Med*. 2004;30(4):612-9.
58. Xiong Y, Sun D, Liu Y, Fan Y, Zhao L, Li X, et al. Clinical and High-Resolution CT Features of the COVID-19 Infection: Comparison of the Initial and Follow-up Changes. *Invest Radiol*. 2020;55(6):332-9.

5- COVID-19 diagnostic chest imaging,

Keywords: chest radiograph, chest x-rays, COVID-19 pneumonia, ground-glass opacities, consolidation, spontaneous pneumothorax, Computed tomography (CT) of the chest, high resolution chest scan, HRCT, CT pulmonary angiogram, CTPA, machine learning method for image-based diagnosis of COVID-19, crazy paving pattern, lung/pleural ultrasound, pleural effusion, chest drain.

A-Chest radiograph (x-rays):

As the first line chest imaging, chest radiograph (x-rays) is an easily accessible and cheap modality that emit low dose radiation. However, it can be normal in COVID-19 pneumonia, for example, a review of chest x-rays of 64 patients with documented COVID-19 in Hong Kong showed no abnormalities (60). Therefore, normal chest x-rays, figure 1, does not exclude COVID-19 pneumonia. In early stages of the disease, up to 63% of patients with covid-19 pneumonia may have normal chest x-rays (61, 62). The appearance of ground glass appearance commonly proceeds consolidation in majority of cases (60, 63). A systematic literature review with meta-analysis of 27% showed that bilateral lung changes are more common than unilateral lung involvement, 72.9% and 25% respectively (64).

In keeping with the natural clinical progression of COVID-19 pneumonia, most patients develop signs on their chest x-rays between 10 to 14 days after the onset of their symptoms (65). There is no one specific signs that is diagnostic of COVID-19 pneumonia on chest radiograph; it is rather a constellation of signs that are seen on chest x-rays, congruent with clinical features and results from blood tests that leads to a diagnosis of covid-19 pneumonia. Validation of the British Society of Thoracic Imaging guidelines for COVID-19 chest radiograph reporting, box 1, states that consolidation and ground-glass opacities, with bilateral, peripheral, and lower lung zone distributions; lung involvement increased over the course of illness are common radiographic findings, figure 2, of COVID-19 pneumonia (62).

Spontaneous pneumothorax, albeit not common, but can be the presenting manifestation of COVID-19 infection. Spontaneous pneumothorax was detected in 40 patients (0.56%) in a retrospective analysis of over 70,000 patients with COVID-19 presented to Spanish emergency rooms(66). There are only very few reports of bilateral pneumothorax caused by COVID-19 without a history of pre-existing lung disease such as chronic obstructive airway disease, including one case report from Qatar, (67).

Several investigators around the world, including from Qatar, have published interesting data showing the role of automated and machine learning algorithm to diagnose COVID-19 pneumonia on chest x-rays(68-70)

B- Computed tomography (CT) of the chest:

Routine use of chest CT is not recommended for screening or to make a diagnosis of COVID-19 pneumonia; as findings from history, physical examination, blood tests and chest x-rays are sufficient, in the majority of cases, to diagnose COVID-19 pneumonia. the American College of Radiology (ACR) recommend chest CT only for hospitalized patients to advise management.

Chest CT might be normal in early disease or in patients with no COVID-19 pneumonia, on the other hands, chest CT can be abnormal in a symptomatic or preclinical patient during the prodromal phase of the infection(71, 72). By enlarge, CT chest is considered to be more sensitive compared to chest radiograph in detecting early changes within the lung interstitium, pleural and the mediastinum(72, 73). Although none of the CT findings are specific to COVID-19 pneumonia as they can occur in most viral, inflammatory or bacterial causes of pneumonia(72, 73).

The CT findings are bilateral in the majority of cases of COVID-19 pneumonia. Ground glass changes (GGC), a feature of viral pneumonia, is the commonest CT finding(72, 74, 75). Other less common CT features (of no specific order) are: a crazy paving pattern (ground-glass opacifications with superimposed septal thickening), lymphadenopathy, pericardial effusion, pleural effusion, and bronchiectasis.

Bao C et al, carried out a systematic review and metanalysis of 2700 patients with acute COVID-19 infection, and produced the following list of commonest CT features(76):

1. Ground-glass opacifications – 83%
2. Ground-glass opacifications with mixed consolidation – 58%
3. Adjacent pleural thickening – 52%
4. Interlobular septal thickening – 48%

5. Air bronchograms – 46%

High resolution CT scan (HRCT), which uses no contrast, hence causes no contrast related complications such as nephrotoxicity or anaphylaxis, not **CT pulmonary angiogram (CTPA)**, is the modality of choice to be used if CT chest is required. CTPA is recommended if there's a clinical suspicion of pulmonary embolism that requires radiological confirmation. To prevent inconsistencies and to standardize the language of radiological reporting, the ACR produced a useful table that is encouraged to be used by health systems, table 1.

C- Lung/pleural ultrasound:

Ultrasound of the lung and or pleura has limited role in the diagnosis of COVID-19 infection.

Lung ultrasound findings in COVID-19 pneumonia includes non-specific changes, for example: multifocal, or confluent; patchy, strip, and nodular consolidations; thickening, discontinuation, and interruption of the pleural line and air bronchogram if consolidation is present(77-79).

Pleural ultrasound is particularly to assess pleural effusion and to guide pleural procedures such as diagnostic and/or therapeutic pleural needle aspiration or insertion of intercostal tube to drain pleural effusion.

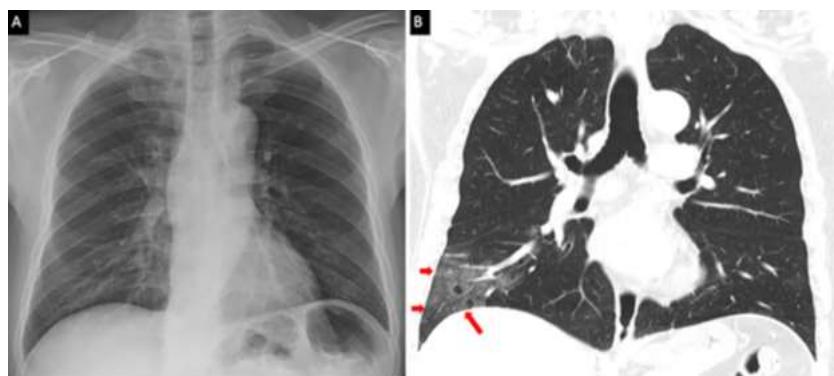


Figure 1:

A: normal chest x-rays in a patient with COVID-19Pneumonia.

B: CT chest of the same patient, within 1 hour of the chest x-rays, showing infective infiltrates (ground glass changes) in the right lower lobe (red arrows).

Ng M. Published Online: February 13, 2020

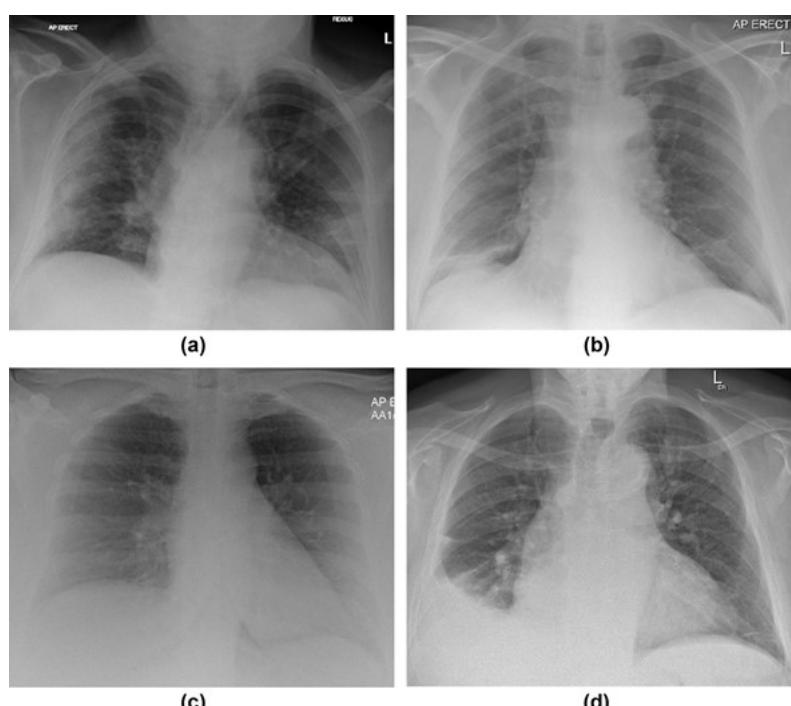


Figure 2: Examples of the COVID BSTI categories for plain films, in each case all radiologists agreed on the categorisation.

(a) Anteroposterior (AP) erect radiograph demonstrating "Classic COVID-19".

(b) AP erect chest radiograph "Indeterminate for COVID-19".

(c) AP erect radiograph classified as "COVID normal".

(d) AP erect radiograph classified as "Non-COVID".

Normal	COVID-19 not excluded, please correlate with PCR
Classic/probable COVID-19	Lower lobe and peripheral predominant multiple opacities that are bilateral (>> unilateral)
Indeterminate for COVID-19	Does not fit Classic or Non-COVID-19 descriptors" or "poor quality film
Non-COVID-19	Pneumothorax/lobar pneumonia/pleural effusion(s)/pulmonary oedema/other

Box 1: The British Society of Thoracic Imaging chest radiography reporting criteria.

S.S. Hare et al. / Clinical Radiology 75 (2020) 710.e9-710.e14

COVID-19 pneumonia imaging classification	Rationale	CT findings	Suggested reporting language
Typical appearance	Commonly reported imaging features of greater specificity for COVID-19 pneumonia.	<ul style="list-style-type: none"> ▪ Peripheral, bilateral, GGO with or without consolidation or visible intralobular lines ("crazy-paving") ▪ Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines ("crazy-paving") ▪ Reverse halo sign or other findings of organizing pneumonia (seen later in the disease). 	"Commonly reported imaging features of (COVID-19) pneumonia are present. Other processes such as influenza pneumonia and organizing pneumonia, as can be seen with drug toxicity and connective tissue disease, can cause a similar imaging pattern."
Indeterminate appearance	Nonspecific imaging features of COVID-19 pneumonia.	<ul style="list-style-type: none"> ▪ Absence of typical features AND Presence of: <ul style="list-style-type: none"> • Multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and are non-rounded or non-peripheral. • Few very small GGO with a non-rounded and non-peripheral distribution. 	"Imaging features can be seen with (COVID-19) pneumonia, though are nonspecific and can occur with a variety of infectious and noninfectious processes."
Atypical appearance	Uncommonly or not reported features of COVID-19 pneumonia.	<ul style="list-style-type: none"> ▪ Absence of typical or indeterminate features AND Presence of: <ul style="list-style-type: none"> • Isolated lobar or segmental consolidation without GGO • Discrete small nodules (centrilobular, "tree-in-bud") • Lung cavitation • Smooth interlobular septal thickening with pleural effusion 	"Imaging features are atypical or uncommonly reported for (COVID-19) pneumonia. Alternative diagnoses should be considered."
Negative for pneumonia	No features of pneumonia.	<ul style="list-style-type: none"> ▪ No CT features to suggest pneumonia. 	"No CT findings present to indicate pneumonia. (NOTE: CT may be negative in the early stages of COVID-19.)"

Table 1: American College of Radiology (ACR) suggested corresponding language for the interpretation report and has categorized features as typical, indeterminate, or atypical for COVID-19(80).

Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19.
Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA.

6- Critical care medicine and COVID-19 infection

Keywords: Intensive care unit (ICU), invasive mechanical ventilation (IMV), adult respiratory distress syndrome (ARDS), ventilation mode, tidal volume, positive end expiratory pressure, tracheostomy, weaning from mechanical ventilation.

A: Epidemiology:

Of the 20% of patients with COVID-19 infection requiring hospitalisation, up to one-quarter need intensive care unit (ICU) admission, which is 5 to 8 % of all infected patients(5). Patients who received ventilation varies from between regions, reflecting differences in population mean age and different ICU protocols for ventilation. For example, 5700 patients hospitalized with COVID-19 in New York, 1151 (20 percent) required mechanical ventilation(81). Younger populations with fewer somebodies are likely to require ICU admission and mechanical ventilation. A good example is that in the State of Qatar 2.0% of confirmed COVID-19 patients had severe or critical illness, in a sample of 5685 cases of COVID-19 (4). In term of sex distribution of ICU admitted patients, results are mixed. In Chinese cohort, ¾ of critically ill cases were male, however other studies showed equal male to female distribution and some studies showed more male preponderance (82-85)

B: Risk factors for critical and rapid progression of disease:

I) Age: Older age is also associated with more risk of critical illness and increased mortality(3, 85). A seminal report by Chinese CDC case stated that fatality rates were 8 and 15 percent among those aged 70 to 79 years and 80 years or older, respectively, in contrast to the 2.3 percent case fatality rate among the entire cohort(3). A large data analysis of from the UK showed that individuals 80 years and older was 20-fold that among individuals 50 to 59 years old(86). By contrast <2 percent of children and adolescent suffered from a fatal disease (86).

II) Comorbidities: the following conditions are likely to be associated with more critical illness(3, 87-89):

- Chronic lung diseases.
- Cardiovascular diseases
- Diabetes
- Obesity
- Chronic kidney diseases
- Hypertension
- Smoking

III) Demographic features: Data from the United States indicates that patients of non-white background have higher incidences of Critical Care illness and admission to ICU. This is likely be due to inequality in healthcare and lack of adequate medical support to individuals from disadvantaged social economic backgrounds(86, 90).

IV) Laboratory findings: the following laboratory abnormalities seem to be associated with more critical illness and higher risk of admission to ICU(91-94)-

- Lymphopenia
- Thrombocytopenia
- Acute kidney injury
- Elevated liver enzymes
- Elevated troponin level
- Elevated D-dimer (>1 mcg/mL)
- Elevated inflammatory markers (eg, C-reactive protein [CRP], ferritin) and inflammatory cytokines (ie, interleukin 6 [IL-6] and tumor necrosis factor [TNF]-alpha)
- Elevated lactate dehydrogenase (LDH)
- Elevated prothrombin time (PT)
- Elevated creatine phosphokinase (CPK)

V) Genetic factors: there are reports of severe illnesses and increased mortality clustering in certain families which gives rise to the possibility of genetic predisposition for severe disease(95, 96). A genome-wide association study identified a relationship between polymorphisms in the genes encoding the ABO blood group and respiratory failure from COVID-19 (type A associated with a higher risk and type B associated with lower risk of infection and severe disease)(97).

VI) Viral load: a higher viral RNA levels in respiratory specimens than those with milder disease(98, 99). However other reports showed conflicting data in relation to the correlation between viral load and disease severity(100, 101). Some studies showed that the detection of viral RNA in the plasma has a higher association with end organ damage (lungs, kidneys and heart), coagulopathy and mortality(102-104).

C: Clinical features of critically unwell patients:

The range of need for invasive mechanical ventilation (IMV) in ICU ranges from 30 to 100%(83, 84).

Severe hypoxia associated with Adult Respiratory Distress Syndrome (ARDS) and very rarely hypercapnia are markers of respiratory failure(5, 6, 83, 87). Patients in ICU commonly have fever of wax and wane pattern(87, 105, 106). The following are commonly seen complications of patients admitted to ICU:

I. ARDS:

An acute, diffuse, inflammatory form of lung injury. ARDS is a frequent complication of COVID-19 infection in ICU patients(92). The degree of hypoxemia determines the severity of ARDS to mild, moderate and severe, as per Berlin classification, table 1. Moderate and severe ARDS mandate IMV.

In ARDS there's excessive fluid leak to lung parenchyma and alveolar space. This is resulted from endothelial injury caused by the release inflammatory cytokines such as tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-8. This fluid leak leads to impaired gas exchange, decreased compliance, and increased pulmonary arterial pressure(107, 108). ARDS results in impairment/dysfunction and three main domains:

- i. Impaired gas exchange: Fluid leakage to the lung parenchyma and the alveolar space causes increases V/Q mismatch and increased physiological dead space.
- ii. Decreased lung compliance: the non-aerated or poorly aerated lung becomes stiff and therefore reduce lung compliance. A small raise in tidal volume will lead to a dramatic rise in airway pressures.
- iii. Pulmonary hypertension – Pulmonary hypertension (PH) occurs in up to 25 percent of patients with ARDS who undergo mechanical ventilation (109, 110)

II. Special consideration of IMV in ARDS:

- Low tidal volume ventilation (LTBV): LTVV is recommended with a target of less than 6ml/kg predicted body weight. A volume-limited assist control mode is a commonly used mode of ventilation.

- Prone ventilation: seems to be more effective in COVID-19 associated ARDS in comparison to the causes of ARDS. Criteria for prone ventilation includes: partial arterial pressure of oxygen/fraction of inspired oxygen [PaO₂:FiO₂] ratio <150 mmHg, a FiO₂ ≥0.6, and PEEP ≥5 cm H₂O; excessively high airway pressures; or recalcitrant hypoxemia)
- Recruitment manoeuvres and high PEEP are often used to improve oxygenation.
- Neuromuscular blockade: muscle relaxants are used in patients with refractory hypoxaemia and/or poor patient ventilator synchrony.
- Extracorporeal membrane oxygenation (ECMO): ECMO is used as a rescue strategy in patients with refractory hypoxaemia with or without hypercapnia who failed to respond to the above interventions. ECMO is not widely available and requires special expertise to be implemented effectively and safely.

III: Extubation and weaning from IMV:

The same criteria of extubation and weaning from IMV due to other pathologies are applied. However, patients are still considered contagious therefore standard precautions for aerosol generated procedures should be deployed. Initial weaning trials of pressure support ventilation (PSV) is the standard. Once the patient successfully breath spontaneously for 16 to 24 hours on PSV, then he/she can progress to spontaneous breathing trials (SBTs). This process might take few days or a few weeks.

IV: Tracheostomy: it's commonly used for patients who are expected to be ventilated for more than one week. Other common indications are failed extubation, secretion management, airway oedema, neurological impairment such as that impairs airway protection. There is no strong evidence to guide the exact timing of tracheostomy, however 7 to 10 days following incubation is a feasible option, this is extrapolated from studies of non-COVID intubated patients(111).

V: Sedation and analgesia:

There is no evidence to guide the use of sedation and analgesia in intubate patients. There is anecdotal evidence indicating that COVID-19 intubated patients seem to require larger doses of sedation to achieve optimum ventilation. Both propofol and fentanyl are used regularly in most ITU units worldwide.

VI: Nutrition and bowel care:

There is no evidence to guide the use of a specific nutritional supplementation to COVID-intubated patients. Early administration of nutritional supplement via nasal gastric tube is encouraged. There is no strong evidence to support the use of high protein formulas or supplementation with specific vitamins or minerals that is different from non-COVID-19 intubated patients. Adequate monitoring of sluggish bowel movement or poor absorption is required; prokinetics such as metoclopramide or domperidone can be administered to improve bowel motion and absorption.

VII: Daily monitoring:

Patients treated in ITU should be regularly monitored for common and important complications. Daily physical examination, reviewing fluid balance, glucose chart, arterial/venous blood gas analysis, ECG and baseline blood investigations are recommended. The aim is to identify complications and intervening promptly. Special attention should be paid to detect DVT, hypoglycaemia, electrolyte disturbances, transaminitis, fluid imbalance, pericarditis/pericardial effusion, plural effusion and barotrauma.

VIII: Management of hospital acquired or ventilation associated infection/pneumonia (HAP and VAP respectively) and other comorbidities:

Patient care for in ITU are at high risk of HAP and in intubated patients VAP. Antibiotic use should be rationalised based on results from culture and sensitivities with advice from clinical microbiologists and infectious diseases specialists. Special attention must be paid to early detection of Central line and other catheter associated infections. Hypothermia and hypothermia should be detected early and corrected according to patient's clinical needs. Important complications such as pressure sores and formation of peripheral ischaemia and gangrene have to be treated aggressively with members of the multidisciplinary team.

Chronic medical conditions, such as chronic obstructive airways disease/asthma, diabetes mellitus, ischaemic heart disease, hypertension, chronic kidney disease and others have to be managed by respective specialities to optimise standard biological outcomes.

XI: Long-term complications:

Early data and anecdotal experience suggest that a significant proportion of COVID-19 intubated patients suffer from long-term sequels of prolonged incubation, use of nerve blockade and corticosteroid therapy. Critical illness myopathy, psychological and cognitive trauma have to be addressed by specialised rehabilitation units that involves physiotherapists, occupational therapists, counsellors and psychologists.

ARDS Severity	PaO ₂ /FiO ₂ Ratio (mmHg)	PEEP (cmH ₂ O)
Mild	200<PaO ₂ /FiO ₂ ≤300	≥5
Moderate	100<PaO ₂ /FiO ₂ ≤200	≥5
Severe	100≤PaO ₂ /FiO ₂	≥5

Table 1: Berlin grades of severity of ARDS:

Reference:

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-13.
2. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020;395(10223):514-23.
3. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-42.
4. Al Kuwari HM, Abdul Rahim HF, Abu-Raddad LJ, Abou-Samra AB, Al Kanaani Z, Al Khal A, et al. Epidemiological investigation of the first 5685 cases of SARS-CoV-2 infection in Qatar, 28 February-18 April 2020. *BMJ Open*. 2020;10(10):e040428.
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-9.
7. Struyf T, Deeks JJ, Dinnis J, Takwoingi Y, Davenport C, Leeftlang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. *Cochrane Database Syst Rev*. 2020;7:CD013665.
8. Wang Y, Liu Y, Liu L, Wang X, Luo N, Li L. Clinical Outcomes in 55 Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Who Were Asymptomatic at Hospital Admission in Shenzhen, China. *J Infect Dis*. 2020;221(11):1770-4.
9. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci*. 2020;63(5):706-11.
10. Wilkerson RG, Adler JD, Shah NG, Brown R. Silent hypoxia: A harbinger of clinical deterioration in patients with COVID-19. *Am J Emerg Med*. 2020;38(10):2243 e5- e6.
11. Helleberg M, Niemann CU, Moestrup KS, Kirk O, Lebech AM, Lane C, et al. Persistent COVID-19 in an Immunocompromised Patient Temporarily Responsive to Two Courses of Remdesivir Therapy. *J Infect Dis*. 2020;222(7):1103-7.
12. Ginsburg AS, Klugman KP. COVID-19 pneumonia and the appropriate use of antibiotics. *Lancet Glob Health*. 2020;8(12):e1453-e4.
13. Sharifipour E, Shams S, Esmkhani M, Khodadadi J, Fotouhi-Ardakani R, Koohpaei A, et al. Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. *BMC Infect Dis*. 2020;20(1):646.
14. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *J Thorac Oncol*. 2020;15(5):700-4.
15. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 Autopsies, Oklahoma, USA. *Am J Clin Pathol*. 2020;153(6):725-33.
16. Wichmann D, Sperhake JP, Lutgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med*. 2020;173(4):268-77.
17. Alattar R, Ibrahim TBH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol*. 2020;92(10):2042-9.
18. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med*. 2020.
19. Fan J, Li X, Gao Y, Zhou J, Wang S, Huang B, et al. The lung tissue microbiota features of 20 deceased patients with COVID-19. *J Infect*. 2020;81(3):e64-e7.
20. Fekkar A, Poignon C, Blaize M, Lampros A. Fungal Infection during COVID-19: Does Aspergillus Mean Secondary Invasive Aspergillosis? *Am J Respir Crit Care Med*. 2020;202(6):902-3.
21. Uplekar M, Weil D, Lonnerholt K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. *Lancet*. 2015;385(9979):1799-801.
22. Togun T, Kampmann B, Stoker NG, Lipman M. Anticipating the impact of the COVID-19 pandemic on TB patients and TB control programmes. *Ann Clin Microbiol Antimicrob*. 2020;19(1):21-.
23. Al-khal AL, Bener A, Enarson DA. Tuberculosis among garment workers in an Arabian developing country: State of Qatar. *Arch Environ Occup Health*. 2005;60(6):295-8.
24. Al-Rifai RH, Pearson F, Critchley JA, Abu-Raddad LJ. Association between diabetes mellitus and active tuberculosis: A systematic review and meta-analysis. *PLoS One*. 2017;12(11):e0187967.
25. Tadolini M, Codecasa LR, García-García JM, Blanc FX, Borisov S, Alffenaar JW, et al. Active tuberculosis, sequelae and COVID-19 co-infection: first cohort of 49 cases. *Eur Respir J*. 2020;56(1).
26. Johansen MD, Herrmann JL, Kremer L. Non-tuberculous mycobacteria and the rise of Mycobacterium abscessus. *Nat Rev Microbiol*. 2020;18(7):392-407.
27. O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? *Nat Rev Immunol*. 2020;20(6):335-7.
28. Miyasaka M. Is BCG vaccination causally related to reduced COVID-19 mortality? *EMBO Mol Med*. 2020;12(6):e12661.
29. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantangkul V, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost*. 2020;18(7):1738-42.
30. Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost*. 2020;18(7):1747-51.
31. Maier CL, Truong AD, Auld SC, Polly DM, Tanksley CL, Duncan A. COVID-19-associated hyperviscosity: a link between inflammation and thrombophilia? *Lancet*. 2020;395(10239):1758-9.
32. Libby P, Luscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J*. 2020;41(32):3038-44.
33. Lowenstein CJ, Solomon SD. Severe COVID-19 Is a Microvascular Disease. *Circulation*. 2020;142(17):1609-11.
34. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol*. 2020;20(7):389-91.
35. Medcalf RL, Keragala CB, Myles PS. Fibrinolysis and COVID-19: A plasmin paradox. *J Thromb Haemost*. 2020;18(9):2118-22.
36. Allegra A, Innao V, Allegra AG, Musolino C. Coagulopathy and thromboembolic events in patients with SARS-CoV-2 infection: pathogenesis and management strategies. *Ann Hematol*. 2020;99(9):1953-65.
37. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, Teixeira L, Barreto EA, Pao CRR, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. *Blood*. 2020;136(11):1330-41.
38. Roncon L, Zuin M, Barco S, Valerio L, Zuliani G, Zoncini P, et al. Incidence of acute pulmonary embolism in COVID-19 patients: Systematic review and meta-analysis. *Eur J Intern Med*. 2020;82:29-37.

39. Fauvel C, Weizman O, Trimaille A, Mika D, Pommier T, Pace N, et al. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J*. 2020;41(32):3058-68.
40. Kaminetzky M, Moore W, Fansivala K, Babb JS, Kaminetzky D, Horwitz LI, et al. Pulmonary Embolism on CTPA in COVID-19 Patients. *Radiology: Cardiothoracic Imaging*. 2020;2(4):e200308.
41. Klok FA, Kruij M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-7.
42. Hill JB, Garcia D, Crowther M, Savage B, Peress S, Chang K, et al. Frequency of venous thromboembolism in 6513 patients with COVID-19: a retrospective study. *Blood Adv*. 2020;4(21):5373-7.
43. Gervaise A, Bouzad C, Peroux E, Helissey C. Acute pulmonary embolism in non-hospitalized COVID-19 patients referred to CTPA by emergency department. *Eur Radiol*. 2020;30(11):6170-7.
44. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost*. 2020;18(6):1324-9.
45. Abdallah I, Eltahir A, Fernyhough L, El-Bardissi A, Ahmed R, Abdulgelil M, et al. The experience of Hamad General Hospital collaborative anticoagulation clinic in Qatar during the COVID-19 pandemic. *J Thromb Thrombolysis*. 2020.
46. Martinelli AW, Ingle T, Newman J, Nadeem I, Jackson K, Lane ND, et al. COVID-19 and pneumothorax: a multicentre retrospective case series. *Eur Respir J*. 2020;56(5).
47. Tucker L, Patel S, Vatsis C, Poma A, Ammar A, Nasser W, et al. Pneumothorax and Pneumomediastinum Secondary to COVID-19 Disease Unrelated to Mechanical Ventilation. *Case Rep Crit Care*. 2020;2020:6655428.
48. Porcel JM. Improving the management of spontaneous pneumothorax. *Eur Respir J*. 2018;52(6).
49. Hsu CW, Sun SF. Iatrogenic pneumothorax related to mechanical ventilation. *World J Crit Care Med*. 2014;3(1):8-14.
50. Gammon RB, Shin MS, Buchalter SE. Pulmonary barotrauma in mechanical ventilation. Patterns and risk factors. *Chest*. 1992;102(2):568-72.
51. Woodring JH. Pulmonary interstitial emphysema in the adult respiratory distress syndrome. *Crit Care Med*. 1985;13(10):786-91.
52. Dreyfuss D, Sauman G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med*. 1998;157(1):294-323.
53. Dreyfuss D, Sauman G. Barotrauma is volutrauma, but which volume is the one responsible? *Intensive Care Med*. 1992;18(3):139-41.
54. Miller MP, Sagy M. Pressure characteristics of mechanical ventilation and incidence of pneumothorax before and after the implementation of protective lung strategies in the management of pediatric patients with severe ARDS. *Chest*. 2008;134(5):969-73.
55. Boussarsar M, Thierry G, Jaber S, Roudot-Thoraval F, Lemaire F, Brochard L. Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. *Intensive Care Med*. 2002;28(4):406-13.
56. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med*. 1998;158(6):1831-8.
57. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF, Jr., Weaver LK, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO₂ removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;149(2 Pt 1):295-305.
58. Anzueto A, Frutos-Vivar F, Esteban A, Alia I, Brochard L, Stewart T, et al. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. *Intensive Care Med*. 2004;30(4):612-9.
59. Xiong Y, Sun D, Liu Y, Fan Y, Zhao L, Li X, et al. Clinical and High-Resolution CT Features of the COVID-19 Infection: Comparison of the Initial and Follow-up Changes. *Invest Radiol*. 2020;55(6):332-9.
60. Wong HYF, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, et al. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology*. 2020;296(2):E72-E8.
61. Yoon SH, Lee KH, Kim JY, Lee YK, Ko H, Kim KH, et al. Chest Radiographic and CT Findings of the 2019 Novel Coronavirus Disease (COVID-19): Analysis of Nine Patients Treated in Korea. *Korean J Radiol*. 2020;21(4):494-500.
62. Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, Raoof S, et al. The Role of Chest Imaging in Patient Management During the COVID-19 Pandemic: A Multinational Consensus Statement From the Fleischner Society. *Chest*. 2020;158(1):106-16.
63. Jacobi A, Chung M, Bernheim A, Eber C. Portable chest X-ray in coronavirus disease-19 (COVID-19): A pictorial review. *Clin Imaging*. 2020;64:35-42.
64. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, Villamizar-Pena R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis*. 2020;34:101623.
65. Li Y, Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. *AJR Am J Roentgenol*. 2020;214(6):1280-6.
66. Miro O, Llorens P, Jimenez S, Pinera P, Burillo-Putze G, Martin A, et al. Frequency, risk factors, clinical characteristics and outcomes of spontaneous pneumothorax in patients with Covid-19: A case-control, emergency medicine-based multicenter study. *Chest*. 2020.
67. Alhakeem A, Khan MM, Al Soub H, Yousaf Z. Case Report: COVID-19-Associated Bilateral Spontaneous Pneumothorax-A Literature Review. *Am J Trop Med Hyg*. 2020;103(3):1162-5.
68. Elaziz MA, Hosny KM, Salah A, Darwish MM, Lu S, Sahlot AT. New machine learning method for image-based diagnosis of COVID-19. *PLoS One*. 2020;15(6):e0235187.
69. Kang H, Xia L, Yan F, Wan Z, Shi F, Yuan H, et al. Diagnosis of Coronavirus Disease 2019 (COVID-19) With Structured Latent Multi-View Representation Learning. *IEEE Trans Med Imaging*. 2020;39(8):2606-14.
70. Mahmud T, Rahman MA, Fattah SA. CovXNet: A multi-dilation convolutional neural network for automatic COVID-19 and other pneumonia detection from chest X-ray images with transferable multi-receptive feature optimization. *Comput Biol Med*. 2020;122:103869.
71. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical Coronavirus Disease 2019 (COVID-19) Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology*. 2020;296(2):E41-E5.
72. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis*. 2020;20(4):425-34.
73. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology*. 2020;296(2):E115-E7.
74. Ojha V, Mani A, Pandey NN, Sharma S, Kumar S. CT in coronavirus disease 2019 (COVID-19): a systematic review of chest CT findings in 4410 adult patients. *Eur Radiol*. 2020;30(11):6129-38.
75. Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. *AJR Am J Roentgenol*. 2020;214(5):1072-7.
76. Bao C, Liu X, Zhang H, Li Y, Liu J. Coronavirus Disease 2019 (COVID-19) CT Findings: A Systematic Review and Meta-analysis. *J Am Coll Radiol*. 2020;17(6):701-9.
77. Peng QY, Wang XT, Zhang LN, Chinese Critical Care Ultrasound Study G. Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. *Intensive Care Med*. 2020;46(5):849-50.
78. Abrams ER, Rose G, Fields JM, Esener D. Point-of-Care Ultrasound in the Evaluation of COVID-19. *J Emerg Med*. 2020;59(3):403-8.

79. Bar S, Lecourtois A, Diouf M, Goldberg E, Bourbon C, Arnaud E, et al. The association of lung ultrasound images with COVID-19 infection in an emergency room cohort. *Anaesthesia*. 2020;75(12):1620-5.
80. Simpson S, Kay FU, Abbala S, Bhalla S, Chung JH, Chung M, et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. *J Thorac Imaging*. 2020;35(4):219-27.
81. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. 2020;323(20):2052-9.
82. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA*. 2020;323(14):1335.
83. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA*. 2020;323(16):1612-4.
84. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med*. 2020;382(21):2012-22.
85. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabriani L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020;323(16):1574-81.
86. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430-6.
87. Petrelli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*. 2020;369:m1966.
88. Team CC-R. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12-March 28, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(13):382-6.
89. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, et al. Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization. *Ann Intern Med*. 2020;173(10):773-81.
90. Gold JAW, Wong KK, Szablewski CM, Patel PR, Rossow J, da Silva J, et al. Characteristics and Clinical Outcomes of Adult Patients Hospitalized with COVID-19 - Georgia, March 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(18):545-50.
91. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-62.
92. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-43.
93. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802-10.
94. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med*. 2020;26(10):1636-43.
95. Severe Covid GG, Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *N Engl J Med*. 2020;383(16):1522-34.
96. van der Made CI, Simons A, Schuurs-Hoeijmakers J, van den Heuvel G, Mantere T, Kersten S, et al. Presence of Genetic Variants Among Young Men With Severe COVID-19. *JAMA*. 2020.
97. Ray JG, Schull MJ, Vermeulen MJ, Park AL. Association Between ABO and Rh Blood Groups and SARS-CoV-2 Infection or Severe COVID-19 Illness : A Population-Based Cohort Study. *Ann Intern Med*. 2020.
98. Magleby R, Westblade LF, Trzebucki A, Simon MS, Rajan M, Park J, et al. Impact of SARS-CoV-2 Viral Load on Risk of Intubation and Mortality Among Hospitalized Patients With Coronavirus Disease 2019. *Clin Infect Dis*. 2020.
99. Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis*. 2020;20(6):656-7.
100. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis*. 2020;20(5):565-74.
101. Yilmaz A, Marklund E, Andersson M, Nilsson S, Andersson LM, Lindh M, et al. Upper Respiratory Tract Levels of Severe Acute Respiratory Syndrome Coronavirus 2 RNA and Duration of Viral RNA Shedding Do Not Differ Between Patients With Mild and Severe/Critical Coronavirus Disease 2019. *J Infect Dis*. 2021;223(1):15-8.
102. Hogan CA, Stevens BA, Sahoo MK, Huang C, Garamani N, Gombar S, et al. High Frequency of SARS-CoV-2 RNAemia and Association With Severe Disease. *Clin Infect Dis*. 2020.
103. Xu D, Zhou F, Sun W, Chen L, Lan L, Li H, et al. Relationship Between serum SARS-CoV-2 nucleic acid(RNAemia) and Organ Damage in COVID-19 Patients: A Cohort Study. *Clin Infect Dis*. 2020.
104. Veyer D, Kerneis S, Poulet G, Wack M, Robillard N, Taly V, et al. Highly sensitive quantification of plasma SARS-CoV-2 RNA sheds light on its potential clinical value. *Clin Infect Dis*. 2020.
105. Jalili M, Payandemehr P, Saghaei A, Sari HN, Safikhani H, Kolivand P. Characteristics and Mortality of Hospitalized Patients With COVID-19 in Iran: A National Retrospective Cohort Study. *Ann Intern Med*. 2021;174(1):125-7.
106. Chand S, Kapoor S, Orsi D, Fazzari MJ, Tanner TG, Umeh GC, et al. COVID-19-Associated Critical Illness-Report of the First 300 Patients Admitted to Intensive Care Units at a New York City Medical Center. *J Intensive Care Med*. 2020;35(10):963-70.
107. Piantadosi CA, Schwartz DA. The acute respiratory distress syndrome. *Ann Intern Med*. 2004;141(6):460-70.
108. Roumen RM, Hendriks T, de Man BM, Goris RJ. Serum lipofuscin as a prognostic indicator of adult respiratory distress syndrome and multiple organ failure. *Br J Surg*. 1994;81(9):1300-5.
109. Vieillard-Baron A, Schmitt JM, Augarde R, Fellahi JL, Prin S, Page B, et al. Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. *Crit Care Med*. 2001;29(8):1551-5.
110. Villar J, Blazquez MA, Lubillo S, Quintana J, Manzano JL. Pulmonary hypertension in acute respiratory failure. *Crit Care Med*. 1989;17(6):523-6.
111. Rosano A, Martinelli E, Fusina F, Albani F, Caserta R, Morandi A, et al. Early Percutaneous Tracheostomy in Coronavirus Disease 2019: Association With Hospital Mortality and Factors Associated With Removal of Tracheostomy Tube at ICU Discharge. A Cohort Study on 121 Patients. *Crit Care Med*. 2021;49(2):261-70.

[Home](#)
[Forward message](#)
[Introduction](#)
[Chapters](#)
[Editors team](#)
[Contact us](#)



Copyright © 2022 Ministry of Public Health. All rights reserved.



Search this site



Epidemiology and Public Health

CHAPTER: Epidemiology and Public Health

Zaina Al Kanaani, Diana H. Jboor, Lamees Abdullah M. Ali, Sarwat Mahmud and Amine Toumi

Table of Contents

Keywords

- [Introduction](#)
- [Relevant Epidemiological Definitions](#)
- [Origins](#)
- [Mode of Transmission](#)
 - Human-Human Transmission
 - Surface-Human Transmission
 - Animal to Human Transmission
- [Infectiousness and Transmissibility](#)
- [The Risk of Exposure To COVID-19 Infection](#)
- [Incubation Period and Serial Interval](#)
- [Severity of COVID-19 Infection and The Risk of Death](#)
- [Immunity Following SARS-CoV-2 Infection](#)
- [Risk of Reinfection](#)
- [SARS-CoV-2 Variants of Concern](#)
- [Epidemic Curve, Global and Local Trends](#)
- [Public Health Actions for Prevention and Control Of COVID-19](#)
 - Isolation
 - Quarantining
 - Social Distancing
 - The Use of Facemasks
 - COVID-19 response in Qatar
 - Governance
 - Public Health Measures
 - Research and Technology
- [Discussion](#)

Keywords

Epidemic Curve, Case Fatality Rate, Reproduction Number, Transmission, Isolation, Quarantine.

1. Introduction

As the number infected and the number of deaths associated with COVID-19 continue to rise, health systems globally are being overwhelmed, and hospital resources are being reprioritized, with potentially dire collateral ramifications to other public health programs (1).

With approximately 22 000 publications worldwide, our understanding of COVID-19 epidemiology is rapidly evolving.

This evolution is critical to designing preventative measures and health policies.

This chapter aims to summarize what is known thus far about the epidemiology of COVID-19 globally in general and Qatar in particular.

The chapter also discusses epidemic trends, transmission routes, the severity of infection, immunity, SARS-CoV-2 variants, and public health responses.

2. Relevant Epidemiological Definitions

Table 1 provides the definitions of relevant epidemiological terms used in this chapter.

Term	Definition
Incidence rate	It is the number of new cases over the total person-time (sum of times at risk from each person).
Prevalence	The proportion of cases (new and pre-existing) at a specified point in time (point prevalence) or during a specified period of time (period prevalence).
Reproduction number/R ₀	A measure of 'contagiousness' represents the average number of people infected by one infected individual in a population that is susceptible to infection. (no immunity or vaccine) (30560777)
Effective reproduction number/R _e	Similar to R ₀ , without the assumption, the entire population is susceptible. (some immune members) (2)
Epidemic curve	A graph showing the progression of cases (new/cumulative) in an outbreak over time.
Case-fatality rate	The proportion of diseased people who die from the condition over a specified period of time. .
Mortality rate	It is the frequency of death in a particular population over a specified period of time.
Incubation period	The time from exposure to a pathogen until the onset of symptoms.
Latent period/pre-infectious period	The time period in which a person is infected but not yet infectious (3).
Infectious period	The time period in which a person is infected and is also infectious (3).
Serial interval	The time interval between the onset of symptoms in the primary case (infector) and the secondary case (infectee) (4).

Table 1. Definitions of relevant epidemiological terms.

3. Origins

At the end of 2019, a cluster of patients with pneumonia of unknown aetiology was identified in Wuhan city, China (5) (6). Early cases were linked to a wet seafood market where other wildlife animals were also available (5-7). In early January, a novel coronavirus, initially referred to as 19-nCOV (now referred to as SARS-CoV-2), was isolated from cases and identified as the causative agent for the disease that is currently referred to as COVID-19 (5, 8). Cases rapidly propagated through community transmission, spreading from China to several countries globally, resulting in WHO declaring the COVID-19 outbreak a pandemic on the 11th of March, 2020, see WHO timeline in this [link](#). As of the 1st of February, 2021, over 100 million people have been infected globally, with more than 2 million deaths , this [link](#) provides live mortality data.

Qatar has approximately 2.9 million residents, with a unique population demographic structure.

Approximately 88% of the population are expatriate workers, 75% of the population are males, and most of the population, particularly among males, are from the age groups 20-50 years (9).

On the 29th of February 2020, Qatar reported its first confirmed case of COVID-19, which was among passengers evacuated from Iran; who were quarantined upon arrival to Qatar.

Qatar's first confirmed community transmission of COVID-19 was reported on the 8th of March 2020 among three expatriate residents. Later a large cluster of 300 cases was identified and linked to three expatriate manual workers living in high-density housing (10).

Many residents returning from international travel were also identified to have been infected, at which point strict restrictions were imposed on incoming flights on the 31st of March 2020 (9).

Despite an array of preventive measures, including extensive contact tracing and testing, in July 2020, Qatar had the highest rate of cases per million population (10). As of the 2nd of February, 2021, over 152 000 people have been infected in Qatar, with 250 deaths

4. Mode of Transmission

Determining the mode of transmission of COVID-19 was the earliest challenge to implementing protective measures to reduce infectivity. Various modes of transmission have been discussed in the literature. However, the human-to-human route has taken precedence in research (11-14) . Most of the evidence on the human-to-human transmission of COVID-19 conclude that the transmission is most likely through respiratory droplets within close contacts by symptomatic and asymptomatic persons (15). Other modes covered in this section are animal-human, surface-human interaction via faecal-oral, respiratory, and air transmission.

4.1 Human-Human Transmission

Human-human transmission is the most probable mode of COVID-19 transmission (12). An individual may transmit to another through respiratory droplets within 2 to 4 meters distance via coughing or sneezing in a confined space with normal airflow (1 m/s) (11). These infectious droplets enter the lungs through the nose or mouth. They have their presence in various body fluids such as bronchoalveolar-lavage fluid, urine, sputum, tears, blood, vomit, breast milk, vaginal discharge, semen, and faeces(16). Research is ongoing on transmissibility via body fluids to better understand (16). Human-human transmission mode includes interfamily, healthcare worker-patient, child-adult, mother-child transmission and vice-versa (12). Close contact is defined as living in the same household with an infected person, direct physical contact such as shaking hands and hugging, having direct and unprotected contact with the infectious secretions of infected COVID-19 patient (14).

The definition and understanding of "close contact" came from reported cases within families (14). Additionally, it was observed that COVID-19 spreads in clusters epidemics in various crowd gathering settings and specific cities. This accounted for at least 50% of the total confirmed cases (17); the most common clustered epidemics observed are among households, shopping malls, medical institutions, and schools (12).

4.2 Surface-Human Transmission

Surface to human Is considered as an indirect mode of transmission of the viruses, usually after touching surfaces and or objects contaminated with droplets contained with the virus. COVID-19 contaminated dry surfaces have been asserted to be the transmission source that includes self-inoculation of mucous membranes of the nose, eyes, and mouth (18).

A study was conducted in Wuhan using 2 viruses (SARS-CoV-2 & SARS-CoV-1) on 5 different surfaces (Aerosols, plastic, stainless steel, copper, and cardboard). It was found that SARS-CoV-2 was more stable on plastics and stainless steel than on cardboard, and after the application on surfaces, it was detected for up to 72 hours on plastic. However, it was less stable on copper, nonviable after 4 hours (19). The half-life of the virus drops to 1 hour with a temperature increase to 35 °C (18).

The potential source of viral transmission is the surfaces contaminated with respiratory droplets or other body fluids. The transmission occurs via contact of hands to the eye, mouth or nose, after accidentally touching the contaminated surface (12).Therefore, it is advisable to incorporate copper in furnishing facilities with a possibly high risk of contamination and implement strict sterilization measures in hospital settings (20).

4.3 Animal to Human Transmission

The emergence of COVID-19 from the Huanan seafood market in Wuhan city was attributed to a zoonotic origin. About 66% of cases diagnosed with COVID-19 were working or had visited the market, where they were exposed to wet animals (20). Evolving evidence shows an intermediate host as COVID-19 is rarely transmitted directly from bats(21). Pangolins, snakes, and some other mammals are considered to be potential intermediate carriers or reservoir hosts for an animal to human contraction of virus(22). However, there is no clear evidence to suggest that animal-human transmission plays a significant role in the transmission of COVID-19. Based on limited information, the USA CDC recommends applying the same isolation measures to domestic animals as a human household member.

In conclusion, the high infection rate estimated at the beginning of the outbreak ($R_0 = 2.2$) indicates that human-human transmission is the main transmission pattern(23). Surface to human transmission was also considered significant in spreading COVID-19(24). Based on these findings, international preventative guidelines and policies were generated, such as social distancing, covering mouth and nose with a mask, and frequent hand washing and sterilization (refer to Section 13)

5. Infectiousness and Transmissibility

The reproduction number (R_0) is an epidemiological metric to quantify the outbreak's intensity and monitor the effectiveness of applied control measures and interventions to mitigate the infection's spread. It measures the average number of cases in a population generated from one infected case within their infection period(2).

Undocumented infection significantly contributes to the infection's spread. It can put a larger portion of the population at risk of exposure.

Detection of infection in undocumented cases could reduce the overall spread. This can be achieved by contact tracing, proactive swabbing, and isolation of infected cases. In an uncontrolled situation, undocumented cases are estimated to reach 86% of all COVID-19 infections(25).

Countries' efforts, such as travel restrictions imposed between cities, quarantine, contact precautions, and population awareness, have reduced the rate of virus spread and decreased the burden on overextended health care systems.

Relative humidity, temperature, and wind speed are strong environmental determinants of other respiratory viral transmissions(26). The spread of COVID-19 is also impacted by climate indicators such as air quality and average to low temperature, as both are strongly associated with COVID-19 transmissions(27).

6. The Risk of Exposure To COVID-19 Infection

The risk of being exposed to the infection is not uniform between people (28). Social determinants of health came to be important factors contributing to the spread of COVID-19.

For instance, housing, neighbourhood, ethnicity, socio-economic status (SES), and occupation are essential factors that contribute to the spread of infection(28). A growing number of epidemiological studies show that the risk of transmission is unevenly distributed across different SES groups(29). People having a lower SES with poor housing are more prone to COVID-19 infection due to lack of preventive care and more impoverished living conditions(29).

Front line healthcare workers like nurses, doctors, janitors are susceptible to infection due to exposure to nosocomial infection in earlier stages of spread and inadequate or shortage of personal protective equipment. As they work closely with

asymptomatic or infected colleagues, the probability of infection is high. Also, low-skilled jobs like social, transport, food, sales, and retail workers exhibit a higher risk of infection (30)

Different behaviour patterns amongst genders put males at higher risk of infection with COVID-19 than females (31, 32)

The infection spread the most among Qatar's younger population, between 30 and 49 years old.

According to Qatar's population statistics, in December 2020, almost 73% of the population was between 25 and 64 years old. This age group is considered the working-age population and have higher socialization and mobility. Moreover, a significant part of this working-age population belongs to the working class with shared accommodation. This puts them at higher risk of transmitting the infection.

The spread of infection is different among different occupations. Those working in aviation, law enforcement, transportation or construction, were the most likely to be infected with SAR-CoV-2.

They are essential-workers in the community and need to work even in complete lockdowns, which potentially exposes them more to the virus.

7. Incubation Period and Serial Interval

Upon exposure to any source of infection, the person can become contagious. The time between exposure to the virus and symptom onset is the "incubation period" or "pre-symptomatic period." In the case of COVID-19, this period is estimated to be 5.7 days on average (99% CI 4.8 to 6.6) and can last for up to fourteen days(33). The time duration between an infector having symptom onset and a secondary case (infectee) having symptom onset is the "serial interval". It is a pivotal factor in measuring the reproduction number (R_0)(34). The serial interval is estimated to be 5 days, ranging between 4 to 13 days(33). Estimating the incubation period of SARS-CoV-2 contributes to developing public health interventions to reduce transmission (Section 13). So infected or suspected individuals are put under active monitoring or isolation for 14 days (32). However, the complication in containing the COVID-19 relies on the asymptomatic persons who are a silent carrier of the infection.

8. The severity of COVID-19 Infection and the Risk of Death

As the cases are rapidly increasing, it becomes mandatory to categorize the severity of infection to increase the healthcare infrastructure's preparedness—the WHO provided a clinical guideline to assign severity for COVID-19 hospitalized cases. In February 2020, an epidemiological study in China (35) analyzed more than 40,000 cases confirmed with COVID-19, 81% of cases had mild symptoms to which no hospitalization was required. Meanwhile, 14% and 5 % were severe and critical cases requiring hospitalization, respectively. However, during the early pandemic, the critical cases were overestimated(25).

Qatar's epidemiological study shows that most confirmed cases (91.7%) were asymptomatic or with minimal symptoms or mild illness with no pneumonia. Around 2% had a mild illness with pneumonia. Severe and critical cases account for 2% of total confirmed cases (9).

The spectrum of COVID-19 severity ranges between mild to critical, based on WHO classification of COVID-19 cases, and can result in death (36). Multiple factors can impact the severity of COVID-19 infection, including age, gender, comorbidities, and presenting symptoms (37). Many studies identified age as a significant factor that impacts severity. Patients over the age of 60 show higher severity and more protracted course of the disease than those aged <60 years(37). Older age is significantly associated with high severity of the disease, higher risk of admission to ICU, and a higher risk of death(37). Moreover, pre-existing comorbidities such as respiratory and cardiac diseases, diabetes mellitus, hypertension, obesity, and chronic kidney or liver disease are risk factors associated with higher severity of COVID-19 (36). In a meta-analysis, chronic obstructive pulmonary disease (COPD), respiratory disease, and cerebrovascular disease are the diseases with the largest effect sizes predicting the severity of COVID-19(38).

The first case of COVID-19 in Qatar was detected on 27/02/20. By the 29th of January, 2021, Qatar reported 150,280 confirmed cases, 145,414 recoveries, and 248 deaths. The case fatality rate (CFR) in Qatar (0.17%) is relatively low compared to the global estimate of COVID-19 CFR 0.02% (95% CI: 0.02% to 0.03%) (39). The CFR significantly differs by age (39). Qatar's low CFR is most likely attributed to the population's lower median age (32.3 years) and excellent healthcare infrastructure. The significantly lower infection rate than other countries was due to the immediate measures taken by Qatar's ministry of public health (MOPH). The measures included an immediate closure of academic institutions and travel restrictions to the worst-affected countries.

9. Immunity Following SARS-COV-2 Infection

Data on immunity following SARS-COV-2 infections are inadequate. Post-SARS-CoV-2 infection, the virus induces specific antibodies (AB) and cell-mediated responses, which are protective and continue for several months.

The mechanisms of this protection against COVID-19 and its exact duration are uncertain.

Concerning humoral immunity, it was found that antibodies to the receptor-binding domain (RBD) of the virus spike protein develop in the vast majority of patients with the associated virus-neutralizing activity(40).

In some patients, AB has been detected at the end of the first week of infection.

After four weeks, almost all patients have neutralizing AB(41)

The neutralizing ABs decline over time. According to some studies, the ABs persist for up to 6-8 months (32555424) (32555388)(32745196)(33408181).

Other studies suggested the potential for a long-term memory humoral immune response after detecting an increase in spike and RBD memory B cells a few months post-infection (33408181)(33115920).

However, this response's magnitude and duration may be related to disease severity; thus, patients with severe disease may have higher titers of ABs and longer detectable neutralizing ABs than those with mild illness or asymptomatic (33397909) (32663256).

The response did not appear to be affected by age, even after adjusting for the severity (33397909).

It is also worth noting that, following re-exposure to the virus, the immune memory will prompt rapid anamnestic AB response even if the level of neutralizing AB has declined below the detectable threshold.

This response likely offers protection against severe illness. Additionally, AB may prevent re-infection that causes severe disease rather than conferring sterilizing immunity (33397909).

People infected with the virus mount cellular immunity.

A durable T cell immune response has also been suggested after detecting specific CD4 and CD8 T cell responses in recovered people and those who received the investigational vaccine(42).

B cell immunity is also proposed after recovery from a mild or severe infection. **Memory B cells** appear not to wane as fast as serum ABs, suggesting long-term protection that relies on maintaining memory cells that can quickly reactivate with the second encounter .

Additionally, individuals can mount an effective immunity that can evolve following recovery, minimizing the possibility of re-infection within 6 months post-infection, even by some variant strains(43).

Studies have identified AB that neutralizes the virus and its reactive CD4 T cells in some people with unknown exposure status. Part of this response seems to be cross-reactive with common cold coronavirus antigens(44).

However, it is unknown if the pre-existing immune response influences the disease's risk or severity. The effect of such pre-existing immunity on an individual's response to the vaccine remains ambiguous.

Animal studies have shown that animals could be protected from covid-19 following prior infection or immune serum transfusion, although this did not offer sterilizing immunity(45).

It is also proposed that immune response to covid-19 infection may protect against re-infection for at least a few months(45). Studies that assessed animal vaccine candidates have suggested a lower level or faster viral RNA clearance in respiratory samples as a result of the immune response to vaccination after experimental viral challenge(46)

In line with the evidence from other parts of the world, data from Qatar showed that most COVID-19 cases developed ABs that remained detectable for over 3 months(47). The findings suggested that initial infection elicits immunity that lasts for at least a few months, which in turn may protect from re-infection(47).

10. Risk of Re-infection

Re-infection involves individuals who tested positive for SARS-CoV-2 and recovered, getting infected with a **genetically different strain of the virus**. This part of the virus's epidemiology is still poorly understood

Based on the current evidence, the risk of SARS-CoV-2 re-infection is low, less than 1% (48). However, re-infection can occur a few months after the initial infection. Sporadic cases of COVID-19 re-infection have been documented(49, 50), and the reported time between the first and second infections varied between 43 to 145 days(51).

A median interval of over 160 days is also reported.

Re-infection likely occurs as a function of increased exposure and waning immunity. Some re-infection cases had well tolerated or no symptoms, raising the possibility of attenuated severity due to the previous infection's immunity. Nevertheless, not all reported cases had less severe disease than the primary infection(50), and fatal re-infection has been documented (52).

Getting sicker with the second encounter could be due to a more potent second strain, infection with a higher viral load, or probably to a robust immune response triggered by ABs from the previous SARS-CoV-2 infection(51).

Another concern is that new SARS-CoV-2 variants have emerged that may circumvent the acquired immune protection and increase the risk of re-infection. Following wild-type virus infection, re-infection with the B.1.1.7 lineage (VOC202012/01) has been reported(53)

The frequency of re-infection and longevity of the immunity, especially with the new strains, are still unclear.

There is conclusive evidence of re-infection with few documented cases in Qatar. All had no or minimal symptoms during the first and second infections, and no fatality has been recorded (47). The gap between the initial and re-infection varied between 45 and 129 days.

The risk of re-infection (confirmed by genome sequencing) was estimated at 0.02%, with an estimated incidence rate of 0.36 per 10,000 person-weeks. This is an extremely low rate, considering Qatar's intense epidemic, where estimations proposed that half of the population have contracted the infection(47).

Repeated exposure to the same virus did not result in any documented re-infection.

This is possibly due to immunity against re-infection or merely a re-infection that went undocumented(47).

11. SARS-CoV-2 Variants of Concern

Since the COVID-19 pandemic started, **several variants of SARS-CoV-2** have been observed across the world. The most notable variants include those recently identified in the UK (B.1.1.7 lineage or Variant of Concern, the year 2020, month 12, variant 01 "VOC 202012/01"), South Africa (B.1.351 lineage or Variant 501Y.V2), and Brazil (Variant P.1 or 501Y.V3).

These three variants have resulted in a deterioration in the epidemiological situations by increasing the transmissibility of the virus or its ability to evade immunity. In effect, these **mutated variants** could increase the chance of re-infection.

The **SARS-CoV-2 variants** may show fast spread and higher transmissibility with a potential alteration in disease severity, straining the healthcare systems by increased resource utilization. Since limited information is currently available, more studies are urgently needed to address aspects of severity, re-infections, vaccination efficacy, the potential for immune evasion, and the impact on the epidemiology of the pandemic.

In particular, understanding these variants' implications on the future of vaccinations is essential.

As of 12/02/2021, none of the new variants has been identified in Qatar.

However, on the 3rd of February 2021, health **authorities expressed concerns** over the presence of these variants in the country, following detections in some neighboring Gulf countries.

12. Epidemic Curve for COVID-19

12.1 Global and Local Trends

An epidemic curve is a statistical chart aimed at describing the distribution of onset and progression of a disease outbreak over time. The epidemic curve for COVID-19, as reported by **World Health Organizations (WHO)**, shows the number of cases over time. Figure 1(a-b) below is based on official data of laboratory-confirmed COVID-19 cases and deaths reported to WHO by countries. The reporting was mainly based on **WHO case definitions and surveillance guidelines**.

12.1.1 Global Epidemic Curve

Figure 1(a) shows the daily distribution of new COVID-19 cases and new deaths (Figure 1(b)) as reported by **various WHO regions** from the 3rd of January 2020 to the 12th of February 2021.

We can divide the epidemic curve into four stages of the quasi-stationary time series period for analysis. The first stage, which was before March 2020, shows a small number of new confirmed COVID-19 cases, with the number of new cases ranging between less than 1,000 to 3,000 daily cases. However, the 13th of February 2020 was an exception when more than 15,000 were registered, with most cases reported from the Western Pacific region.

This is expected as the pandemic originated from Wuhan, China(8, 54).

The number of new positive COVID-19 cases increased consistently during the second stage of the pandemic, which started in March 2020. Resultantly, the epidemic curve reached more than 50,000 new cases on the 24th of March 2020 and more than 70,000 new cases on the 1st of April 2020. This was mainly due to the high number of new confirmed COVID-19 cases in Europe and the Americas (figure 1(a)).

Globally, on the 31st of March 2020, the total new confirmed cases were 791,863, with 460,861 from Europe and 163,014 new cases were from the Americas. These statistics also explain the exponential increase in the **number of global deaths**, which increased dramatically with less than 500 deaths (306 in Europe and 1 case in Americas) on the 15th of March 2020 to more than 12,500 deaths on the 17th of April 2020 (4,145 in Europe and 6,837 in Americas).

During June and July 2020, there was substantial growth in the **number of new cases** was reported. From 123,267 new cases on the 1st of June 2020 (cumulative number of confirmed new cases was 6,070,955), the numbers doubled to 248,541 new cases on the 23rd of July 2020 (cumulative number of confirmed new cases was 15,026,666).

The 3rd stage of the pandemic started on the 23rd of July and lasted till the 7th of October 2020.

During this period, a seasonality of 5 days was detected with a higher number of confirmed cases than the previous stage. The **number of deaths** seemed stationary with occasional peaks, mainly due to the high number of deaths from the Americas and South-East Asia with a minor contribution from Europe. Between the 23rd of July and the 7th of October 2020, the total number of deaths increased from 317,962 to 574,122 in the Americas, from 205,476 to 245,122 in Europe and from 37,203 to 122,474 in South-East Asia.

A sharp increase in the daily new confirmed cases was seen from the 8th of October to the 8th of November 2020, and the number of daily new cases increased from 360,280 to 602,521.

This was mainly due to the high increase in the number of new cases in Europe, i.e., from 119,390 new cases to 347,356 confirmed cases.

The pandemic's 4th stage was from the 9th of November 2020 till the 16th of January 2021. Globally, since the beginning of this pandemic, the highest number of daily new confirmed COVID-19 cases were registered during the 4th stage. With 843,250 new confirmed cases, the peak was observed on the 20th of December 2020. Most of these cases were from the Americas (511,893 cases) and Europe (247,892 cases).

Moreover, the number of **daily new deaths** also peaked with 16,639 deaths reported on 22nd January 2021, with Americas and Europe reporting most of these deaths with 8,537 and 6,087 deaths, respectively.

The epidemic curve decreased for the first time from the 17th of January 2021 onwards. Between the 17th of January 2021 to the 12th of February 2021, the number of daily new confirmed cases dropped from 743,856 cases (406,967 in the Americas and 241,497 in Europe) to 417,768 new cases (207,664 in the Americas and 174,171 in Europe). However, the number of daily new deaths was very high during the same period and was mainly due to the high number of deaths reported in the Americas and Europe.

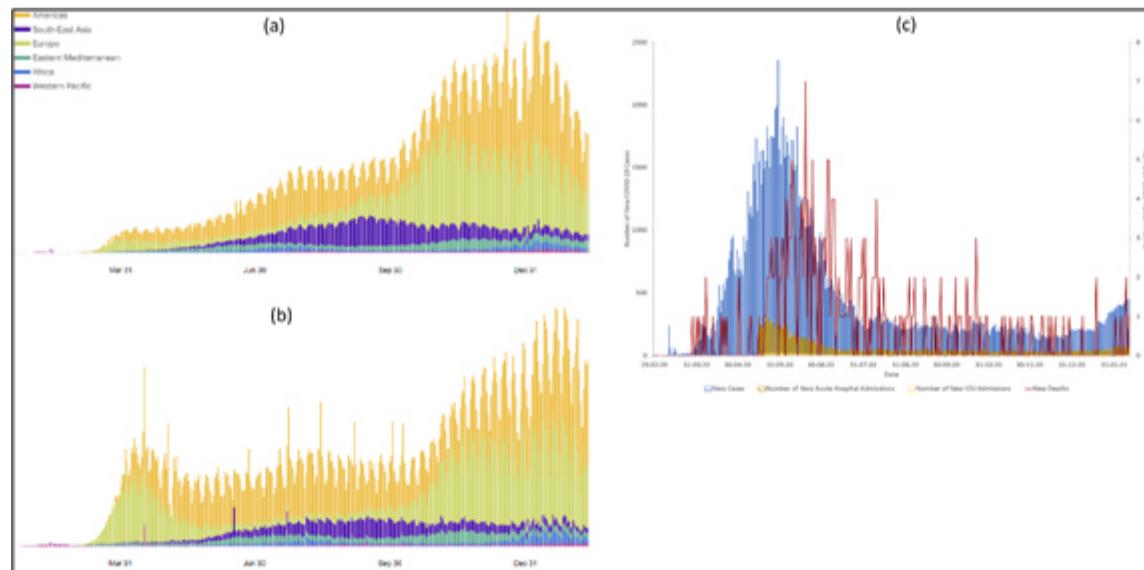


Figure 1: Global and locally COVID-19 epidemic curve and new registered daily deaths by **WHO regions**.

- (a) New COVID-19 cases reported daily by WHO region,
- (b) New COVID-19 deaths reported daily by WHO region and
- (c) Epidemic curve of Qatar with the daily distribution of new acute hospital admissions and new ICU admissions and daily number of deaths

12.2 Qatar Epidemic Curve

For Qatar, the epidemic curve in Figure 1(c) from the 29th of February 2020 to the 11th of February 2021 shows the number of daily new hospital and intensive care unit admissions on the first axis (Y-left axis in Figure 1(c)) along with the number of daily new deaths on the second axis (Y-right axis in Figure 1(c)). The data used to create this figure was collected from the [Qatar Open Data Portal](#).

The first local case of positive COVID-19 was registered on the 29th of February 2020. Qatar had exponential growth in daily new positive cases until its peak with 2355 new confirmed cases on the 30th of May 2020. During this period, there were a total of 55,262 confirmed cases in the country and a total of 36 news deaths.

The number of deaths reached a peak on the 19th of June 2020, with 7 deaths a day.

Since the 12th of August 2020, the number of deaths has been less than 3 per day.

On the other hand, the highest hospitalization period was reported from the 16th of May 2020 to the end of June 2020.

After reaching the peak on the 30th of May 2020, the number of daily new confirmed cases experienced a constant decrease, with less than 400 new cases reported since 22nd July 2020.

However, since January 2021, there has been a progressive increase in the number of new daily COVID-19 cases.

Overall, as of the 11th of February 2021, the total number of confirmed cases was 155,901 and 256 total deaths (Figure 1(c)).

13. Public Health Actions for Prevention and Control Of COVID-19

As the pandemic was spreading across the globe, and as severe cases and deaths were on the rise, one primary concern was at the forefront of the decision maker's agenda, namely, hospital capacity.

While reducing the infection rate is essential, the main driver is to avoid hospitalizations and eventually deaths, especially where resources are scarce.

With the absence of a vaccine or antiviral treatment, non-pharmaceutical public health measures targeting minimizing the virus's spread and avoiding the collapse of healthcare systems needed to be in place. These measures were to be implemented to ultimately enable timely treatment of severe complications and avoid deaths(55). Such measures have been historically adopted to control epidemics and reduce the spread of infectious diseases. These include isolation, quarantining, social distancing, and community containment strategies(56).

This section will discuss the use of these measures, their effectiveness, and their implications.

13.1 Isolation

- Isolation is defined as separating infected from uninfected individuals to reduce the disease's risk of transmission. However, this measure's effectiveness can be limited if those infected individuals have not been identified at an early stage. COVID-19 infected individuals are highly infectious during the first 4 to 7 days; hence isolation must be within this period(57, 58), (refer to section 7). In General, a well-coordinated surveillance system will need to be in place, by which early detection of cases derives the isolation strategy. The mass utilization of screening allowing infected individuals to be detected is essential for isolation to be effective(56).

13.2 Quarantining

Quarantining is defined as confining the movement of individuals who are suspected of having been exposed to a contagious disease. These individuals are not ill either because they are still within the incubation period of the disease or because they have not been infected(55). Quarantine is one of the oldest public health measures to control epidemics, and its effectiveness was previously demonstrated when it was implemented during the SARS epidemic in 2003(59). In the case of COVID-19, asymptomatic individuals may be contagious and will not be identified otherwise. Hence implementing this approach is vital as asymptomatic infections at initial testing for COVID-19 have been observed to be high and such individuals may contribute to the spread of COVID-19 substantially(60).

The quarantine can be implemented at the individual or group level by providing quarantine designated facilities or at an individual's own homes (32520287). However, like all others, this measure requires a high level of compliance to ensure effectiveness and detect a reduction in transmission of COVID-19.

During quarantine, individuals must be observed for symptoms.

If symptoms develop, the individuals must be isolated and treated. Like isolation, identifying suspected cases and further screening their contacts must take place rapidly for this measure to be most effective(61).

13.3 Social Distancing

Social distancing refers to public health interventions that reduce interactions within a community.

Social distancing may include infected individuals not yet identified(55).

Since COVID-19 transmission through respiratory droplets requires 2 to 4 meters of physical proximity (refer to section 7), a social distancing of that proximity will reduce transmission, which will lead to reduced infection.

According to the [CDC](#), a spacing of 6 ft (1.8 meters) decreases the spread of COVID-19.

In addition to maintaining a physical distance between individuals, social distancing can be implemented on the community level by the closure of schools, workplaces, business, leisure facilities and cancelling events that entail mass gatherings(56).

Social distancing is most effective when there are clusters of community transmission. In COVID-19, community transmission clusters have been observed(17). Total lockdown, which has been implemented in various countries worldwide, is an extreme type of social distancing. Lockdown is a rigorous public health intervention applied to a specific community, such as a city or a region, or even an entire country(55). This measure entails forbidding people from leaving their homes except for vital tasks. Implementation of community-wide lockdown measures is very complex, given the more significant number of individuals involved(56). Until COVID-19 vaccination is fully rolled out, social distancing remains the most effective measure to slow the infection rate and reduce the peak of incidence, which will translate to fewer hospitalizations and deaths(62).

13.4 The Use of Facemasks

Enforcing mask-wearing has been observed worldwide as an intervention to reduce COVID-19 transmission. Wearing a facemask has been shown to play an essential role in preventing both droplets and aerosols from transmitting the disease from an infected person to a host(63).

Facemasks effectively control and prevent transmission and have been previously implemented in response to the epidemics caused by SARS-CoV, MERS-CoV(64).

There is much debate regarding the types of facemasks and their effectiveness(64).

This debate stems from the variability in various masks' filtration efficiency. The efficiency depends on the filter features such as fibre diameter, a charge of fibres, packing density, filter thickness, and particle properties, such as diameter, density, and velocity(65). The surgical mask, N95 respirator, and elastomeric respirator have been widely used in many countries with varying levels of success against the SARS-CoV-2 virus(63). Surgical masks, which are more commonly used, prevent droplets from spreading.

N95 respirators prevent both droplets and aerosol transmission. Hence N95 is recommended for the population at risk, such as health care workers(66). When considering comfort and breathability, the N95 respirators are tight-fitting and have lower breathability than the surgical mask(67).

With these aspects discussed, it is worth stating that none of these masks provides guaranteed protection against SARS-CoV-2 which has a size ranging from 60 to 140 nm, smaller than bacteria, dust, and pollen. Masks made of cotton and synthetic fabric are ineffective due to large pore sizes(63).

Similarly, masks and respirators made of coated and water-resistant materials are less effective against smaller particles while providing better protection against large respiratory droplets and fluid spills(67).

For prevention and control measures among patients and HCW, refer to Hospital Management Chapter.

13.5 COVID-19 response in Qatar

The State of Qatar has put tremendous efforts into establishing well-informed public health strategies to respond to the COVID-19 pandemic. These strategies were scientifically informed and tailored to serve the country's unique demand.

13.5.1 Governance

After the first case was reported on the 29th of February 2020, a national committee for COVID-19 was established, chaired by Her Excellency, the public health minister. The committee comprised of senior members of other ministries and government decision-makers.

A detailed national response plan was produced, incorporating evidence and lessons learnt by other countries' experience and the international health organizations such as [WHO and CDC](#).

MOPH guided governmental entities, the public and both the public and private health sector, regarding the response to COVID-19.

To ensure clarity, accuracy, timely decision making, and effective operations, a health sector command structure was established, led by HMC and PHCC and supported by the private sector. Resources, including clinical staff, were mobilized to prepare for adequate hospital capacity.

This clear governance structure has enabled timely decisions based on evidence-based information and the development of protocols specific to Qatar.

13.5.2 Public Health Measures

Based on the [National Response plan](#), the first public health step was to prepare health services in term of capacity by; establishing an inventory of essential medical supplies, including PEE.

The plan involved educating and training medical staff on various aspects of COVID-19 and awareness campaigns for the public.

This step was followed by setting up a thorough surveillance and detection system to ensure early diagnosis.

A robust surveillance system aids in getting real-time information.

This information is vital to contain outbreaks.

The testing strategy included home community testing, contact tracing, a port of entry screening, and investigating clusters and outbreaks.

This was followed by the response and containment phase, which is designed to limit the spread of the COVID-19 outbreak and ensure that the health system is supported with guidelines that ensure sufficient capacity to treat severe cases on a large scale.

Home isolation was mandated for cases, and mandatory quarantine was introduced for contacts. Transportation protocols were established for infected and suspected cases.

Home health care monitored people with chronic conditions and handled medication refills.

The committee also established repatriation guidelines for citizens and residents. Activities to prevent community infections were introduced, such as cancellation of the fingerprint system, advice on the proper use of PPE, hygiene and sanitation protocols.

The plan's final phase was to return to business as usual and document the gaps and lessons learned to support future responses. This stage included establishing discharge and recovery definitions and pathways.

The committee also conducted a review of the capacity of home care services, business continuity plans, and risk-informed plan for public health measures. Key performance indicators were generated for monitoring and evaluating Qatar's response.

13.5.3 Research and Technology

Given the fast-evolving nature of the pandemic, research has become more time-critical than ever. Research provided insight into the nature of transmission, exposure, and the virus's behaviour with direct implications on capacity requirements, clinical practice, and therapeutic guidelines. The MOPH has established formal links to the relevant national health and academic organizations and has established the scientific reference and research taskforce (SRRT) to advise on the strategic response to COVID-19, based on scientific evidence and any new relevant development. This committee was also mandated to define Qatar's specific research areas according to WHO's international research framework. As an example of the SRRT work, a novel finding concerning CT (cycle threshold) values has been implemented as a proxy of severity and infectiousness. The CT value was used in updating the isolation policy. Furthermore, research efforts are well on the way to finalize the COVID-19 database. This database is generated based on WHO COVID-19 epidemiological minimum dataset. Several months of data collection and preparation have taken place, and current arrangements are made to enable researchers from various institutions in Qatar to access and utilize this data. Qatar has employed technological advancements and designed and built a telephone application (EHTERAZ) monitored by the Ministry of Interior (MOI). This application is used to monitor the pandemic digitally, enables strict observation of individuals under isolation and quarantine, including incoming travellers, and ensures that public spaces have no infected individuals.

14. Discussion

COVID-19 pandemic has resulted in an unprecedented strain on resources and public health responses revisions. Early on in the pandemic, public health measures helped decrease the healthcare system's burden by delaying the pandemics' peak to give healthcare systems time to commit more resources to COVID-19(62). These interventions, including country-wide lockdowns and social distancing, minimized human contact to limit social interaction, break the transmission chain, and reduce the new COVID-19 cases(65). Strategies differ globally, but the most effective public health measures include sufficient testing, swift isolation, contact tracing, and quarantining of all contacts(68). A selective test, trace, and quarantine strategy can be applied from a cost-effectiveness perspective if social distancing is challenging(68). Epidemiological and other disease parameters are the basis for designing response strategies. With a new disease, some uncertainty level is inevitable(69). Most of the global and national response was designed based on various modelling techniques. These models are used to assess the dynamics of the spread of COVID-19, predict its future course and evaluate the impact of different control measures(70). Studies show that compartmental and statistical growth models are the most popular modelling techniques to predict COVID-19 dynamics(70). A systematic review assessing the accuracy of modelling techniques has found that 1/3 of the models overestimated and 1/3 underestimated predictions(70). This highlights the importance of improving modelling techniques to ensure data accuracy. In addition to the epidemiologic perspective, the pandemic's socio-economic and cultural impacts need consideration. The global response has been variable in addressing infected and non-infected individuals' needs. Some countries have reported food insecurity, economic difficulties, and reduced access to health among the pandemic's negative social consequences(71). Cultural norms may expose individuals to high-risk activities(72). Policymakers need to be aware of the cultural norms and design policies accordingly(72). The economy has also been negatively affected by the global COVID-19 response. Flight cancellations lost sales, and service reductions across industries are some examples. The negative social and economic consequences of long-term social distancing-based responses may heavily burden countries with a larger public health emergency(71). Therefore, policymakers must continuously evaluate the effects of any public health measures to achieve the best possible equilibrium(61). Compliance with public health measures is critical to ensure optimal results. Most people may comply out of fear of contracting the infection, but is fear alone enough? Behavioural psychology theorists argue that an individual may not comply with public health recommendations in the absence of punishment as he sees no personal gain. Compliance will only occur if an individual cares about collective well-being and expects others to comply(73). Compliance is fundamental to the success of public health response strategies to COVID-19. Hence these strategies must prioritize measures with high expected compliance over others to ensure the best results. The world faces a pandemic. Asymptomatic, pre-symptomatic, or patients with mild symptoms can transmit the disease. Severe forms of the disease tend to affect the elderly and those with underlying chronic diseases, requiring hospitalization, intensive care, and mechanical ventilation. Different public health response strategies have been implemented to reduce the infection rate, protect the at-risk population, and reduce hospitalizations and deaths. The measures are eased off and switched back according to the epidemic curve. Most countries have benefitted from these measures (mainly social distance-based) reflected by the flattening of the curve. However, prolonged periods of social distancing and limiting social interactions may result in economic damage, long-term psychological impact, and societal malfunction. With the recent development of vaccines, there is hope to gradually go back to "normal". However, there are still several milestones to reach, such as the equitable distribution of vaccines, prioritizing the most vulnerable groups, and eventually achieving universal immunity.

Reference

1. Dorward J, Khubone T, Gate K, Ngobese H, Sookrajh Y, Mkhize S, et al. The impact of the COVID-19 lockdown on HIV care in 65 South African primary care clinics: an interrupted time series analysis. *Lancet HIV*. 2021;8(3):e158-e65.
2. Delamater PL, Street EJ, Leslie TF, Yang YT, Jacobsen KH. Complexity of the Basic Reproduction Number (R_0). *Emerg Infect Dis*. 2019;25(1):1-4.
3. Gianicolo E, Riccetti N, Blettner M, Karch A. Epidemiological Measures in the Context of the COVID-19 Pandemic. *Dtsch Arztebl Int*. 2020;117(19):336-42.
4. Rai B, Shukla A, Dwivedi LK. Estimates of serial interval for COVID-19: A systematic review and meta-analysis. *Clin Epidemiol Glob Health*. 2021;9:157-61.
5. Sun J, He WT, Wang L, Lai A, Ji X, Zhai X, et al. COVID-19: Epidemiology, Evolution, and Cross-Disciplinary Perspectives. *Trends Mol Med*. 2020;26(5):483-95.
6. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol*. 2020;92(4):401-2.
7. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-42.
8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-9.
9. Al Kuwari HM, Abdul Rahim HF, Abu-Raddad LJ, Abou-Samra AB, Al Kanaani Z, Al Khal A, et al. Epidemiological investigation of the first 5685 cases of SARS-CoV-2 infection in Qatar, 28 February-18 April 2020. *BMJ Open*. 2020;10(10):e040428.
10. Abu-Raddad LJ, Chemaiteily H, Ayoub HH, Al Kanaani Z, Al Khal A, Al Kuwari E, et al. Characterizing the Qatar advanced-phase SARS-CoV-2 epidemic. *Sci Rep*. 2021;11(1):6233.
11. Adeniran JA, Mohammed IA, Muniru OI, Oloyede T, Sonibare OO, Yusuf MO, et al. Indoor transmission dynamics of expired SARS-CoV-2 virus in a model African hospital ward. *J Environ Health Sci Eng*. 2021;1:1-11.
12. Vella F, Senia P, Ceccarelli M, Vitale E, Maltezou H, Taibi R, et al. Transmission mode associated with coronavirus disease 2019: a review. *Eur Rev Med Pharmacol Sci*. 2020;24(14):7889-904.
13. Sun C, Zhai Z. The efficacy of social distance and ventilation effectiveness in preventing COVID-19 transmission. *Sustain Cities Soc*. 2020;62:102390.
14. Jones NR, Qureshi ZU, Temple RJ, Larwood JPJ, Greenhalgh T, Bourouiba L. Two metres or one: what is the evidence for physical distancing in covid-19? *BMJ*. 2020;370:m3223.
15. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020;395(10223):514-23.
16. Kutti-Sridharan G, Vegunta R, Vegunta R, Mohan BP, Rokkam VRP. SARS-CoV2 in Different Body Fluids, Risks of Transmission, and Preventing COVID-19: A Comprehensive Evidence-Based Review. *Int J Prev Med*. 2020;11:97.
17. Special Expert Group for Control of the Epidemic of Novel Coronavirus Pneumonia of the Chinese Preventive Medicine A. [An update on the epidemiological characteristics of novel coronavirus pneumonia (COVID-19)]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;41(2):139-44.
18. Biryukov J, Boydston JA, Dunning RA, Yeager JJ, Wood S, Reese AL, et al. Increasing Temperature and Relative Humidity Accelerates Inactivation of SARS-CoV-2 on Surfaces. *mSphere*. 2020;5(4).
19. Suman R, Javaid M, Haleem A, Vaishya R, Bahl S, Nandan D. Sustainability of Coronavirus on Different Surfaces. *J Clin Exp Hepatol*. 2020;10(4):386-90.
20. Karpanen TJ, Casey AL, Lambert PA, Cookson BD, Nightingale P, Miruszenko L, et al. The antimicrobial efficacy of copper alloy furnishing in the clinical environment: a crossover study. *Infect Control Hosp Epidemiol*. 2012;33(1):3-9.
21. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*. 2020;109:102433.
22. Ji W, Wang W, Zhao X, Zai J, Li X. Cross-species transmission of the newly identified coronavirus 2019-nCoV. *J Med Virol*. 2020;92(4):433-40.
23. Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. *Euro Surveill*. 2020;25(4).
24. Lenarcic B, Kos J, Dolenc I, Lucovnik P, Krizaj I, Turk V. Cathepsin D inactivates cysteine proteinase inhibitors, cystatins. *Biochem Biophys Res Commun*. 1988;154(2):765-72.
25. Li R, Pei S, Chen B, Song Y, Zhang T, Yang W, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). *Science*. 2020;368(6490):489-93.
26. Yuan J, Yun H, Lan W, Wang W, Sullivan SG, Jia S, et al. A climatologic investigation of the SARS-CoV outbreak in Beijing, China. *Am J Infect Control*. 2006;34(4):234-6.
27. Bashir MF, Ma B, Bilal, Komal B, Bashir MA, Tan D, et al. Correlation between climate indicators and COVID-19 pandemic in New York, USA. *Sci Total Environ*. 2020;728:138835.
28. Karaye IM, Horney JA. The Impact of Social Vulnerability on COVID-19 in the U.S.: An Analysis of Spatially Varying Relationships. *Am J Prev Med*. 2020;59(3):317-25.
29. Baggett TP, Keyes H, Sporn N, Gaeta JM. Prevalence of SARS-CoV-2 Infection in Residents of a Large Homeless Shelter in Boston. *JAMA*. 2020;323(21):2191-2.
30. Dyal JW, Grant MP, Broadwater K, Bjork A, Waltenburg MA, Gibbins JD, et al. COVID-19 Among Workers in Meat and Poultry Processing Facilities - 19 States, April 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(18).
31. de la Vega R, Ruiz-Barquin R, Boros S, Szabo A. Could attitudes toward COVID-19 in Spain render men more vulnerable than women? *Glob Public Health*. 2020;15(9):1278-91.
32. Bwire GM. Coronavirus: Why Men are More Vulnerable to Covid-19 Than Women? *SN Compr Clin Med*. 2020;1:1-3.
33. Yang L, Dai J, Zhao J, Wang Y, Deng P, Wang J. Estimation of incubation period and serial interval of COVID-19: analysis of 178 cases and 131 transmission chains in Hubei province, China. *Epidemiol Infect*. 2020;148:e117.
34. Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. *Proc Biol Sci*. 2007;274(1609):599-604.
35. Epidemiology Working Group for Ncip Epidemic Response CCfDC, Prevention. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;41(2):145-51.
36. Bai J, Shi F, Cao J, Wen H, Wang F, Mubarik S, et al. The epidemiological characteristics of deaths with COVID-19 in the early stage of epidemic in Wuhan, China. *Glob Health Res Policy*. 2020;5(1):54.
37. Sim BLH, Chidambaram SK, Wong XC, Pathmanathan MD, Peariasamy KM, Hor CP, et al. Clinical characteristics and risk factors for severe COVID-19 infections in Malaysia: A nationwide observational study. *Lancet Reg Health West Pac*. 2020;4:100055.
38. Fang X, Li S, Yu H, Wang P, Zhang Y, Chen Z, et al. Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis. *Aging (Albany NY)*. 2020;12(13):12493-503.
39. Khalili M, Karamouzian M, Nasiri N, Javadi S, Mirzazadeh A, Sharifi H. Epidemiological characteristics of COVID-19: a systematic review and meta-analysis. *Epidemiol Infect*. 2020;148:e130.
40. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med*. 2020;26(5):672-5.

41. Wang X, Guo X, Xin Q, Pan Y, Hu Y, Li J, et al. Neutralizing Antibody Responses to Severe Acute Respiratory Syndrome Coronavirus 2 in Coronavirus Disease 2019 Inpatients and Convalescent Patients. *Clin Infect Dis.* 2020;71(10):2688-94.
42. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. *Cell.* 2020;181(7):1489-501 e15.
43. Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, et al. Evolution of antibody immunity to SARS-CoV-2. *Nature.* 2021;591(7851):639-44.
44. Mateus J, Grifoni A, Tarke A, Sidney J, Ramirez SI, Dan JM, et al. Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. *Science.* 2020;370(6512):89-94.
45. Chandrashekhar A, Liu J, Martinot AJ, McMahan K, Mercado NB, Peter L, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. *Science.* 2020;369(6505):812-7.
46. Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. *N Engl J Med.* 2020;383(16):1544-55.
47. Abu-Raddad LJ, Chemaitelly H, Malek JA, Ahmed AA, Mohamoud YA, Younuskunju S, et al. Assessment of the risk of SARS-CoV-2 reinfection in an intense re-exposure setting. *Clin Infect Dis.* 2020.
48. Ledford H. COVID reinfections are unusual - but could still help the virus to spread. *Nature.* 2021.
49. Gupta V, Bhoyar RC, Jain A, Srivastava S, Upadhyay R, Imran M, et al. Asymptomatic reinfection in two healthcare workers from India with genetically distinct SARS-CoV-2. *Clin Infect Dis.* 2020.
50. Lee JS, Kim SY, Kim TS, Hong KH, Ryoo NH, Lee J, et al. Evidence of Severe Acute Respiratory Syndrome Coronavirus 2 Reinfection After Recovery from Mild Coronavirus Disease 2019. *Clin Infect Dis.* 2020.
51. To KK, Hung IF, Ip JD, Chu AW, Chan WM, Tam AR, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. *Clin Infect Dis.* 2020.
52. Mulder M, van der Vegt D, Oude Munnink BB, GeurtsvanKessel CH, van de Bovenkamp J, Sikkema RS, et al. Reinfection of SARS-CoV-2 in an immunocompromised patient: a case report. *Clin Infect Dis.* 2020.
53. Harrington D, Kele B, Pereira S, Couto-Parada X, Riddell A, Forbes S, et al. Confirmed Reinfection with SARS-CoV-2 Variant VOC-202012/01. *Clin Infect Dis.* 2021.
54. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.
55. Aquino EML, Silveira IH, Pescarini JM, Aquino R, Souza-Filho JA, Rocha AS, et al. Social distancing measures to control the COVID-19 pandemic: potential impacts and challenges in Brazil. *Cien Saude Colet.* 2020;25(suppl 1):2423-46.
56. Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. *J Travel Med.* 2020;27(2).
57. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol.* 2020;92(6):568-76.
58. Kraemer MUG, Yang CH, Gutierrez B, Wu CH, Klein B, Pigott DM, et al. The effect of human mobility and control measures on the COVID-19 epidemic in China. *medRxiv.* 2020.
59. May CR. Baclofen overdose. *Ann Emerg Med.* 1983;12(3):171-3.
60. Yanes-Lane M, Winters N, Fregonese F, Bastos M, Perlman-Arrow S, Campbell JR, et al. Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: A systematic review and meta-analysis. *PLoS One.* 2020;15(11):e0241536.
61. Mayr V, Nussbaumer-Streit B, Gartlehner G. [Quarantine Alone or in Combination with Other Public Health Measures to Control COVID-19: A Rapid Review (Review)]. *Gesundheitswesen.* 2020;82(6):501-6.
62. Sen-Crowe B, McKenney M, Elkbuli A. Social distancing during the COVID-19 pandemic: Staying home save lives. *Am J Emerg Med.* 2020;38(7):1519-20.
63. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. *Environ Res.* 2020;188:109819.
64. Long Y, Hu T, Liu L, Chen R, Guo Q, Yang L, et al. Effectiveness of N95 respirators versus surgical masks against influenza: A systematic review and meta-analysis. *J Evid Based Med.* 2020;13(2):93-101.
65. Balachandar V, Mahalaxmi I, Kaavya J, Vivekanandhan G, Ajithkumar S, Arul N, et al. COVID-19: emerging protective measures. *Eur Rev Med Pharmacol Sci.* 2020;24(6):3422-5.
66. Leung WWF, Sun Q. Electrostatic charged nanofiber filter for filtering airborne novel coronavirus (COVID-19) and nano-aerosols. *Sep Purif Technol.* 2020;250:116886.
67. Chua MH, Cheng W, Goh SS, Kong J, Li B, Lim JYC, et al. Face Masks in the New COVID-19 Normal: Materials, Testing, and Perspectives. *Research (Wash D C).* 2020;2020:7286735.
68. Amaku M, Covas DT, Bezerra Coutinho FA, Azevedo Neto RS, Struchiner C, Wilder-Smith A, et al. Modelling the test, trace and quarantine strategy to control the COVID-19 epidemic in the state of São Paulo, Brazil. *Infect Dis Model.* 2021;6:46-55.
69. Meidan D, Schulmann N, Cohen R, Haber S, Yaniv E, Sarid R, et al. Alternating quarantine for sustainable epidemic mitigation. *Nat Commun.* 2021;12(1):220.
70. Gnani JE, Salako KV, Kotanmi GB, Glele Kakai R. On the reliability of predictions on Covid-19 dynamics: A systematic and critical review of modelling techniques. *Infect Dis Model.* 2021;6:258-72.
71. Chu IY, Alam P, Larson HJ, Lin L. Social consequences of mass quarantine during epidemics: a systematic review with implications for the COVID-19 response. *J Travel Med.* 2020;27(7).
72. Bruns DP, Kraguljac NV, Bruns TR. COVID-19: Facts, Cultural Considerations, and Risk of Stigmatization. *J Transcult Nurs.* 2020;31(4):326-32.
73. Barrios JM, Benmelech E, Hochberg YV, Sapienza P, Zingales L. Civic capital and social distancing during the Covid-19 pandemic(). *J Public Econ.* 2021;193:104310.

[Home](#)
[Forward message](#)
[Introduction](#)
[Chapters](#)
[Editors team](#)
[Contact us](#)



Copyright © 2022 Ministry of Public Health. All rights reserved.





Hospital Management and Service

Chapter: System Response

Hospital Management and Service Configuration During Pandemics

Lead: Dr Mohamed Gaafar Mohamedali

Contributors: Dr Tanweer Hussain, Dr Manish Barman, Dr Ahmad A/latif Abujaber, Dr Mehdi Moh. Errayes, Mr Junaid Abu, Dr Hatem Abusriwil, Dr Memon Noor Illahi, Dr Magdi Hassan Osman Abdel Rahman, Mr Ali Mousa Alnaimat, Dr Muayad Kasem Khaled Ahmad, Mr Hussein Ishaq, Dr Ahmed Ali Al-Mohammed

Table of Contents

- [List of figures](#)
- [List of tables](#)
- [Abstract](#)
- [Review of literature](#)
- [The Importance of Designing Pandemic Strategies](#)
- [Experience in Qatar](#)
- [New and Repurposed Facilities](#)
- [Emergency Department](#)
- [Other coordinated efforts](#)
- [Local response](#)
- [System wide response](#)
- [Challenges](#)
- [Telemedicine](#)
- [Discussion and future challenges](#)
- [Results](#)
- [Conclusions](#)
- [What is next](#)
- [Lessons learned](#)
- [Acknowledgements](#)
- [Abbreviations](#)
- [References](#)

List of Figures

- Figure 1: Key levels for outbreak management (8)
- Figure 2: The framework of system governance and leadership
- Figure 3: Action framework for control of pandemic COVID-19
- Figure 4: The three-tier process: strategic, tactical and operational
- Figure 5: The Go-No Go commissioning plan
- Figure 6: HMGH COVID-19 ED statistics for March–June 2020

List of Tables

- Table 1: Details of master go-live schedule
- Table 2: Details of critical care/inpatient (IP) bed capacity increase at HMGH
- Table 3: Hospital roles and responsibilities
- Table 4: Patient illness severity and management

Abstract

Background

Hospitals and other healthcare facilities play a critical role in national and local responses to disaster management and communicable disease epidemics. This review intends to highlight how a nodal-designated COVID-19 centre in Qatar, under the guidance of a national leadership team, effectively adapted to its specific challenges by building on existing knowledge, practice, capabilities and capacity, the health system and the community.

It managed to control the menace by altering its priorities and work routines to mount a coordinated, systemic response to a rapidly evolving, potentially complex situation.

Hazm Mebaireek General Hospital (HMGH), as part of an integrated delivery system of Hamad Medical Corporation, Qatar (HMC) was designated as a nodal COVID-19 centre as soon as the outbreak was confirmed in Qatar near the end of February 2020.

It was a challenge to improve the care of and experience for COVID-19 patients visiting the hospital.

This initiative included the building and implementation of evidence-based protocols by assigning a physician-led team to research, strategize and organize improved patient flow and communication by deploying analytics to provide near real-time feedback on compliance and performance.

Through these ongoing efforts, HMGH has realised significant outcome improvements, such as increasing capacity building, reducing healthcare waste and increasing patient satisfaction rates whilst successfully achieving one of the lowest COVID-19 mortality rates in the world.

Methods

This is a retrospective review of the institutional policy implementation and institutional frameworks during the COVID-19 pandemic, characterizing the service approach with the aim to understand and improve regulatory and policy options that advance pandemic management strategic objectives.

Conclusions

In healthcare policy and strategy formation, there are only trade-offs, which with uncertainty are akin to gambles. National organizations play a key role in pandemics through expression of physician motivation.

Effective strategies can facilitate physician action through economies of scale that lower the costs for physicians to meet both community and patient needs.

Moreover, no matter how well clinicians are motivated and positioned to act, their collective actions are likely to fall short without complementary systems for population-based care that require the operational support of an organization.

As we have been recently reminded, our healthcare organization with its healthcare professionals in Qatar are a good bet.

The strategies outlined in this article might not be all-inclusive or fit other models of healthcare system, but they generate a veritable interest to pursue and be subjected to further rigorous study.

Keywords: population health, quality and process improvements, outcomes, health policy, pandemic, teamwork, human factors, COVID-19.

Review of Literature

The global impact of the COVID-19 pandemic on healthcare systems across the world has led to major and rapid changes in the provision of efficient and value-based care whilst expanding delivery modules through varied approaches.

The coping strategy formulations are usually tailored to individual healthcare systems (1).

In a recent synthesis of the global response to the COVID-19 pandemic, most healthcare systems tried their best to rapidly deploy analytics best suited to their population at large to regulate the pandemic (2).

The differences, however, were attributed to the available resources, including healthcare workers.

The literature highlights the importance of iteratively designing strategies to ensure that the development, delivery and implementation of care processes are optimized to a specific local context.

This requires effective planning and risk analysis tools to understand the complexities of risk occurrence, healthcare preparedness and impact on public health to create a collaborative team and design executable strategies in accordance to perceived risks and benefits (3).

Moreover, it involves an ongoing understanding and needs assessment of the healthcare system and individual facilities (4).

Collaborative and synergistic interactions between government and the healthcare sector enhances the capacities and capabilities to protect population health (5).

The COVID-19 pandemic posed multiple challenges for major healthcare organizations, including insufficient capabilities, supply chain difficulties, medical goods shortages, the need to reinvent care and financial loss.

Providing non-COVID-19 clinical care during the pandemic was another acute challenge, and guidelines have been continually evolving and being published (4).

Herein, it is important to realize that the healthcare sector is an adaptive structure that functions in an environment that is highly complex and unpredictable.

During the crisis, this sector used communication, coordination and creativity as its tools to respond to the pandemic.

This was carried out expeditiously and was ably supported by knowledge and evidence from the frontline.

Establishments deviated from many conventional practices as the challenge grew, and the emergence of new leaders, combined with the modesty of current leaders, encouraged timely developments (6).

The Importance of Designing Pandemic Strategies

In preparing for and responding to any pandemic, the guiding principles remain the same. We need to perform dynamic risk assessments using the available scientific evidence for decision-making to slow the spread and reduce infection, illness, and death.

The goal is to share scientific information to support international efforts and to minimize the potential impact on society and the global economy, including key public services, whilst providing a dignified treatment of all affected, including those that die (7).

Designing effective strategies requires careful consideration of many interrelated factors. The factors include the previous experience and population participation, the experience of the providers, the available technology, political flexibility and resource prioritization and arrangements.

All these factors are unique to a specific local context, and optimization requires a close alignment between the different factors within each context and plays an important part of redesigning model of care.

Several recent open-access practical articles have been produced that offer best practice recommendations from development to delivery and implementation, including recommendations for meeting the increased challenges in low and middle-income countries.

The concerns mainly relate to use of a rapid iterative design method, such as action research or educational design research, to ensure that each phase of the development, delivery and implementation process can be modified in response to the comments and evaluations from all the stakeholders in an ongoing unpredictable scenario.

This methodology needs to have rapid cyclical evaluation because each evaluation will determine the strategy of the next phase. This 'fine-tuning' approach allows the progressive refinement of each phase to ensure that there is an effective alignment of the factors that are specific to the context. The active participation of all stakeholders is essential to ensure that a range of different perspectives can inform the design.

During pandemics, a coordinated and multidisciplinary management between various agencies and the workforce is of paramount importance to produce optimal care (Fig. 1) and ideal logistics.

With the day-to-day evolution of new evidence-based scientific information, it is necessary to adapt in real time to new data and guidelines being shared at a rapid pace.

Education and frequent training need to be regularly organized for frontline staff to ensure up-to-date information and training on personal protective equipment (PPE) and the clinical management of patients (8).

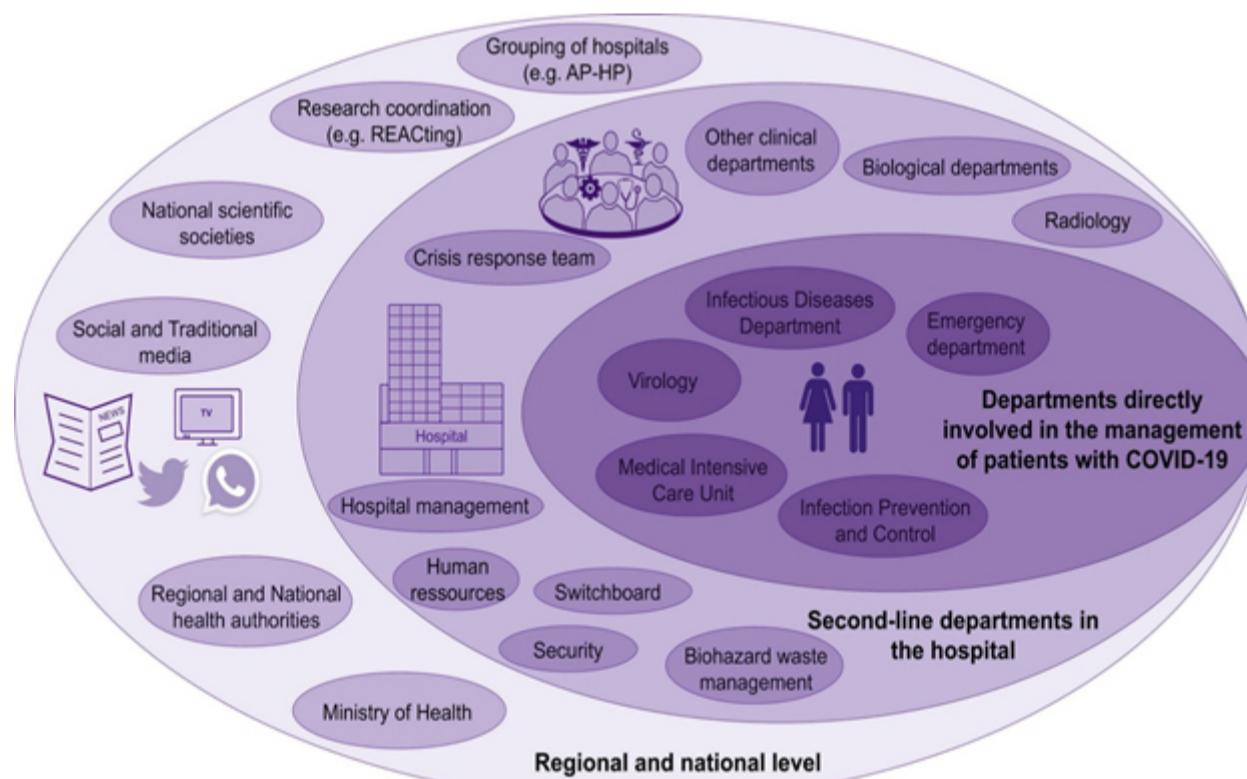


Figure 1: Key levels for outbreak management (8)

As societies aim to 'flatten the curve', COVID-19 has modified social expectations and human behaviour in significant ways. As a result, public policy strategies were developed to reduce the effects on the healthcare system of a 'surge' of patients who needed hospitalisation (9). In early March 2020, the Qatar government rolled out an action plan to ensure the well-being of its residents.

This included a detailed roadmap for response preparedness, monitoring and the road to recovery from COVID-19 (10) based on the World Health Organization's (WHO) recommended pillars of country-level coordination, risk stratification, surveillance, capacity building, infection control, case management and logistical support (11).

Interim guidelines were also published later by WHO on risk communication and community participation (RCCE), detailing checklists for preparedness and initial responses to the 2019 novel coronavirus (2019-nCoV) with an aim to provide evidence-based advice for implementing effective RCCE strategies to help protect public health (12).

Experience in Qatar

Introduction

The Process

In the last two decades, major emergency plans were developed and modified during the localized pandemics, such as H1N1, SAR-COV1, MERS, and Ebola. These emergency plans are a part of the facility management program for hospitals to handle pandemics. However, the nature of the COVID-19 pandemic was different because previous pandemics were limited to certain geographic locations or a subset of the population. Although the COVID-19 pandemic created a fluid environment in which information about the virus was limited, the frontline hospitals had to be ready to handle the potential influx of patients needing care.

Therefore, HMC's System-Wide Incident Command Committee (SWICC), under the direction of H. E. Dr Hanan, decided to use the newly commissioned hospital, HMGH, to handle COVID-19 along with the Communicable Disease Centre(CDC). The framework of system governance and leadership (Fig. 2, 3) was developed to ensure multidirectional communication.

The integral components are collaboration, standardization, coordination, real-time feedback, transparency and safety, and empowerment to ensure a safe patient care environment.

This system has been the foundation of all the procedures and processes at HMGH.

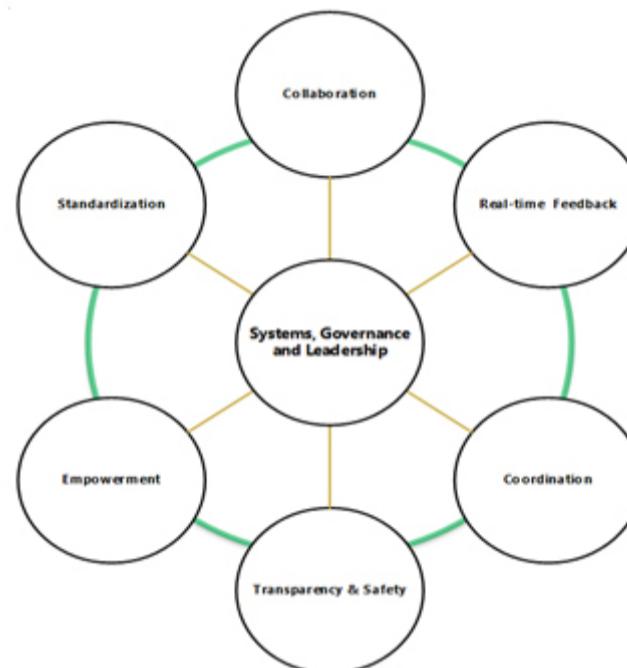


Figure 2: The framework of system governance and leadership

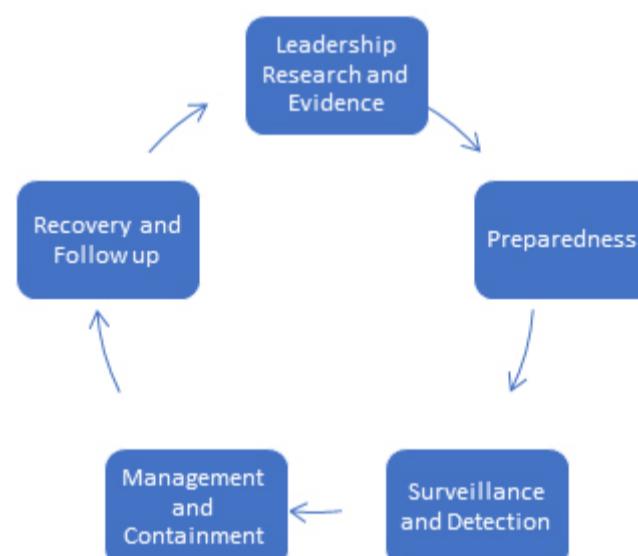


Figure 3: Action framework for control of pandemic COVID-19

New and Repurposed Facilities

In March, as the pandemic escalated, HMGH was designated a COVID-19 facility. Shortly after, four new hospitals, Ras Laffan Hospital, Mesaieed Hospital, ILeksayyer Field Hospital, and the Field Hospital Old Industrial Area, were also commissioned. The Cuban Hospital was also designated a COVID-19 facility. This is in addition to the quarantine facilities that were established.

Teams across the organization worked around the clock to have these hospitals open and ready for patients.

The rapid transformation of HMGH into a COVID-19 treatment facility is an example of the healthcare sector's proactive approach to confront this pandemic.

COVID-19 Testing Regime

As the central laboratory in Qatar, Department of Laboratory Medicine and Pathology (DLMP) teams were deputed to work around the clock to process the anticipated large volume of COVID-19 tests required in Qatar every day. To handle this demand, the DLMP significantly increased the number of tests they could process and reduced the time taken to analyse and release results.

Services Transformed

The strategic, tactical, and operational three-tier process (Fig. 4) was used to provide a unified approach to handle the COVID-19 pandemic response in Qatar. The national response priorities were established at the National Command Centre (NCC) where multiple governmental agencies, along with the Ministry of Public Health (MOPH), played a role in ensuring that all resources were available to provide a world-class response to the COVID-19 pandemic. At the tactical level, HMC, through the SWICC, developed the scope of service for each frontline COVID-19 hospital to unify pandemic response as a system.

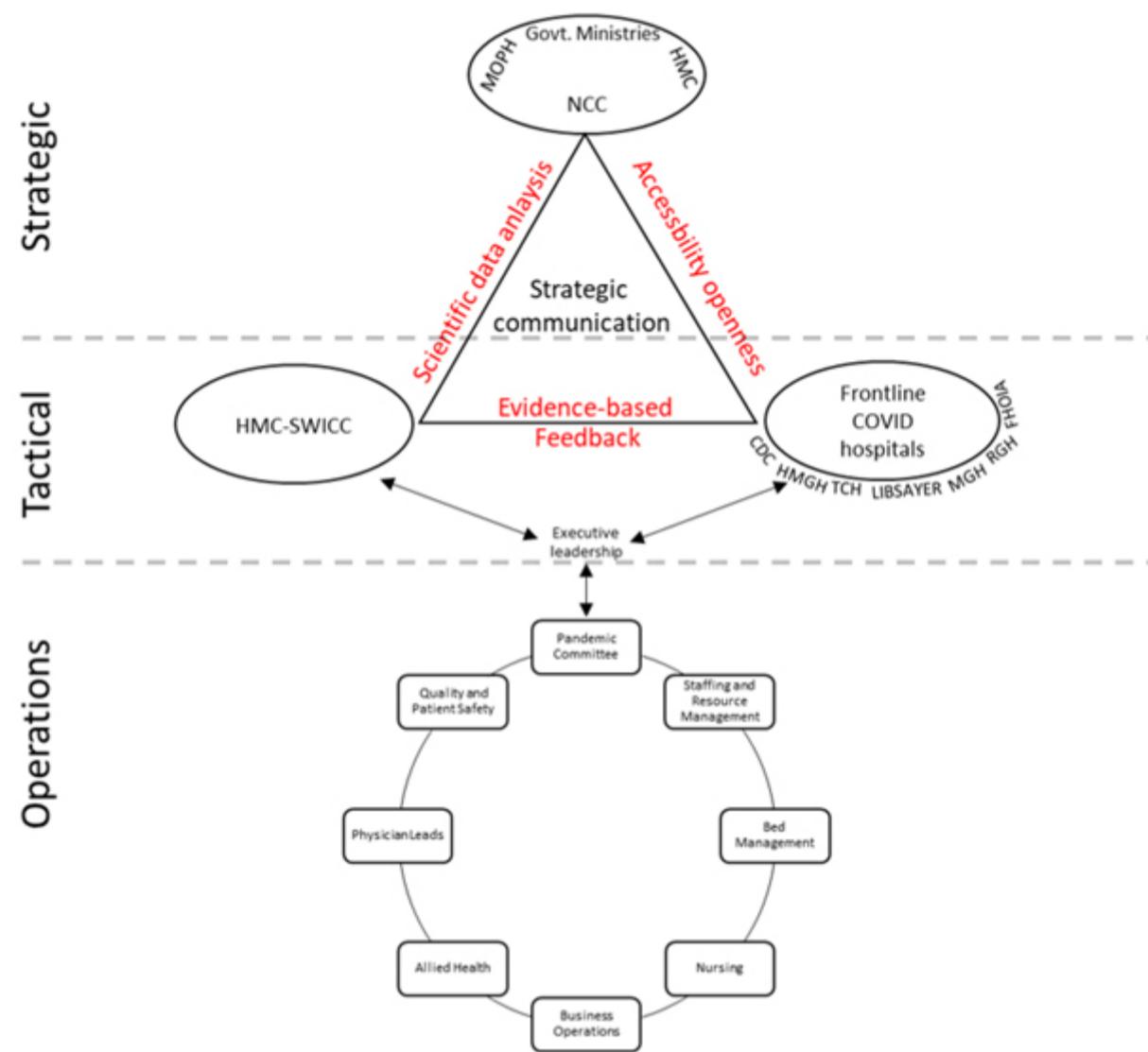


Figure 4: The three-tier process: strategic, tactical and operational

At the operational level, the HMGH pandemic committee was responsible for implementing the operational strategy that would match the requirement set forth by the NCC through the SWICC. The pandemic committee leveraged a forward-looking strategy to meet the potential demands of the pandemic.

The phased ramp-up plan details are listed below.

Also, the Go-No Go commissioning sheet (Fig. 5) was used by the pandemic committee to handle diverse data streams and integrate the clinical operation components for a safe patient care environment.

HMGH GO – NO GO Report for: Department Name

This ‘Sign Off’ sheet is in support of opening of the new service/ department.

LEGEND RAG STATUS

WHITE: Refers to Departmental Decision pending

BLUE: Refers to a **Go Decision** based on there being no issues whatsoever

GREEN: Refers to a **Go decision** and comments made are issues requiring resolution, however, do not impact the decision

AMBER: Refers to the issues added in the Comments **needing resolution ASAP, however, are not showstoppers**, and suitable workaround solutions have been found.

RED: Refers to the issues addressed in the Comments column are of immediate urgency for resolution and will likely impact on the safe operational activity to be decided. This is a **NO-GO decision**.

SN	SYSTEM	RAG STATUS	COMMENTS	DEPARTMENT HEAD	SIGNATURE
001	HICT				
002	FIRE & SAFETY (SMS)				
003	INFECTION PREVENTION & CONTROL				
004	BIOMEDICAL ENGINEERING				
005	OHS AND RISK MANAGEMENT				
006	ENVIRONMENTAL SAFETY				

Figure 5: The Go-No Go commissioning plan

This report is written from the frontline operational viewpoint to highlight the achievements of clinical and nonclinical teams at HMGH. The hospital conversion process was laid out in phases.

The first phase established a decant unit at HMGH to prepare the Centers for Disease Control and Prevention (CDC) for the pandemic response.

Phase two included having a screening site for passengers who travelled from February 14 to February 23, 2020.

Phase three included the redesignation of HMGH as a frontline COVID-19 facility.

The details of each phase are listed below:

Phase 1

- Decant unit for pulmonary tuberculosis (PTB) patients from the CDC- Unit 33
 - Unit 33 received 20 PTB patients from the CDC from March 1 to March 15, 2020.

Phase 2

- Screening site for COVID-19 patients
 - The screening was conducted in partnership with the ambulance service for the passengers who travelled from February 14 to February 23, 2020.
 - The screening was conducted from March 2 to March 14, 2020. 1846 travellers were screened during the two weeks.

Phase 3

- COVID -19 frontline hospital
 - As a frontline hospital, HMGH ramped up services to meet the growing demands in the hospital. The ramp-up was possible due to the unified strategy of HMC, and the resources were mobilised and prioritised accordingly. The detailed department mobilisation is listed in the sections for the intensive care unit (ICU) and acute care conversions.
 - HMGH changed the scope of service to accommodate adult female patients instead of limiting to the adult male population only.
 - HMGH converted two dental clinics into negative-pressure rooms to accommodate COVID-19 patients.
 - ICU bed capacity increased from seven to 42 beds within one week of March 15, 2020.
 - Three tents were built as an emergency department (ED), and the ED capacity increased from 34 to 150 beds.
 - The tents served as a key triage hub for COVID-19-positive patients across Doha to reduce the load of unnecessary admissions.
 - The field hospital included multiple tents which were built on the east side of the campus.
 - Multiple tents were built with O₂ provisions and set up as double occupancy, increasing bed capacity in the field hospital to 505 beds.
 - On April 30, 2020, portable tents sustained major damage due to strong winds.

- Fortunately, patients did not sustain serious injuries and were attended to at the HMGH ED and other COVID-19 designated hospitals.
- 59 COVID-19 patients were transferred to other COVID-19 facilities.
- 15 COVID-19 patients were seen at the HMGH ED and admitted to the HMGH inpatient facility.
- Unfortunately, 17 staff members were injured during the incident.
- The damaged tents were rebuilt to provide patient care.
- Within 24 hours of the incident, the ED resumed normal operations.
- The frontline staffing strength increased to facilitate the ramp-up plan.
 - The nursing staffing level increased from 500 to 1300.
 - The pharmacy staffing levels increased from 30 to 48.
 - The number of doses of antibiotics increased from 8,000 (pre-COVID-19) to 80,000 (post-COVID-19).
 - HMGH commissioned and opened an IV prep area of the pharmacy.
- With the increased ICU capacity:
 - The number of ICU doctors increased to 43, including 13 consultants and 30 ICU specialists.
 - The respiratory therapy staffing levels increased from 10 to 38.
 - The ICU nursing staffing level increased to 650.
- The department of medicine redistributed medical staff from the HMGH outpatient and other HMC facilities to the inpatient acute care service. Total staff increased from 19 to 180 physicians and supporting staff.
- The department of surgery reassigned some acute care, hand, and bariatric surgeons to other non-COVID-19 facilities.
- Physical therapy and rehabilitation increased staffing strength from 22 to 42.
 - The number of physiotherapy sessions rose from 1500 to 2800 during April and May 2020 with a current patient turnover of 170 per day.
- Bed management capacity increased to accommodate the increased patient flow.
- The ancillary support (contracted services) staffing levels were also increased across all service lines to accommodate the increased patient care activities.
- Staff well-being was taken into consideration during the crisis.
 - The administration, in collaboration with mental health services, provided access to psychological support for all staff.
 - The administration provided three meals per day for the on-duty staff.
 - Return transportation for all staff was provided three times per day.
 - The administration coordinated with SWICC to provide access to hotels for staff who lived with families.

Acute Care and ICU Bed Capacity Increase with Go-Live Dates

- The department conversion schedule was developed in collaboration with the SWICC's equipment planning committee, engineering, biomedical engineering, and HICT. Robust criteria were developed for installing the equipment and proceeding with go-live prep within the deadlines established by the SWICC.
- The initial response aimed to prepare the hospital to provide care for a high volume of COVID-19 patients while maintaining the limited delivery of surgical care to emergency and high-priority elective cases.
- Department conversions and go-live dates were closely coordinated between multiple stakeholders, such as the equipment planning and commission team, engineering, HICT, bed management, nursing, medical staff and support services.
- To meet the timelines for increasing bed capacity in response to COVID-19, equipment was received from several sources. Concerned teams worked on the scale of equipment per bed:
 - HMGH team retrieved equipment from warehouses in lockdown areas through special permission from the SWICC and the Ministry of Interior (MOI).
 - Special permission was also obtained to source equipment from the Sidra Hospital warehouse.
 - Other HMC facilities also helped with the procurement and delivery of new equipment as HMGH faced logistical challenges due to lockdown procedures.
- For more than three months, priority was given to converting the following departments: Post Anaesthesia Care Unit (PACU), Day Care Unit (DCU), outpatient rehabilitation, ED, inpatient units, urgent care, and Surgical Outpatient Department (SOPD). This led to a 226 ICU bed capacity at HMGH. These areas were chosen based on the availability of uninterrupted electricity, presence of medical air, O₂, and suction ports, and operational proximity to the areas that were converted for acute care service within the hospital.
- The outpatient care areas and nonpatient care areas inside the HMGH building were refitted to become an inpatient unit (178 beds). The area included General Internal Medicine (GIMC) and SOPD clinics, main hallways, an auditorium, a cafeteria, a mosque and a library. Hence, 25% of the total beds were placed in a non-acute care setting across the hospital and repurposed to meet the current demand.
- The field hospital tents (545 beds) were built on the east side of the campus. Initially, the portable solution was used for medical gases. However, after the April 30, 2020, incident, the redesign included piped O₂ and functional patient care areas with the input from the medical and infection control team.

COVID 19 BED CAPACITY TRACKER 22/06/2020						
HOSPITAL BUILDING			TENTS			
HMGH - In Patients Bed Capacity - HOSPITAL BUILDING		HMGH - In Patients Bed Capacity - TENT				
IP No. (Cerner)	Location	Capacity	Status	Opening Date		
Ward D (GIMC)	GIMC Clinic	23	Operational	29-Apr-20		
Ward F	SOPD Cubicles	36		29-Apr-20		
Ward F	Switch Board GF	6		18-May-20		
Ward G	Staff Dining	16		29-Apr-20		
Ward H	Auditorium	13		29-Apr-20		
Ward I	Main Corridor	50		09-May-20		
	Library	14				
Ward J	Class Room - 11229	6		13-May-20		
	Class Room - 11147	4				
Ward K	Unit 33	10		18-May-20		
Total Beds		178				
HMGH - ICU Bed Capacity						
ICU No. (Cerner)	Location	Capacity	Status	Opening Date		
ICU 1	Unit 29 (East)	7	Operational	18-Mar-20		
ICU 2	Unit 30 (West)	8		18-Mar-20		
ICU 3	PACU	12		18-Mar-20		
ICU 4	DCU	15		18-Mar-20		
ICU 5	Rehab	8		04-Apr-20		
ICU 6	Old ED	32		12-Apr-20		
ICU 7	Unit 33	24		22-Apr-20		
ICU 8	Unit 34	34		28-Apr-20		
ICU 9	Unit 35	34		06-May-20		
ICU 10	SOPD	13		18-May-20		
ICU 11	GIMC (Urgent Care)	17		11-May-20		
ICU 12	Med Com	8		27-May-20		
ICU 13 expansion	Unit 29 (East)	7		04-Jun-20		
ICU 2 expansion	Unit 30 (West)	7				
Total bed		226				
HMGH - Total Bed Capacity						
Beds in Hospital		178				
Beds in Tent		545				
ICU beds		226				
Total Capacity		949				

Table 1: Details of master go-live schedule

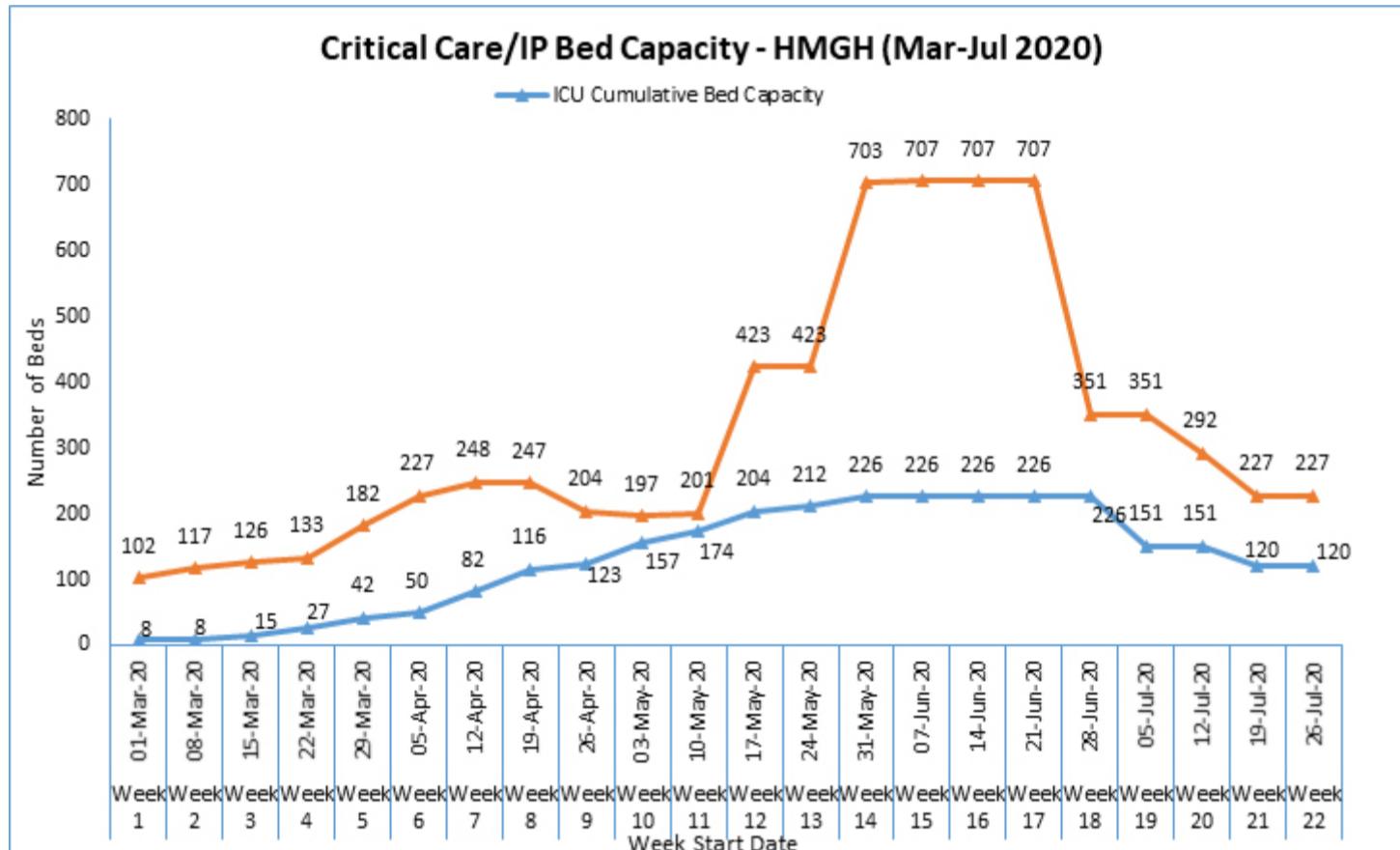


Table 2: Details of critical care/inpatient (IP) bed capacity increase at HMGH

Emergency Department

With the onset of the novel coronavirus pandemic, the ED at HMGH had to cope with the unprecedented changes in patient caseloads, structural and functional changes, and several relocations.

Through all this, the ED continued to deliver effective patient care, absorbing several complications while the situation evolved within the system and the country.

The department is still thriving and preparing for a surge as activities elsewhere are beginning to diminish.

Some of the activities in the ED at HMGH are summarised below:

- The evidence-based clinical algorithm (EBCA) was designed, and physician resources were allocated by the ED chairman and corporate department before the first case of COVID-19 was identified. The EBCA is continually updated.
- The fever clinic and its pathways were established.
- Figure 6 shows the number of COVID-19 cases seen in the ED from March 1 to June 30, 2020.

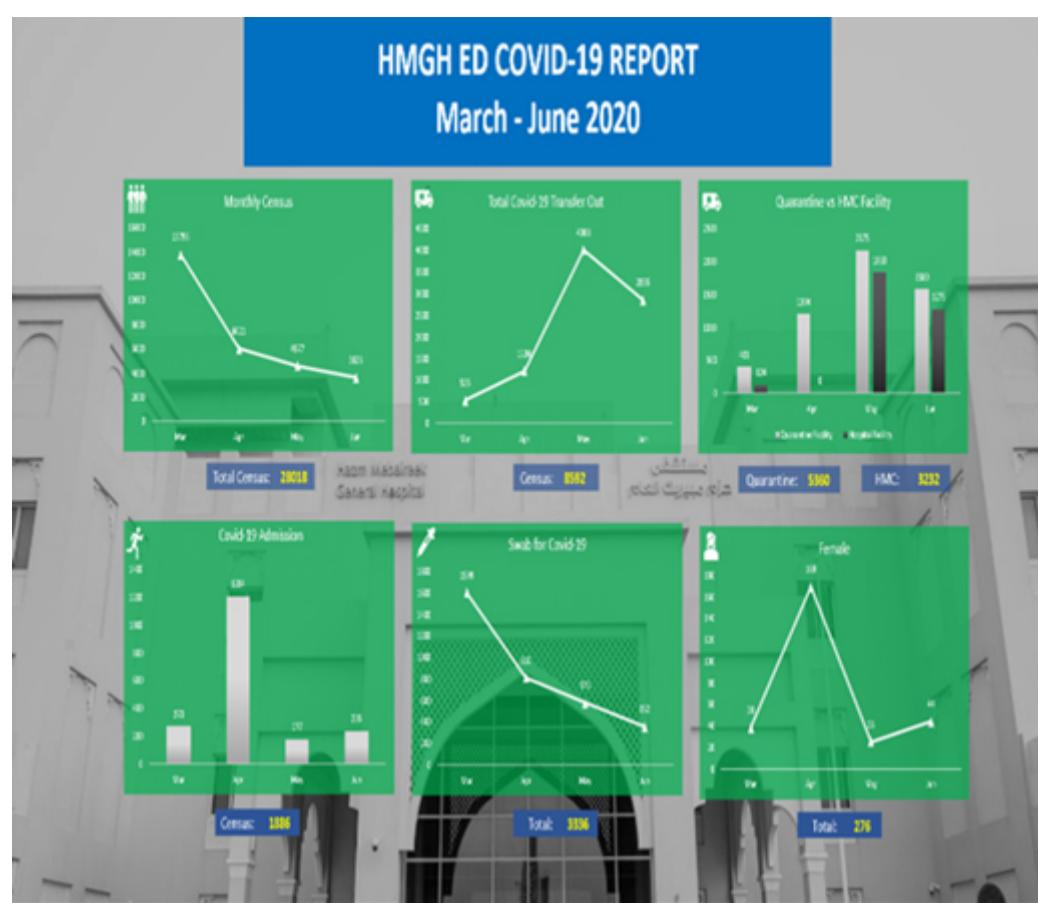


Figure 6: HMGH COVID-19 ED statistics for March–June 2020

- The ED managed overcrowding at various stages, including incorporating protocol revisions per evolving disease information, managing the influx of patients and developing support systems and facilities.
- The department continued regular emergency patient care while supplementing with other categories of activity.
- Staff vacated the ED beds which were released to the ICU and used Out Patient Department (OPD) rooms as the ED. Thereafter, the ED moved operations to three large tents outside the hospital, while retaining the OPD registration and waiting areas to manage patient loads during the crisis and after the tent collapse.

The operational layout for the ED was as follows:

- Tent 1 received all confirmed COVID-19 cases from the community and other facilities. It was the high acuity tent and was fitted with a resuscitation area.
- Tent 2 was mostly on stand-by as the change in the protocols has decongested most areas.
- Tent 3 received non-COVID-19 patients.
- The mosque served as a discharge lounge.

Other Coordinated Efforts

Working with our partners in Primary Health Care Corporation (PHCC) and the MOPH, a range of innovative, remote services were developed and offered for our patients. The urgent consultation service launched in April 2020, offering patients access to telephone consultations in 14 specialties.

Up to December 2020, the service handled more than 220,000 calls. The mental health helpline was also launched, offering mental

health support and counselling for members of the community and healthcare professionals. To date, they have handled approximately 20,000 calls. The pharmacy home delivery service was also launched, and up to December 2020, more than 250,000 patients received their medications through this service and more than 860,000 medication items were dispensed to those patients.

To ensure our community elders received the care they needed, the elderly telephone reassurance service was established, calling more than 17,000 people aged over 65 years.

Whilst HMGH was the dedicated COVID-19 facility, clear roles and responsibilities were defined for neighbouring hospitals as summarized in the table below.

Healthcare Facility	Role	Patient Cohorts	Normal Bed Capacity
HMGH	Dedicated COVID-19 facility	Potential unstable patients and dialysis patients	118
CDC	Dedicated Covid 19 facility	Stable patients	63
Cuban	Dedicated COVID-19 facility	Potentially unstable patients and pregnant patients	75
HMG WWRC	Non Covid facility On going essential medical services	All patient groups	603 260
Heart Hospital Al Wakra Al Khor			116 400 115
Ras Laffan	Quarantine facility	Stable patients	112
Mesaieed	Quarantine facility	Stable patients	112
Lebsayer field Hospital	Dedicated covid 19 facility	Stable patients	504

Table 3: Hospital roles and responsibilities

Plans were made to increase the quarantine capacity in phases in response to the increasing number of patients. Staff, including physician assistants, were recruited from private clinics and, informally, from the local indigenous community of expatriate workers. Furthermore, staff from elective services were redeployed to HMGH, and non-essential medical services (e.g. elective surgery and medical OPD) were cancelled.

Also, doctors from the PHCC were redeployed to the dedicated COVID-19 facility. Senior doctors who had no previous experience in internal medicine were provided appropriate training and were buddied with senior consultants in internal

medicine.

There was dedicated 24/7 medical coverage compromised of medical specialists and off-site senior consultant teams who worked together in a collegial manner with dedicated 24/7 intensivists.

Guidelines were regularly disseminated from SWICC and the infection control team to ensure that there was appropriate use of PPE. At the beginning of the pandemic when the infectivity of COVID-19 was unclear and the magnitude of the threat was uncertain,

PPE was changed between each patient, which resulted in initial shortages. However, when there was more evidence available, this was changed to rationalise PPE use.

Because all cases were treated as suspected COVID-19 and full PPE was used, sickness and absence rates were minimal at the dedicated COVID-19 facility. Rates were higher amongst nonmedical staff, such as cleaning and catering staff, but this was quickly rectified.

PPE use was further rationalised when only the senior decision-makers would see patients, and the consultants would discuss with the juniors after the ward round.

Local Response

Mathematical modelling was employed to predict the peak and number of patients at the peak of the pandemic. Appropriate staff were redeployed to the dedicated COVID-19 facility to ensure that there were sufficient staff to deal with the number of cases at the peak. Plans were put into place to ensure that the number of ED, medical and ICU beds increased in response to the surge.

Initially medical beds and the ED were converted to ICU beds, whilst outpatient and corridor spaces were utilised for medical patients. However, as the number of cases increased, field tents were utilised to provide additional medical capacity, and the ED was transferred to a field tent. Single bed occupancy was not possible, and sometimes two patients shared a cubicle in a tent, always using a surgical mask. In the corridor,

multiple occupancy glass rooms were used. Nursing stations were centrally located for patients managed in the corridors. The ICU capacity was increased in phases beginning in March 2020 from 15 operational beds to a total of 221 beds when the ED and non-ICU beds were converted.

In addition, the medical beds and the ED were replaced by three modular tents with a capacity of 68 beds.

The patients were graded and managed according to the severity of their illness.

Asymptomatic patients were quarantined in a hospital facility if they lived in shared accommodations; if they had a single room, they were quarantined at home.

Symptoms	Facility	Shared accommodation	Single room
Asymptomatic	Community	Hotel quarantine	Home
Mild	Quarantine	Quarantine facility	Home
Moderate	Hospital wards	Quarantine facility	Home
Severe	Hospital ICU	Quarantine facility	Home

Table 4: Patient illness severity and management

At the beginning of the pandemic when the degree of infectivity was unclear, young, fit asymptomatic patients were quarantined in hotel facilities. A dedicated hospital-discharge team was used, and all hospital discharges were referred to them daily to ensure patients were discharged consistently to the appropriate facilities.

There was no significant sickness or absenteeism amongst the medical teams due to a consistent policy for PPE use; however, the incidence was higher in non-COVID-19 facilities where asymptomatic patients later developed COVID-19.

Standard treatment protocols were employed to recognise patients who were at risk of developing acute respiratory distress syndrome (ARDS), and rapid response teams comprised of physicians and critical care staff were used.

Nursing staff were well versed in the escalation protocols and the appropriate use of oxygen masks, proning techniques and Continuous Positive Airway Pressure (CPAP) masks to minimize the need for mechanical ventilation.

Medical management was overseen by a central dedicated infectious disease team to ensure consistent use of interventional therapies, such as tocilizumab and convalescent plasma.

Infection control measures were strictly enforced by ensuring all staff entering the building used hand sanitizer, had their temperature checked and were wearing a face mask. All staff involved in direct patient care used separate donning and doffing areas.

To ensure that ICU staff were not overwhelmed with the workload, senior clinical fellows were cross-trained to work in the critical care facilities.

Visitors were given restricted access to their relatives during the pandemic, and only those essential to patient support were allowed in.

Having a dedicated COVID-19 facility allowed for a consistent policy of wearing PPE with all patients suspected or confirmed as having COVID-19. Therefore, there was a very low number of sicknesses and absences among staff. It also ensured a consistent response to the management of COVID-19, allowing rapid change in guidelines based on emerging evidence.

System wide response

Qatar's broader public health response to the COVID-19 global pandemic has been summarised in this article and was distinguished by acting early and rapidly adopting a carefully planned and organized governance structure that supported the rapid flow of information and quick decision-making(14).

Qatar implemented many preventive measures early in the pandemic, including border control for early detection of cases and thermal screening for passengers entering the country at Hamad International Airport and at seaports as early as January 2020, with the first quarantine facilities opening on February 1(14).

With a diverse population, Qatar instigated its national public health communications plan on January 23, 2020, disseminating essential public information on protection against COVID-19 in eight different languages. They used a variety of media, including SMS direct messaging, social media, press conferences, daily TV and radio coverage, short educational videos in multiple languages, online workshops, and meetings with community leaders (14).

Qatar produced daily information and advice to all of its citizens. It also opened a toll-free central helpline for members of the public, which has received over 657,272 calls to date. The MOPH also engaged the private health sector early in the pandemic to enhance early detection of cases and to strengthen infection control measures (14).

Qatar acted swiftly to enhance its laboratory capacity to ensure that it could deliver up to 20,000 polymerase chain reaction (PCR) tests per day, producing a daily testing rate among the highest in the world (over 2/1000 people/day). In addition to the central COVID-19 laboratory, Qatar opened two new COVID-19 laboratories and four rapid PCR facilities in the main hospital sites to support critical and urgent care. Laboratory facilities

validated and supported the introduction of rapid IgG/IgM serology testing and are now undertaking an extensive seroprevalence study, one of the first in the region. Recently, the central laboratory also introduced rapid antigen testing, which is under validation(14).

HMC's virology team validated and introduced reverse transcription PCR (RT-PCR) assays for COVID-19 in January 2020 and was providing this test for four weeks before the first case was confirmed on February 28, 2020. Qatar was one of the first countries in the region to introduce the RT-PCR test for SARS-CoV-2(14).

Access to testing for COVID-19 is provided for free and is readily available to the public if they have signs or symptoms of the virus or if they were in close contact with a confirmed case. Qatar has also dedicated four health centres throughout the country where the public can go to get free testing, as well as three dedicated, drive-through facilities. To date, over 420,000 people have been tested for COVID-19 in Qatar(14).

Qatar significantly enhanced its test, track and trace capability, expanding its public health team 12-fold during the course of the pandemic. This supported the early detection of cases in the community and limited the spread of the virus by isolating positive cases early in the course of the infection(14).

For a time, Qatar implemented a strict lockdown policy in which all nonessential travel was banned, all mosques were shuttered, shopping malls were closed except for essential pharmacy and grocery shopping, and parks, public places, schools and universities were closed(14).

Ehteraz, a mandatory mobile public health application for people aged 18 and over was launched to ensure that people could be alerted when they were in the vicinity of anyone infected or awaiting test results. It gives an early warning to people who were potentially exposed to the virus, so they can get tested early. Only people who have a healthy status on their Ehteraz application can access public facilities as lockdown begins to ease(14).

Qatar ensured that all members of the public had access to masks, gloves and hand sanitizer. Face masks were and are mandatory for everyone outside of their home. Clear and regular messages were posted on the MOPH website and in social media on the importance of masks and keeping physical distance as preventive measures(14).

Owing to these active interventions and public health measures, it is estimated that there has been a 76% reduction of the peak number of infections with the flattening of the curve, which has led to a 74.6% reduction in potential acute care admissions and a 65.1% reduction in potential ICU admissions at the peak of the epidemic, diluting the occurrence of cases over time. In other words, without these measures, Qatar would have increased the risk of its hospital sector being overrun with COVID-19 cases. This also helped it maintain its normal non-COVID-19-related clinical operations(14).

Qatar is in the middle of a four-phase reopening plan, in which lockdown measures are being cautiously lifted. His Highness, the Amir of Qatar, has provided a QAR 75 billion package to prevent the spread of the virus, retain jobs, help companies stay in business and ensure that people are still paid their salaries when in quarantine, isolation, or the hospital. This has helped keep the economy strong throughout the pandemic(14).

Challenges

The lockdown of the industrial area caused thousands of patients to be cut from medical services, including chronic medications. The area had a few private clinics and pharmacies, but these were incapable of providing the care needed.

One of the private clinic buildings and an adjacent commercial building were identified and taken over by the HMC team to serve as the main medical service provider for the area. This was later was the Field Hospital of the Industrial Area (FHOIA).

A tent was built in front of the building to serve as the ED. The private clinic was transformed into an outpatient clinic, and the commercial building was turned into a short-stay and COVID-19 holdup area.

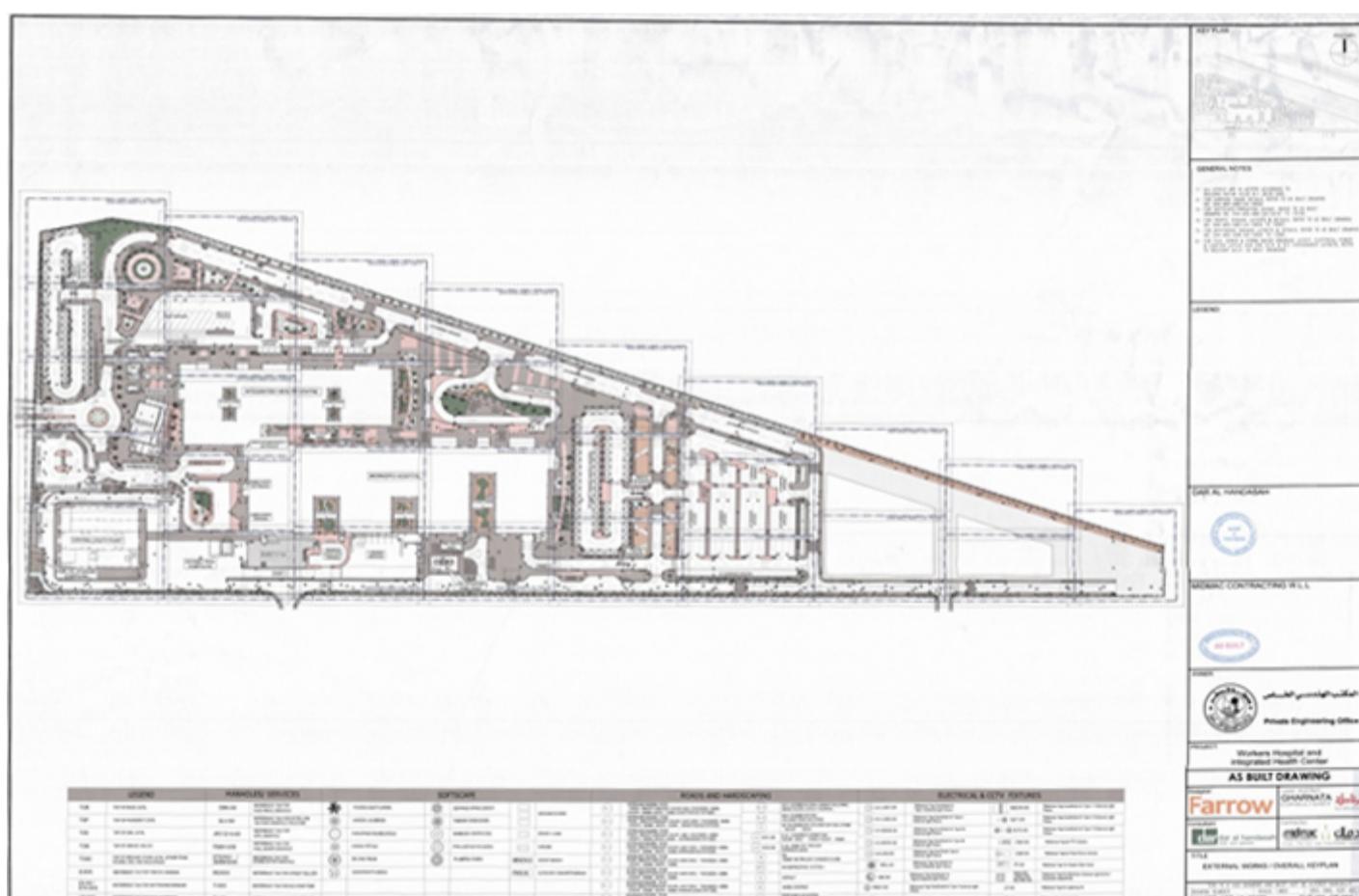
Two other buildings were acquired for quarantine facilities. The main challenge was to transform these buildings in a short period of time into medical facilities upholding the standards of other HMC facilities. This required a lot of work at a fast pace to provide equipment, staff and training as well as linking the facilities to HMC and QRC electronic medical systems.

In due time, FHOIA started to provide medical services to the industrial area, serving around 300–500 patients in the ED and 100–150 patients in the outpatient area.

The hospital was equipped with a pharmacy, laboratory and radiology with all services and medications provided free of charge. Later, another facility called Industrial Area Emergency Department (IASED) was added to the area and provided emergency medical services.

Telemedicine

- On March 12, 2020, all OPD services were put on hold, and the OPD team joined the COVID-19 task force. This team performed various tasks, such as:
- Inpatient coverage
- Quarantine facility coverage
- Field hospital coverage
- OPD patients pool was maintained during the peak of the pandemic by calling patients, rescheduling appointments and re-prescribing medications.
- OPD activity resumed gradually with telemedicine services. In the General Internal Medicine Clinics (GIMC) alone, the staff saw 327 patients in August 2020 and 1,492 in November 2020.
- To compensate for lack of face-to-face visits and to improve the quality of outpatient consultations, the OPD adopted video consultations in collaboration with the MOPH. This service started in October 2020 with 145 video consultations which was doubled to 308 in November 2020.





Pictures: Layout of HMGH

Discussion and Future Challenges

Effective planning, people, and processes merge to make meaningful differences in patient care to face the overwhelming challenges posed by COVID-19 pandemic.

To successfully address the care needs of a widespread and complex clinical condition such as COVID-19, the workgroup represented a diverse range of disciplines and care locations. Long years of extensive training and healthcare exposure enhance a unique understanding amongst physicians to what constitutes high-quality care and how to deliver it. Within organizations, administrators and managers can still implement further strategies to fan the intrinsic motivation of physicians. The workgroup's goals were strongly aligned as a team at a time of unusual pressure and common purpose. The chance to focus almost exclusively on COVID-19 patient care likely fuelled the professional response as the organization became more responsive to the needs of the professionals and patients.

While having so many different stakeholders might pose a challenge, the COVID-19 workgroup exceeded all expectations. It modelled what has turned out to be a highly effective, patient-centred and outcomes-focused approach to making quality improvements for COVID-19 patients. This started with strategic planning to ensure the right issues were addressed. Workgroup members brainstormed, reviewed and analysed workflow charts to pinpoint the processes, interventions and outcomes that our patients were experiencing. Concurrently, members reviewed literature, articles and case studies for best practice recommendations to leverage the experience and knowledge of other organisations and experts.

What became evident through intensive research and chart audits was that not all COVID-19 patients are the same. The orders and care routines built into the protocol needed to accommodate the legitimate variation and different care needs among different sets of patients. Once data analytics and problem identification were marked, the workgroup progressed to identify several key process improvement efforts:

- Realigning and developing strategies for effective initial screening of patients with symptoms.

- Developing and deploying the comprehensive standard order set for COVID-19 patients, including lab investigations, medications, oxygenation requirements and escalations along with nursing care protocols.
- Realigning optimal lab and radiology procedure order sets to reduce waste whilst delivering optimal care in the right clinical setting.
- Improving the process for discharge appointments and follow-up phone calls/telemedicine. A clear pathway was established for contacting patients post-discharge to answer questions about their condition and confirm that they had scheduled their follow-up appointments, decreasing the likelihood of readmission. This patient engagement activity was undertaken by case managers and social workers on the care management team.

The protocols were carefully constructed to respect the individual department workflows and was implemented simultaneously across the board. The feedback loop was reviewed and analysed every two weeks.

Team leadership overcame provider resistance by acting as external change agents charged with motivating changes in physician behaviour by increasing compliance to initial screening tools.

This chapter highlights process analysis and an action plan in the wake of the recent ongoing pandemic to assist others in the development of regulatory, institutional and national policy regimes.

The main target audience for this guide is hospital management, hospital emergency committees and staff who are responsible for establishing and maintaining the preparedness of hospitals for epidemics.

The information is relevant for all stakeholders including public, private, non-government and healthcare providers.

The wider audience is all stakeholders across many sectors including governments, health authorities, financial institutions, disaster management organizations and local suppliers who support and contribute to hospital preparedness through policy guidance and health sector and intersectoral coordination for emergency preparedness and response to logistics provision.

Results

The success of this team was not only what was done, but how. The COVID-19 workgroup set a precedent for doing the work differently and used innovative methods of communication to assure a high level of participation, engagement, adoption and collaboration across the organization and the communities that it serves.

The current pandemic has provided a unique opportunity for healthcare systems across the globe to transform into more agile and resilient learning systems.

Many healthcare and other frontline workers have been exposed to training in quality process improvements and patient safety methods.

This opportunity can be used to support and design new health learning systems and adapted practices by the application of approaches, methods and tools in any future crisis situations.

The article also uses several resources which may be of use to those keen to advance their knowledge.

Conclusions

Optimising hospital flow, and eventually enhancing outcomes and patient care experience, requires an understanding of the hospital as an integrated, interdependent care system.

Strong leadership is required and is, in fact, critical to success.

The priorities are a long-term strategy and its rationale, initiating mechanisms to enforce system-wide changes, timely responsive systems for spike in demands and a focus on integrated hospital outcome measures. In this nodal COVID-19 hospital, the participation of most of the staff and the desire to go above and beyond resulted in improvement in the processes of care.

Workgroup members acted as external change agents, motivating staff to comply with standardized protocols for COVID-19 patients to improve patient outcomes.

This article demonstrates that clear strategies have the potential to improve patient outcomes whilst reducing healthcare waste.

What is Next?

HMGH is determined to continue to improve the care for COVID-19 patients.

The next areas of focus are to determine whether inpatient (hospital versus isolation) or outpatient treatment is needed and to implement the use of the pandemic protocols in the electronic healthcare records system, CERNER, used across the organization for risk stratification of morbidity.

To advance these gains, HMGH will be doing further process validation and vetting performance reviews for ongoing improvement.

Meanwhile, the pharmacy plans to continue to increase their engagement with patients to ensure smoother transitions of patient care.

The healthcare community and academia have initiated tremendous research activities to gather, analyse and learn from the vast data generated during the pandemic.

While this list of next steps is ambitious, the organization has shown what it can accomplish in a short period of time and the lengths to which it will go to improve the care and clinical outcomes for its patients.

Lessons Learned

As with many other global healthcare systems, HMGH has absorbed humility and learned many important lessons from this worldwide crisis.

The pandemic has effectively strengthened our healthcare delivery model, including both primary and tertiary care centres, nationally.

Moreover, this has accelerated our embrace of digital health platforms, including telehealth consultations and refill prescription deliveries, to deliver safe, equitable and effective healthcare.

Our weaknesses and vulnerabilities have been rectified or strengthened quite impressively in a short span. We have realized the value of knowledge sharing and believe all humankind will eventually emerge much stronger than ever.

Acknowledgements

We would like to acknowledge their contribution and sincerely thank all HMC staff and volunteers deployed at or working remotely for HMGH during the pandemic for their excellence, commitment, devotion and selfless hard work. Needless to say, without their helping hands nothing would have been possible.

Abbreviations

- SWICC** - System Wide Incident Command Committee
- COVID-19** - Coronavirus Disease 2019
- DCU** - Day Care Unit
- DLMP** - Department of Laboratory Medicine and Pathology
- GIMC** - General Internal Medicine Clinic
- HCW** - Health Care Workers
- HICT** - Hamad Information and Communications Technology
- HMC** - Hamad Medical Corporation
- HMGH** - Hazm Mebaireek General Hospital
- IPC** - Infection Prevention and Control
- KPI** - Key Performance Indicator
- MOI** - Ministry of Interior
- MOPH** - Ministry of Public Health
- OPD** - Out Patient Department
- PACU** - Post Anaesthesia Care Unit
- PHCC** - Primary Health Care Corporation
- PPE** - Personal Protective Equipment
- SOPD** - Surgical Out-Patient Department
- WHO** - World Health Organization
- WWRC** – Women's Wellness and Research Centre

References

1. World Health Organization. Hospital preparedness for epidemic [Internet]. 2014. Available from: https://apps.who.int/iris/bitstream/handle/10665/151281/9789241548939_eng.pdf? [Accessed 20th September 2020]
2. Ramos G. COVID-19: Protecting people and societies [Internet]. 2020. Available from: <https://www.oecd.org/coronavirus/policy-responses/covid-19-protecting-people-and-societies-e5c9de1a/> [Accessed 10th November 2020]
3. Deloitte. Thoughts on healthcare management in an epidemic [Internet]. 2020. Available from: <https://www2.deloitte.com/cn/en/pages/risk/articles/thoughts-on-construction-of-large-health-management-system-under-2019-ncov.html> [Accessed 10th November 2020]
4. Centers for Disease Control and Prevention. Healthcare facilities: Managing operations during the COVID-19 pandemic [Internet]. 2020. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-hcf.html> [Accessed 5th January 2021]
5. Institute of Medicine (US) Committee on Assuring the Health of the Public in the 21st Century. In: The future of the public's health in the 21st century [Internet]. Washington, D.C.: National Academies Press; 2003. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK221227/> [Accessed 15th December 2020]
6. Begun JW, Jiang HJ. Health care management during Covid-19: Insights from complexity science [Internet]. NEJM Catalyst Innovations in Care Delivery. 2020. Available from: <https://catalyst.nejm.org/doi/full/10.1056/CAT.20.0541> [Accessed 15th December 2020]
7. Department of Health and Social Care. Coronavirus action plan: a guide to what you can expect across the UK [Internet]. 2020. Available from: <https://www.gov.uk/government/publications/coronavirus-action-plan/coronavirus-action-plan-a-guide-to-what-you-can-expect-across-the-uk> [Accessed 3rd January 2021]
8. Peiffer-Smadja N, Lucet J-C, Bendjelloul G, Bouadma L, Gerard S, Choquet C, et al. Challenges and issues about organizing a hospital to respond to the COVID-19 outbreak: Experience from a French reference centre. Clinical Microbiology and Infection. 2020;26(6): 669-672 ISSN 1198-743X, (PMID 32278082)
9. Razonable RR, Pennington KM, Meehan AM, Wilson JW, Froemming AT, Bennett CE, et al. A collaborative multidisciplinary approach to the management of coronavirus disease 2019 in the hospital setting. Mayo Clinic Proceedings. 2020;95(7):1467-1481 Epub 2020 May 30. PMID: 32622450; PMCID: PMC7260518. (32622450)
10. Ministry of Public Health. Qatar national response action plan March 2020 [Internet]. 2020. Available from: <https://www.moph.gov.qa/Style%20Library/MOPH/Videos/COVID-19%20REPORT%20WEB.pdf> [Accessed 20th July 2020]
11. World Health Organization. Strategic preparedness and response plan for the novel coronavirus [Internet]. 2020. Available from: <https://www.who.int/publications/i/item/strategic-preparedness-and-response-plan-for-the-new-coronavirus> [Accessed 10th June 2020]
12. World Health Organization. Risk communication and community engagement (RCCE) action plan guidance COVID-19 preparedness and response [Internet]. 2020. Available from: [https://www.who.int/publications/i/item/risk-communication-and-community-engagement-\(rcce\)-action-plan-guidance](https://www.who.int/publications/i/item/risk-communication-and-community-engagement-(rcce)-action-plan-guidance) [Accessed 15th August 2020]
13. Ministry of Public Health and Hamad Medical Corporation.
14. Al Khal A, Al-Kaabi S, Checketts RJ. Qatar's response to COVID-19 pandemic. Heart Views [serial online] 2020 [cited 2021 Apr 25];21:129-32. Available from: <https://www.heartviews.org/text.asp?2020/21/3/129/297805>

[Home](#)[Forward message](#)[Introduction](#)[Chapters](#)[Editors team](#)[Contact us](#)

Copyright © 2022 Ministry of Public Health. All rights reserved.



Search this site



Renal Medicine

Coronavirus disease 2019 and the kidneys

Muftah Othman, Muhammad Asim, Mohamad Alkadi, Sagar Babu, Hassan Almalki and Omar Fituri

Keywords:

COVID-19, Acute Kidney Injury, AKI, End-Stage Renal Disease, ESRD, renal transplant, hemodialysis, renal replacement therapy, angiotensin-converting enzyme, cytokine release syndrome, extracorporeal blood purification therapy, dialysis patient, dialysis unit.

Introduction:

Coronavirus disease 2019 (COVID-19) is a respiratory infectious disease that greatly affected nephrology practice. It is characterised by diffuse alveolar damage, acute respiratory failure and may result in acute kidney involvement. COVID-19 has unique implications for patients developing acute kidney injury (AKI), as well as patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD) and kidney transplant recipients.

COVID-19 is proposed to evolve in three different severity stages.

Stage I (mild)- the early infection phase: due to viral entry to the host cell by adhesion of the spike protein to the angiotensin-converting enzyme-2 receptor (ACE2 receptor), following priming by cellular transmembrane serine protease 2 (TMPRSS2), which leads to viral replication and tissue damage.

It is manifested by mild constitutional symptoms such as fever, malaise, dry cough, and lymphopenia.

Stage II (moderate)- the pulmonary phase (IIa) without and (IIb) with hypoxia: due to viral replication and localised inflammation in the lung. Patients manifest with cough, fever, shortness of breath with or without hypoxia. Other features include abnormal chest imaging, increasing lymphopenia, transaminitis, and low to normal serum procalcitonin in most cases of COVID-19 pneumonia.

Stage III (severe)- the hyper inflammation phase is the most severe stage of COVID-19 infection.

It is due to activation of the innate immune system and T- lymphocytes depletion. It results in a cytokine storm with extrapulmonary systemic hyperinflammation. The clinical characteristics resemble the hyperferritinemia syndromes like the hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Patients present with shock, acute respiratory distress syndrome, acute kidney injury, myocarditis, and cardiopulmonary collapse. Inflammatory markers, including C-reactive protein, lactate dehydrogenase, D-dimer, ferritin, pro-inflammatory cytokines such as IL-2 and IL-6, granulocyte colony-stimulating factor, and tumour necrosis factor- α are significantly elevated (1).

This chapter aims to discuss Acute Kidney Injury (AKI) in COVID-19 infection, general considerations, and recommendations for COVID-19 in ESRD on dialysis and kidney transplant patients' management during the COVID-19 pandemic.

1. SARS-CoV-2 infection and acute kidney injury

COVID-19 patients are at high risk of acute kidney injury. This risk is correlated with COVID-19 disease severity. The presence of AKI and the need for renal replacement therapy (RRT) are associated with an increased risk of mortality. The causes of AKI in COVID-19 are multifactorial. They may include sepsis, direct viral invasion, cytokine release syndrome, hemodynamic instability, cardiorenal syndrome, activation of the renin-angiotensin-aldosterone system, coagulopathy, and micro thrombosis.

We aim to discuss the incidence, pathophysiology and provide practical tips to treat acute kidney injury in the COVID-19 pandemic.

1.1 Incidence of AKI in COVID-19

The incidence of AKI is widely ranged from 0.5% to 56.9% in various COVID-19 studies in China and the United States. AKI seems to develop at a median of 15 days (IQR13 - 19.5 days) (2).

In contrast, in another study that used a more sensitive Kidney Disease Improving Global Outcomes (KDIGO) criteria, most AKI developed within 7 days of admission (3). In critically ill patients, AKI incidence was 60-76 %.

The need for renal replacement therapy (RRT) of all patients admitted to a critical care unit ranges between 25-45% (4-6).

Fisher and colleagues found that AKI incidence in hospitalised patients with COVID-19 was higher than those without COVID-19 during the same period (56.9% vs 37.2%) (7).

Other renal abnormalities reported in COVID-19 infection included albuminuria 34%, proteinuria 63%, and hematuria 26.7% (8).

1.2 Causes and pathogenesis of AKI in COVID-19

The entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) into host cells is determined mainly by the co-expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2).

After the SARS-CoV2 spike (S) protein binds to ACE2 receptors in the host cell, the S protein is cleaved and activated by TMPRSS2, which allows the virus to release fusion peptides that help in the fusion of viral membrane to host cell membrane resulting in the release of the viral genome into the host cell (9). Several mechanisms have been proposed to cause AKI in COVID-19, including acute tubular necrosis (ATN) in the setting of sepsis, multi-organ dysfunction with acute lung injury, cytotoxic effects, cytokine release syndrome, hemodynamic instability, and cardiorenal syndrome. Toxic agents like drugs and contrast media, rhabdomyolysis, microangiopathy, and collapsing glomerulopathy have been reported as a potential culprit for AKI in COVID-19 infection (Figure 1) (10, 11).

1.2.1 Acute lung injury

The acute lung injury and acute respiratory distress syndrome (ARDS) associated with COVID-19 leads to AKI by releasing pro-inflammatory mediators, hemodynamic changes, and reduced cardiac output with high intrathoracic pressure. The systemic inflammation in the context of cytokine storm, microangiopathy, and reduction in kidney medullary hypoxia contributes to AKI (12).

Additionally, many studies showed that mechanical ventilation is associated with a threefold increase in the odds ratio of AKI in critically ill patients (13).

1.2.2 Sepsis

Sepsis and septic shock, due to viral or bacterial infection, is associated with hemodynamic instability and increased AKI risk. Higher inflammatory cytokines, including interleukin 6 (IL-6), coagulopathy, microangiopathy, increased vascular permeability, hypoperfusion, and tissue damage, are postulated AKI mechanisms in patients with sepsis. A study found that 59% of COVID-19 patients developed sepsis, 20% developed septic shock, and 15% developed a secondary infection. Superimposed bacterial infections have been reported in severely ill COVID-19 patients, which raises the possibility of sepsis playing a role in AKI in these patients (2, 4).

1.2.3 Hemodynamic instability and cardiorenal syndrome

The cardiorenal syndrome is another possible mechanism of AKI in patients with COVID-19. Viral myocarditis and cardiomyopathy with low cardiac output could decrease renal perfusion and AKI.

1.2.4 Cytokine release syndrome

It is characterised by excessive release of inflammatory cytokines, including IL6, IL8, and interferon-gamma, resulting in increased vascular permeability, diffuse alveolar damage, AKI, and other organ damage (14).

1.2.5 Rhabdomyolysis

Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China showed 9 patients with clinical evidence of kidney injury. Pigmented casts in the renal tubules containing high creatine phosphokinase levels, consistent with rhabdomyolysis, were seen in 3 out of the 9 cases (15).

1.2.6 Coagulopathy and micro thrombosis

Endothelial cell dysfunction leading to activation of the coagulation cascade and micro thrombosis plays a vital role in AKI in patients with COVID-19 (16). Coagulopathy has been reported in COVID-19 patients, with altered prothrombin time, activated partial thromboplastin time, D-dimer levels, fibrinogen levels, and fibrin degradation product levels, and disseminated intravascular coagulation (17).

The release of pro-inflammatory mediators and the uninhibited effects of angiotensin II stimulate the coagulation cascade, predispose to hypercoagulability and increase the incidence of thrombotic complications of COVID-19 (18, 19).

Histopathological analysis of 26 postmortem renal biopsy findings of patients with COVID-19 reported fibrin thrombi in the absence of red blood cell fragmentation and platelet thrombi (15).

1.2.7 Cytotoxic effects leading to tubular and podocyte injuries

SARS-CoV-2 infection can potentially cause tubular cell and podocyte injuries, leading to proteinuria, hematuria, and AKI.

Angiotensin-converting enzyme-2 (ACE2) receptors are present in type 2 alveolar cells of the lungs, heart, intestine, and kidneys.

In the Kidneys, they are mainly expressed in the podocytes and brush border apical membrane of the proximal tubular epithelial cells. Transmembrane protease serine 2 (TMPRSS2) is expressed in the distal tubule (20). These two surface membrane receptors are involved in SARS-CoV-2 entry into host target cells.

Angiotensin-converting enzyme-2 (ACE2) is counter-regulatory to the angiotensin-converting enzyme (ACE) by catalysing the hydrolysis of angiotensin II (a vasoconstrictor peptide and enhance inflammation) into angiotensin-(1–7) (a vasodilator peptide and attenuates angiotensin II-mediated inflammation). Several studies have shown that SARS-CoV infection can downregulate ACE2 expression on cells, thereby disrupting the physiological balance between ACE/ACE2 and angiotensin-II/angiotensin-(1–7); subsequently,,, causing severe organ injury (Figure 2) (21).

Given that SARS-CoV-2 is a species of SARS-related coronaviruses and utilises ACE2 as its receptor, the downregulation of ACE2 expression may involve multiple organ injury in COVID-19.

Whether the SARS-CoV-2 virus is detected in kidney tissue of patients with AKI remains unclear. However, there is conflicting evidence regarding the cytopathic effects of the SARS-CoV-2 virus on renal tubular epithelial cells.

The presence and detection of viral particles in the tubular epithelium and podocytes have been reported in some studies (15), and viral sequences were identified in some patients' urinary samples (22).

Corona virus-like particles were also observed under electron microscopy in the proximal tubular epithelium and podocytes (23).

However, another study did not detect any virus RNA in kidney tissue by in situ hybridisation (24).

1.2.8 Collapsing glomerulonephritis

A postmortem study showed that the AKI in 9 out of 26 autopsied COVID-19 patients, characterised by diffuse proximal tubule injury and necrosis on light microscopy (15). Other pathologic features in COVID-19 have been reported. They include focal segmental glomerulosclerosis in patients with high-risk APOL1 genotype (24), membranous nephropathy, anti-glomerular basement membrane (anti-GBM) disease, allograft rejection (25), and thrombotic microangiopathy (26). It is postulated that either the direct viral cytopathic effect or presence of increased cytokines from the systemic inflammatory response or both can lead to a collapsing variant of focal segmental glomerulosclerosis, especially in patients with high-risk alleles of the APOL1 gene (27).

1.3 AKI and COVID-19 outcomes

As described in non-COVID-19 patients, AKI is associated with worse outcomes and increased mortality. In 2005 the mortality rate in patients with SARS was higher in patients with AKI than without AKI (92% versus 8% respectively) (28). In a hospitalised cohort of 5,449 patients admitted with COVID-19, AKI incidence was 36.6%. Of these, 14.3% required dialysis. AKI was reported in 89.7% of ventilated patients compared to 21.7% of non-ventilated patients. Renal replacement therapy was required in 276/285 (96.8%) of patients on mechanical ventilation. About half of the patients who required ventilation developed AKI within 24 hours of intubation. The mortality rate was 35% in those with AKI compared to 6% in those without AKI. Moreover, the mortality rate was 55% in those requiring dialysis (6).

1.4 Management of AKI in COVID-19 infection

The treatment of AKI in COVID-19 is not different from other settings. It begins with an evaluation of the cause of AKI. A broad framework of prerenal, renal, and postrenal causes should be analysed. Good history, physical examination, ascertaining the timeline of AKI through chart review, medication reconciliation, and stopping any potentially nephrotoxic agents are essential components in AKI management. Laboratory tests, including blood and urine analysis and imaging studies, will help diagnose different AKI causes. The treatment of AKI in COVID-19 can be divided into general measures, pharmacologic management of COVID-19, optimising hemodynamic and volume status, applying lung-protective ventilation strategies, dialysis, and extracorporeal blood purification therapies. Fluid overload is an important reason to initiate dialysis in AKI. Close attention is needed to keep the patient in euolemia.

1.5 Renin-angiotensin system inhibitors and COVID-19

Initial concerns were raised regarding the association of ACE inhibitors and angiotensin II receptor blockers with increased risk of COVID-19. Up to date, there is no clinical evidence of harm with renin-angiotensin system inhibitors in COVID-19. Many professional societies, including the American College of Cardiology, American Heart Association, and European Society of Hypertension, emphasised that these agents should not be discontinued in stable patients with COVID-19. However, for inpatients with COVID-19, discontinuation should be based on hemodynamic and clinical status and renal function (29).

1.6 Pharmacologic management of COVID-19

Antiviral therapy, immunomodulatory and anti-inflammatory therapy have been tried in COVID-19 patients. Broad-spectrum antibiotics are usually used to treat secondary bacterial infections in patients with COVID-19. At present, there are no specific drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of COVID-19. However, the FDA issued emergency use authorisations for remdesivir.

1.7 Optimising hemodynamics and volume status

Sepsis and hemodynamic alterations in the setting of COVID-19 related acute respiratory distress syndrome may lead to impaired gas exchange, kidney medullary hypoxia, and right heart failure resulting in AKI.

COVID-19 may also lead to cardiogenic shock due to myocarditis, cytokine release syndrome, sepsis-induced systemic vasodilation, and hypovolemic shock due to capillary leak and loss of intravascular volume because of cytokine storm (30, 31).

Therefore, optimising hemodynamic and volume status are essential steps in managing COVID-19 infection.

Close attention with frequent hemodynamic assessment is needed to keep the patient in euvoolemia rather than volume depletion or overload.

Fluid infusion needs to be initiated to prevent hypoperfusion of vital organs in hemodynamically unstable COVID-19 patients who showed volume depletion signs.

Blood pressure support with vasopressors is needed to optimise hemodynamics in patients with septic and cardiogenic shock.

Diuretic therapy should be considered in patients with volume overload and cardiorenal syndrome. Renal replacement therapy should be considered in any patient with AKI and volume overload refractory to diuretics.

1.8 Lung-protective ventilation:

The mechanisms of AKI during mechanical ventilation with high positive pressure are multifactorial. High intrathoracic pressure due to ventilator interaction with injured or stiff lungs results in decreased cardiac output that leads to both reductions of renal blood flow and gas exchange abnormalities with hypoxemia, hypercarbia, and acidosis that diminish renal perfusion pressure and subsequently predispose to AKI.

Other ventilator-induced AKI mechanisms include releasing inflammatory cytokines from a ventilator-induced lung injury, hemodynamic compromise, and activation of neurochemical pathways that impair intra-renal blood flow.

The risk of ventilator-induced AKI can be prevented by applying ventilation strategies that combine low tidal volumes to prevent alveolar over-distention (volutrauma) and high positive end-expiratory pressure (PEEP) to prevent repeated alveolar collapse and expansion (atelectrauma) with an appropriate inspired fraction of oxygen (FiO₂).

1.9 Renal replacement therapy (RRT) and AKI in COVID-19:

In general, the early initiation of RRT in AKI is debated.

Many trials reported no difference in early versus late RRT outcomes (32). Therefore, in the setting of AKI in COVID-19, traditional clinical indications for RRT should be applied to minimise the need for additional workforce, dialysis machines, and healthcare workers' exposure to COVID-19 risk. There is no reported evidence suggesting differences in outcomes between sustained low-efficiency dialysis (SLED) or continuous renal replacement therapy (CRRT) in critically ill patients.

Both dialysis modalities are accepted for use in AKI with COVID-19 depending on available resources, workforce, machines, and consumables.

Many challenges arise during renal replacement therapy for patients with COVID-19.

Significant challenges are dialysis staff and equipment shortage. One way of conserving the workforce is to cohort dialysis patients with COVID-19 with a higher nurse: patient ratio.

As no evidence suggests, a higher RRT dose improves patient outcomes (33).

There are concerns about the availability of dialysis equipment and consumables (fluids, filters, etc.), a lower dose of RRT or dialysis time reduction after achieving metabolic control may be considered.

Intermittent hemodialysis sessions have often been shortened, with potassium binding resins between sessions to accommodate the increased number of dialysis patients. If CRRT is available, treatments with higher flow rates may be used to provide adequate clearance while allowing the CRRT machines to be used on two patients daily.

Sustained low-efficiency dialysis has been used in hemodynamically unstable patients in facilities without CRRT capabilities.

Some centres used peritoneal dialysis fluid as replacement fluid and performed acute peritoneal dialysis as a modality for renal replacement therapy in AKI due to COVID-19 (34, 35).

Severe COVID-19 disease is accompanied by hyper inflammation and thrombosis, leading to increase dialysis circuit clotting tendency and more significant filter clotting.

This might be reduced by using unfractionated heparin infusion in the dialysis circuit, locking the dialysis catheter with heparin or tissue plasminogen activator, and increase blood flow during RRT.

Prone-position ventilation is required for COVID-19 patients with Acute Respiratory Distress Syndrome (ARDS). This poses enormous difficulty in providing hemodialysis treatment and increases machine pressure alarms and dialysis circuit clotting tendency.

In this case, an internal jugular dialysis catheter is preferred over others, and catheter insertion to be performed before putting the patient in the prone position.

Another challenge during renal replacement therapy in COVID-19 patients is the long exposure of dialysis nurses and technicians. Some centres used long extension tubing to place the dialysis machines outside the patient room.

However, this method increases the risk of hypothermia, line and filter clotting, and blood loss (34).

Extracorporeal membrane oxygenation (ECMO) is being used in critically ill COVID-19 patients to support both the heart and the lungs. When renal replacement therapy (RRT) is performed in conjunction with ECMO, it can be provided independently via a separate catheter and circuit (parallel system), which is the preferred method, or by introducing the dialysis circuit into the ECMO circuit (integrated system) in various ways. However, in the last case, the blood should always be returned to the ECMO circuit before the oxygenator reduces the risk of air entering the circuit and thrombosis.

1.10 Extracorporeal blood purification therapy in COVID-19

Cytokine release syndrome with an overactive immune response is evidenced in the severe hyper inflammation phase of COVID-19 infection with subsequent multi-organ dysfunction.

Various modes of extracorporeal blood purification therapies to restore immune homeostasis by eliminating and deactivating inflammatory mediators have been used in cytokine release syndrome and multi-organ dysfunction including, continuous renal replacement therapy with high volume hemofiltration, hemoperfusion with special cartridges targeting endotoxins or cytokines, high cut-off membranes and membranes with enhanced adsorption properties (e.g., CytoSorb and oXiris). Currently, there are no randomised controlled trials to demonstrate a beneficial effect of blood purification therapy and no comparative study between immunomodulatory therapy (e.g., tocilizumab) with extracorporeal blood purification therapies. The early use of polymyxin B hemoperfusion in abdominal septic shock (EUPHAS trial) in 64 patients demonstrated a statistically significant improvement in hemodynamics and organ dysfunction (36).

However, data from the large EUPHRATES trial in 450 patients with septic shock and high circulating endotoxin levels showed no difference in mortality between polymyxin B hemoperfusion and conventional medical therapy with sham hemoperfusion (12, 37).

CytoSorb, a hemoabsorption device containing hemocompatible porous polymeric beads capable of removing cytokines, has been approved by the U.S Food and Drug Administration for use in COVID-19.

Various studies using cytoSorb in animal models of sepsis have reduced cytokine levels, reduced organ injury, and improved survival (38, 39). However, a large randomised controlled trial in 100 patients with sepsis, septic shock, and acute lung injury who were randomly assigned to either treatment with cytoSorb hemoperfusion for 6 hours daily for up to 7 consecutive days (n= 48), or no hemoperfusion (n=52), showed that CytoSorb hemoabsorption removed IL-6 by 5-18% in each treatment. Nevertheless, overall, there were no reductions or differences in plasma IL-6-levels, multiple organ dysfunction scores, ventilation time, and time course of oxygenation in the two groups (40).

COVID-19 patients may develop superimposed gram-negative bacterial sepsis or cytokine release syndrome; therefore, they may use hemoperfusion using polymyxin B cartridge to provide endotoxin elimination. CytoSorb devices for cytokine removal is justified. Moreover, renal replacement therapy should be provided if dialysis support is needed.

The U.S Food and Drug Administration authorises oXiris filter during the COVID-19 pandemic. The oXiris filter is a new generation of extracorporeal blood purification filters that remove both endotoxins and cytokines, in addition to the routine hemodialysis function using the Prismaflex CRRT machine. However, no randomised trial explores the oXiris filter's benefit as blood purification therapy (41).

There are no specific criteria to perform blood purification therapy in COVID-19 infection.

A suggested cytokine removal strategy, not yet based on substantial evidence but instead on clinical experience, should be reserved for COVID-19 patients with evidence of high cytokine levels (IL-6 and IL-8), high inflammatory markers, high plasma ferritin, high sequential organ failure assessment (SOFA) score, clinical symptoms of hemodynamic instability requiring vasopressors, and signs of immune dysregulation. If endotoxin removal is indicated for superimposed suspected sepsis (high procalcitonin and/or positive bacterial culture) or confirmed sepsis (with elevated endotoxin activity assay), 2 hours' sessions of polymyxin hemoperfusion over 2 days are advised.

These sessions may or may not be followed by hemoperfusion with CytoSorb device. However, if hemoperfusion is required for cytokine removal, multiple sessions with CytoSorb device can be arranged in the following days. The oXiris filter can also be used with CRRT machine for cytokine removal, endotoxin removal, and dialysis support (42).

1.11 Drug dosing in AKI with or without RRT in COVID-19

Various drugs have been tried to treat COVID-19 infection without clear evidence. Some of them (e.g., hydroxychloroquine) has been around for many years, whereas others (e.g., remdesivir) are part of clinical trials. A careful review of pharmacokinetics and discussion with a clinical pharmacist is essential before starting them. Moreover, some drugs with a small molecular weight are dialysable while other protein-bound drugs are not. Some drugs also interact with and lead to a toxic level of transplant medications by inhibiting cytochrome P450.

Table 1 summarises the common drugs tried in COVID-19 treatment with their dose adjustment during AKI and dialysis.

Remdesivir is a prodrug, metabolised into its active anti-viral agent form (GS-441524).

It inhibits the action of viral RNA-dependent RNA polymerase resulting in the termination of viral RNA transcription and replication (43). The prodrug half-life is about 20 minutes, whereas the active metabolite half-life is about 20 hours (44).

Remdesivir is 75% eliminated in the urine and 18% eliminated in the faeces. Remdesivir is 88-93% bound to plasma proteins with a high distribution volume.

Remdesivir formulation includes the vehicle sulfobutylether-beta-cyclodextrin sodium (SBECD), cleared by the kidneys and accumulates when the GFR is < 30ml/min.

There is an additional concern that SBECD can cause AKI via osmotic tubulopathy, as reported from its use as an excipient for intravenous voriconazole (45). The 10-day course of remdesivir was associated with more AKI than the 5-day course at 8% versus 2%, respectively, explained by its excipient (SBECD) accumulation (46).

Owing to the small molecular weight of remdesivir (602.6 gm/mol) that make it a dialysable drug, it is reasonable to give the dose after dialysis (47).

There is no reported drug interaction between remdesivir and transplant medications.

2. COVID-19 infection in patients with end-stage renal disease (ESRD) on dialysis

2.1 Dialysis patients and risk of COVID-19

Patients with ESRD on dialysis are at higher risk for COVID-19 infection due to frequent travel, gathering, cross-contamination in the dialysis units, and abnormalities in the adaptive and innate immune systems.

Defective innate and adaptive immune systems are responsible for a reduced antiviral response in this group of patients. Moreover, chronic activation and reduced function of the innate immune system and endothelial dysfunction may result in severe COVID-19 infection.

Additionally, the dialysis population has other comorbidities such as diabetes mellitus, hypertension, and cardiovascular disease, associated with a higher risk of adverse COVID-19 outcome.

Apart from logistic challenges and the need for strict preventive strategies within dialysis units, treating patients with ESRD and COVID-19 is not different from that of the general population.

2.2 Clinical presentation, incidence, course, and outcome of dialysis patients with COVID-19

Dialysis patients are considered a high-risk group for COVID-19, both in terms of infection risk and outcome. Patients with ESRD are less likely to have typical COVID-19 symptoms than patients with and without CKD.

Moreover, a high degree of clinical suspicion is required as the clinical presentation may be masked by the chronic dyspnea due to fluid overload and inadequate febrile response that is commonly seen in the dialysis population.

Interestingly, they are more likely to present with altered sensorium.

Several studies have reported the clinical presentation, incidence, and outcome of dialysis patients with COVID-19 infection.

Xiong et al. reported from a multicenter, retrospective, observational study that 154 of the 7154 hemodialysis patients in 65 medical institutions (2.2%) had COVID-19 infection.

Of these, only 21.4% were asymptomatic, whereas 52% had a fever, 37% had a cough, and 82% had radiological abnormalities, including ground-glass or patchy opacities. On further analysis of the available 131 patients, 101 patients were categorised as mild/moderate, and 30 patients with a severe or critical illness. At the end of the follow-up period, 41 (31%) patients were deceased, whereas 41 (31%) patients still hospitalised, and 47 (36%) patients had been discharged home (48).

In a study from Japan, 99 dialysis patients

were reported, of whom 16 (16.2%) died, which was higher than in the general population (5.3%).

Fever was reported in 95.1%, and cough in 63.5% of patients presented with computed tomography (CT) abnormalities typical for COVID-19 pneumonia (49). Alberici et al. reported from a study in 4 dialysis units in Brescia, Italy that, 94 of 643 (15%) of hemodialysis patients had positive COVID-19 tests.

Of the 94 patients, 18 (20%) were asymptomatic, 68% had a fever, 23% had a cough, and 25% had shortness of breath. Whereas 37 (39%) patients were managed in an outpatient setting, 57 (61%) patients were admitted to the hospitals. In 13 of the 18 (72%) asymptomatic patients at diagnosis, chest X-ray was negative.

From those admitted to the hospital (N=57), 42% had died, and 79% had developed ARDS. However, the overall reported mortality was 29% in the entire cohort (50).

A report from France's COVIDIAL study showed that 123 patients out of 1346 hemodialysis patients tested positive with COVID-19.

Only 3 % of positive patients were asymptomatic, whereas fever was present in 57%, cough in 69%, shortness of breath 51%, and diarrhoea in 34%.

Out of 123 patients, around 71% were admitted to the hospital, and 24% had died (51). In a large retrospective study of 10,482 patients with COVID-19 who were admitted to 13 New York hospitals, only 419 had ESRD.

Of whom 408 (97.4%) were on hemodialysis and 11 (2.6%) were on peritoneal dialysis.

Patients with dialysis had a higher mortality rate than those without (31.7% vs 25.4%, odds ratio 1.38). However, the rates of mechanical ventilation were similar in both groups with or without ESRD (89 [21.2%] vs 2076 [20.6%], respectively) (52).

The studies in peritoneal dialysis patients are limited. From the same New York cohort of 419 hospitalised patients with ESRD, 11 patients (2.6%) were on chronic peritoneal dialysis.

Nine of them were discharged alive, whereas three patients required mechanical ventilation, and 2 of them died.

The main presenting symptoms were fever (64%), diarrhoea (55%), shortness of breath, and cough (45%).

Initial chest radiographs showed bilateral pulmonary infiltrates in nine cases (82%). One patient had lobar pneumonia, and another had no acute radiologic findings (53).

An intriguing finding is that dialysis patients may not clear the virus easily.

In a cohort of 39 COVID-19 positive patients, 41% did not clear the virus by day 15.

Therefore, the authors recommended maintaining COVID-19 positive patients' isolation until the virus is cleared by PCR testing rather than a symptom-free strategy (54).

2.3 Management of COVID-19 in patients with ESRD

2.3.1 Treatment of COVID-19 in the dialysis population is largely supportive with oxygen and prophylactic heparin.

Specific treatment with antiviral or immunomodulatory agents has been tried in many studies. The trials of hydroxychloroquine and lopinavir/ritonavir in COVID-19 infection have yielded negative results. However, the use of remdesivir appears to be a promising treatment for COVID-19 infection. In a randomised controlled trial including 1063 patients, remdesivir reduced the median time of recovery from 15 to 11 days compared to placebo. However, no patients with ESRD were included in this study.

Safety data on the use of remdesivir in kidney failure are scarce, and its use is generally contraindicated in patients with eGFR below 30 mL/min (55). A study from India described the use of remdesivir in 16 patients with ESRD and 30 patients with AKI admitted to the intensive care unit.

Eight of 46 patients were recipients of kidney transplants.

Thirty-six (78.2%) patients were on dialysis (ESRD [n=16] and AKI [n=20]) at the time of initiation of remdesivir.

In this cohort, most patients tolerated the infusion without severe elevations in liver enzymes (>5 times the upper limit of normal) or decline in renal function. Only one patient experienced a hypersensitivity reaction during treatment.

Fourteen (30.4%) patients died, 24 (52.2%) patients were discharged from the hospital after recovery, and 8 (17.3%) patients are still hospitalised.

This study concluded that remdesivir is well tolerated in patients with AKI and CKD, including those on hemodialysis (56).

The RECOVERY trial was designed to evaluate dexamethasone treatment's effects compared to usual care in hospitalised COVID-19 infected patients in the United Kingdom.

In this trial, 2104 patients were assigned to receive dexamethasone and 4321 patients to receive usual care.

The mortality rate at 28 days was significantly lower in the dexamethasone group than in the usual care group (22.9% vs 25.7%, respectively).

The use of dexamethasone resulted in lower 28-day mortality than that in the usual care group among those who were receiving either invasive mechanical ventilation (29.3% vs 41.4%; odds ratio, 0.64) or oxygen alone without invasive mechanical ventilation (23.3% vs 26.2%; odds ratio, 0.82) but not among those receiving no respiratory support (17.8% vs 14.0%; odds ratio, 1.19) (57).

Another immunomodulatory drug used in COVID-19 is interleukin-6 (IL-6) inhibitor, tocilizumab, which may be used in renal insufficiency patients. Moreover, it is not removed by dialysis therapy (58).

Also, adequate dialysis treatment in the hypercatabolic state for ESRD patients with COVID-19 infection must be provided. However, under exceptional circumstances, logistic demands may necessitate a reduction in dialysis time and frequency to preserve supplies and allow for more patients' dialysis treatment. Table 1 summarises some drugs tried in COVID-19 treatment with their dose adjustment during AKI and dialysis.

2.4 Iron and erythropoietin use in patients infected with COVID-19

Anaemia is a prevalent problem in patients with ESRD on dialysis, treated with iron and erythropoietin. However, during an active infection, intravenous iron use is generally avoided because iron is an essential nutrient for nearly all microbial species, including bacteria, fungi, and parasites that infect humans. Also, iron is required for viral replication and other cellular activities of many viruses such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), and coronaviruses. Moreover, iron accumulation has been associated with increased mortality (59-61).

A rise of serum ferritin as an acute phase reactant is commonly seen in the severe inflammation associated with various microbial infections, including COVID-19 (62). While the emerging COVID-19 infection is much less understood compared with HIV, HCV, or SARS-CoV, it is reasonable that reducing or withholding iron therapy during COVID-19 infection could be an appropriate approach.

Similarly, patients with severe inflammation are hyporesponsive to erythropoietin, and higher doses of erythropoietin might increase the tendency of thromboses (63).

Consequently, treatment of anaemia with erythropoietin stimulating agents in patients with COVID-19 infection would not only have limited effectiveness but could also be potentially harmful due to a high prothrombotic state seen in severe COVID-19 infection.

Hence, withholding erythropoietin or giving small maintenance doses and having a low blood transfusion threshold to maintain a haemoglobin target range of 8-9 gm% are suggested approaches (62).

2.5 Preventive strategies of COVID-19 spread in outpatient dialysis units and centres

Various nephrology societies worldwide have issued specific guidelines for patients and staff screening, dialysis facilities adjustment, management of suspected and confirmed cases, and health education to limit outbreaks of COVID-19 in dialysis units. However, these guidelines may differ based on logistics and resources available in different countries. Most international dialysis organisations emphasised the importance of wearing masks, hand hygiene, social distance, and alertness to the atypical symptoms of COVID-19.

For patients with confirmed COVID-19, a visor mask and gloves are suggested by all guidelines. Additionally, isolation gowns are suggested throughout procedures with a higher risk of transmission, like initiating and terminating dialysis, manipulating access needles and catheters. Below is a summary of the main differences between the main three international renal societies guidelines (64).

2.5.1 American Society of Nephrology (ASN) guidelines:

Screening test policy: For suspected patients only.

Facility adjustment: Medical staff and shift adjustment, adjustment of dialysis area, provide tissue for every patient.

Mask and other equipment: Surgical masks acceptable, Masks only for symptomatic patients, Prioritise medical supply.

Suspected Cases: Treat as confirmed cases.

Confirmed Cases: Airborne isolation not required, separate rooms with the door closed, assign isolation shift or facility or dialysis in a corner or end-of-row two meters of separation from other patients (65).

2.5.2 European renal Association (ERA-EDTA) guidelines:

Screening test policy: For suspected patients, only

Facility adjustment: Self-monitoring symptoms of medical staff, separate teams to avoid cluster infection, install hand sanitisers, adequate air ventilation.

Mask and other equipment: FFP2 or FFP3 medical masks for caregivers caring for confirmed COVID-19 cases.

Suspected Cases: Dialysis in the isolation room or the last shift.

Confirmed Cases: Airborne isolation room, Do not dialyse in the outpatient dialysis facility.

Others: Screening test before vascular surgery, a home visit by staff for PD patients, keep away from the young population (66).

2.5.3 International Society of Nephrology (ISN) guidelines:

Screening test policy: For all dialysis patients.

Facility adjustment: Build a backup list of medical staff, assign area/shifts for symptomatic patients, supplies for hand and respiratory hygiene.

Mask and other equipment: Surgical masks for all patients.

Suspected Cases: Treat as confirmed cases.

Confirmed cases: Separate with two meters from others, provide surgical masks and fixed medical equipment (67).

2.6 Management of dialysis patients exposed to people who were tested positive for COVID-19

A vital management step for preventing the spread of COVID-19 in the dialysis unit is to perform screening for every patient every time they present for dialysis in the unit. Dialysis staff should follow the guidelines implemented by their institution and public health.

2.6.1 Exposed patients without symptoms suggestive of COVID-19

These patients must wear a surgical mask during the entire dialysis session with rigorous disinfectants.

Ideally, they should be tested for COVID-19 and transferred to a separate dialysis unit for patients with suspected/confirmed COVID-19.

If a separate dialysis unit is not available, they have to be dialysed in their parent unit (with other non-COVID-19 patients) using isolation or private rooms. However, if there are no isolation rooms in the unit, the exposed patients can be cohorted together in the last shift of the day to minimise exposure to other patients (68).

2.6.2 Exposed patients with symptoms suggestive of COVID-19

These patients must be tested for COVID-19 in the dialysis unit or sent to the local outpatient testing centre or hospital for COVID-19 PCR testing and further workup and management. If they become COVID-19 positive, these patients should be dialysed either at bedside if they are symptomatic and get admitted to the hospital or in a separate dialysis unit dedicated for COVID-19 patients until their COVID-19 PCR test come back as negative, or they are no longer infectious (usually we used two weeks' period) (65, 68).

2.6.3 Providing transportation to suspected or infected patients with COVID-19 to the dialysis unit

Dialysis is considered an essential medical treatment, so patients should come to the dialysis unit even if a lockdown is in place.

The lack of public transport during the pandemic has been a significant barrier for many dialysis patients who do not have private transportation.

Patient transport should be arranged either with private vehicles or ambulance service to and from dialysis facilities while following safety guidelines.

Dialysis facilities should provide a letter to the patients and transportation company explaining that the patient will require continued dialysis treatment service even during the lockdown. Some ambulances might be assigned exclusively to transport confirmed or suspected COVID-19 patients between the health facilities.

The staff should wear the recommended personnel protective equipment, and the ambulance undergoes deep-clean disinfection after each trip.

Suspected or infected patients should wear masks during the dialysis unit trip.

2.6.4 Return of dialysis patient from COVID-19 dedicated dialysis unit to their parent unit

This is very challenging as every patient course is slightly different from others, and some patients may remain COVID-19 positive for a longer duration. Two strategies are widely adopted to determine the time of discontinuation of infection prevention and control precautions and the return time of dialysis patients to their parent dialysis unit, including PCR testing-based strategy or symptom-based strategy (68).

2.6.4.1 PCR testing-based strategy

In this strategy, the dialysis patient should remain under isolation and dialysed in a separate dialysis unit or isolation room or cohorted dialysis shift until their COVID-19 PCR test becomes negative for two consecutive tests.

Although it seems to be the safest approach, it might be inconvenient.

It also increases the burden and reduces the slots available in the dedicated COVID-19 dialysis unit. Because prolonged shedding of viral RNA in COVID-19 patients with positive PCR testing for up to 12 weeks in some cases, like immunocompromised dialysis patients, may prevent timely discharge from the hospital or quarantine facilities.

Nevertheless, patients with severe COVID-19 infection may shed infectious virus for a longer duration than patients with mild infection. It should be noted that a prolonged viral shedding does not mean someone is still infectious, and the presence of the RNA might only reflect the presence of dead viral particles. Therefore, PCR testing-based strategy is not recommended except in those who are severely immunocompromised and shed the virus for more than 20 days.

Bullard et al.

reported that infectious virus could not be detected in respiratory tract samples obtained more than 8 days after onset of symptoms despite continued detection of high viral RNA levels (69). On the other hand, Van Kampen et al.

studied the shedding of infectious virus in 129 severely ill COVID-19 patients. They found that the median duration of virus shedding was 8 days after onset of symptoms (IQR 5-11).

The probability of detecting infectious virus dropped below 5% at the time point of 15.2 days post-onset of symptoms. This study implies that a symptom-based strategy to discontinue patient isolation from COVID-19 should also consider disease severity and give a more extended period for severely ill patients (70).

2.6.4.2 Symptom/time -based strategy

Accumulating evidence supports discontinuing isolation and precautions for persons with COVID-19 using a symptom-based strategy, including non-respiratory symptoms. In this strategy, the patients should wait for a fixed period after symptoms appear and disappear. It has the advantage of limiting unnecessarily prolonged isolation and unnecessary use of laboratory testing resources.

2.6.4.2.1 Patients with mild to moderate COVID-19 infection who are not severely immunocompromised

- At least 10 days after first symptom appearance and
- At least 24 hours after being afebrile without the use of paracetamol and
- Symptomatic improvement (e.g., cough, shortness of breath).

2.6.4.2.2 Patients with severe and critical COVID-19 infection or who are severely immunocompromised

- At least 10 days and up to 20 days after first symptom appearance and
- At least 24 hours after being afebrile without the use of paracetamol and
- Symptomatic improvement (e.g., cough, shortness of breath).

2.6.4.2.3 Asymptomatic patients throughout their COVID-19 infection

- For patients who never developed symptoms, the date of the first positive COVID-19 PCR test should be used in place of the date of symptom onset. The isolation precautions should be done 10 days after the first positive COVID-19 PCR test in those who are not immunocompromised, at least 10 days and up to 20 days after the first positive COVID-19 PCR test for severely immunocompromised patients.
- Patients with ESRD are, by definition, immunocompromised and may have prolonged viral shedding, posing a potential risk if returned to their parent dialysis units earlier, based purely on a symptom/time-based strategy. Therefore, many international dialysis organisations continue to use a test-based strategy to discontinue isolation.

2.7 Contingency plan when hemodialysis unit capacity is overwhelmed

2.7.1 Overwhelmed outpatient dialysis units

In many circumstances, the outpatient dialysis units will be challenged to perform dialysis treatments over their usual capacities due to:

- Dialysis staff and physicians need self-isolation due to exposure to or developing COVID-19.
- New ESRD patients
- New patients with AKI who remain dialysis-dependent awaiting recovery of AKI
- Failing peritoneal dialysis patients who are transferred to hemodialysis
- Home dialysis patients with either patient or caregiver infection and need to self-isolate.
- Movement of dialysis patients from other areas due to lockdown.

2.7.2 Contingency hemodialysis plan

A continuous increase in numbers of dialysis patients with COVID-19 will stretch the available dialysis units and machines' available capacity, resulting in a marked reduction in the dialysis slots for providing hemodialysis to this population. Therefore, a contingency plan when hemodialysis capacity is overwhelmed is highly needed, which might include:

2.7.2.1 Increase hemodialysis units' capacity

Increasing the working hours of hemodialysis units to 24/7 will potentially add 1-2 extra shifts daily. This is one of the easiest and feasible first steps. In this case, the infrastructure is ready, and the old group of patients can continue dialysis in the daytime. Simultaneously, overnight shifts can be used for inpatient and new dialysis populations. Staff and machines workload will undoubtedly increase. Therefore, staff duty arrangement and redistribution are the main challenges here.

2.7.2.2 Modifying dialysis prescription

If the above strategy is not possible or fails, then changes to the dialysis prescription can be considered by either:

- Reduction of dialysis duration while keeping the same frequency or
- Same or increase dialysis duration while reducing dialysis frequency: e.g., twice a week dialysis for most patients. This is most suitable for residual kidney function without hyperkalemia or fluid overload. It is practical, but it adds significantly to the logistical complexity of scheduling patients or
- Reduction of both dialysis duration and frequency: This can be a challenge. However, this option is possible only for patients with good urine output and dietary compliance.

3 COVID-19 infection in patients with a Kidney transplant

Kidney transplant patients are at higher risk of COVID-19 infection due to their suppressed immunity.

Like the general population, social distancing and avoiding non-essential travel are essential measures to reduce COVID-19 infection risk in patients with a kidney transplant.

Therefore, most kidney transplant outpatient follow-up should be restricted to a combination of phone and video consultations with prior arrangement of laboratory blood testing. Most transplant societies agree in urging patients with kidney transplant not to change immunosuppression medications preemptively, even with the ongoing COVID-19 community spread.

This is mainly because reducing immunosuppression medications may precipitate kidney allograft rejection that will require hospitalisation and even greater immunosuppression doses and additional risk to COVID-19 infection.

Moreover, there is no proven role to support drug prophylaxis for COVID-19 in transplant patients.

These agents may be harmful and sometimes fatal, as in hydroxychloroquine, which may cause prolonged QT interval putting people at risk of cardiac arrhythmias and death.

In kidney transplant patients with confirmed COVID-19, immunosuppression medications should be reviewed and reduced on a case by case basis.

It might involve withholding mycophenolate or azathioprine in those patients who also take tacrolimus or cyclosporine. Many transplant programs have suspended their living kidney transplantation during the COVID-19 pandemic.

However, there are no reported cases of COVID-19 transmission from a live or deceased donor to the recipient.

The virus has been isolated in the kidney and urine of some COVID-19 patients, and thus, the use of deceased organs from diagnosed COVID-19 patients remains controversial.

3.1 Clinical presentation and outcomes of kidney transplant recipients with COVID-19 infection

Several studies reported that kidney transplant patients with COVID-19 infection typically present with similar symptoms and signs as in the general population, including fever, cough, and bilateral infiltrates on chest x-ray.

In a case series of 15 kidney transplant patients admitted with COVID-19, around 87% reported fever and 60% reported cough, whereas 47% of the cohort showed multifocal opacities on chest x-ray. Only 33% had normal radiographs.

Additionally, most patients had elevated inflammatory markers, including ESR, CRP, and IL-6.

Approximately 27% of these cases required intubation, 20% required dialysis, and 28% had died (71).

A similar finding in an Italian cohort of 20 kidney transplant patients admitted with COVID-19 infection, where all patients reported fever, 50% reported cough, 50% had bilateral pulmonary infiltrates on chest x-ray.

Only 15% had normal chest radiographs.

In this cohort, about 25% of the patients died despite immunosuppression withdrawal and early administration of antiviral therapy (72).

3.2 Treatment of COVID-19 in kidney transplant recipients:

Currently, there are no clinical trial data to guide the treatment of COVID-19 infection in the kidney transplant population. Moreover, a viral infection may precipitate acute allograft rejection, which may cause graft failure and an even greater need for further immunosuppression.

Additionally, COVID-19 treatment regimens have included high dose steroids, IV immunoglobulin, and other antiviral and immunomodulatory agents, which require careful monitoring of transplant medications dosage.

Kidney transplant management with COVID-19 infection is extrapolated from evidence obtained from treating other life-threatening infections, which involves reducing or stopping immunosuppression.

Various studies reported that elective withdrawal of calcineurin inhibitors (CNI) increases the risk of acute allograft rejection more than mycophenolate mofetil withdrawal (73, 74).

Moreover, Carbajo-Lozoya et al. suggested that CNI agents might inhibit the growth and replication of coronaviruses (75).

These findings may support the continued use of CNI agents while reducing or withholding antiproliferative drugs (mycophenolate and azathioprine) in transplant recipients with COVID-19 infection.

Reintroducing antimetabolite agents may be delayed for up to 2 weeks after discharge or cure from COVID-19 infection.

CNI Levels should be frequently monitored and minimised during active viral infection and drug interaction. It is well known that withdrawal of one of the immunosuppressive agents necessitates increasing the dose of steroids to prevent renal allograft rejection.

Furthermore, high doses of steroids are sometimes used in critically ill patients for other reasons, which should be discussed between the intensivists and nephrologists.

Various societies have suggested management guidelines for transplant recipients with COVID-19 infection.

3.3 The British Transplantation Society management guideline for transplant recipients with COVID-19 infection (Updated 22nd January 2021) (76)

3.3.1 General management for transplant patients with suspected COVID-19 infection

- Assess the patient and exclude other causes of fever and symptoms (CMV, pneumocystis, community or hospital-acquired pneumonia, influenza, urinary sepsis, etc.).
- Nasopharyngeal swab for COVID-19 PCR in all potential cases.
- A negative swab result requires repeat testing if clinical or radiological suspicion is high.
- The suspected patient should wear a surgical mask to reduce infection risk.

3.3.2 Patients who do not require hospital admission

- Stop antiproliferative agents (mycophenolate and azathioprine).
- Review the total burden of immunosuppression and consider a reduction of CNI.
- High or increased dose steroid is NOT recommended at this stage.
- Patients should self-isolate in line with local guidance.
- Call patients for any change in symptoms.
- Consider restarting immunosuppression 14 days after onset of symptoms or if asymptomatic without paracetamol for a minimum of 3 days.
- Early monitoring of renal function when safe to do so and risk of transmission to other people is low.
- Due to prolonged viral shedding in immunocompromised patients and to prevent the risk of COVID-19 transmission, COVID-19 cured transplant recipients must be examined in a separate area from non-affected individuals.

3.3.3 Patients who are unwell and admitted to hospital

- Stop antiproliferative agents (mycophenolate and azathioprine).
- Reduce or stop CNI.
- Dexamethasone 6mg daily for 10 days.
- Remdesivir may be considered in line with local guidance.
- Oxygen therapy achieves saturation of 92-96% (unless COPD).
- Regular observation of oxygen saturation to monitor for rapid deterioration.
- Fluid administration to maintain a euvoemic state.
- Consider stopping ACE inhibitors/ARBs in patients at risk of AKI.
- Consider antibiotics if the superadded bacterial infection is suspected.

3.3.4 Patients who are progressively unwell and require ventilatory support

- Stop antimetabolite agents (mycophenolate and azathioprine)
- Dramatically reduce or stop CNI.
- Dexamethasone 6mg daily for 10 days.
- Remdesivir and other biologic or antiviral agents may be considered in line with local guidance.
- Ventilatory support in line with local practice.
- Consider the use of tocilizumab in critically ill patients.

3.4 Drugs dosing and interaction in transplant recipients with COVID-19 infection

During the treatment of COVID-19 in kidney transplant patients, careful drug dosing and transplant medication level monitoring are crucial parts of the management.

Some of these drugs inhibit cytochrome P450, responsible for CNI metabolism, leading to a high level and, sometimes, CNI toxicity, including nephrotoxicity and neurotoxicity.

Table 2 summarises some of the drugs tried in COVID-19 treatment in kidney transplant patients with their dose adjustment and transplant medications interactions.

Figures and Tables Legend:

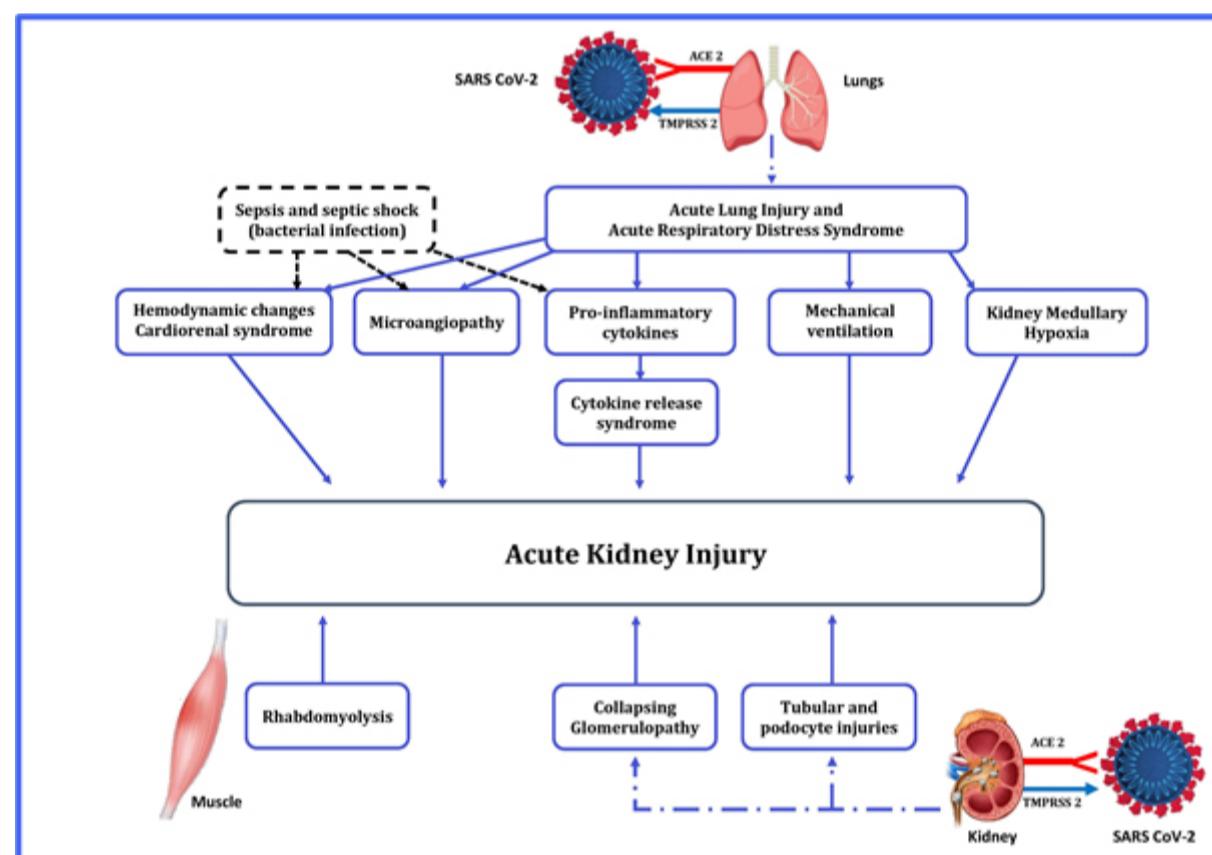


Figure 1: Possible causes and pathogenesis of acute kidney injury in patients with COVID-19.

(ACE2 = angiotensin-converting enzyme 2, TMPRSS2 = transmembrane protease serine2, SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2).

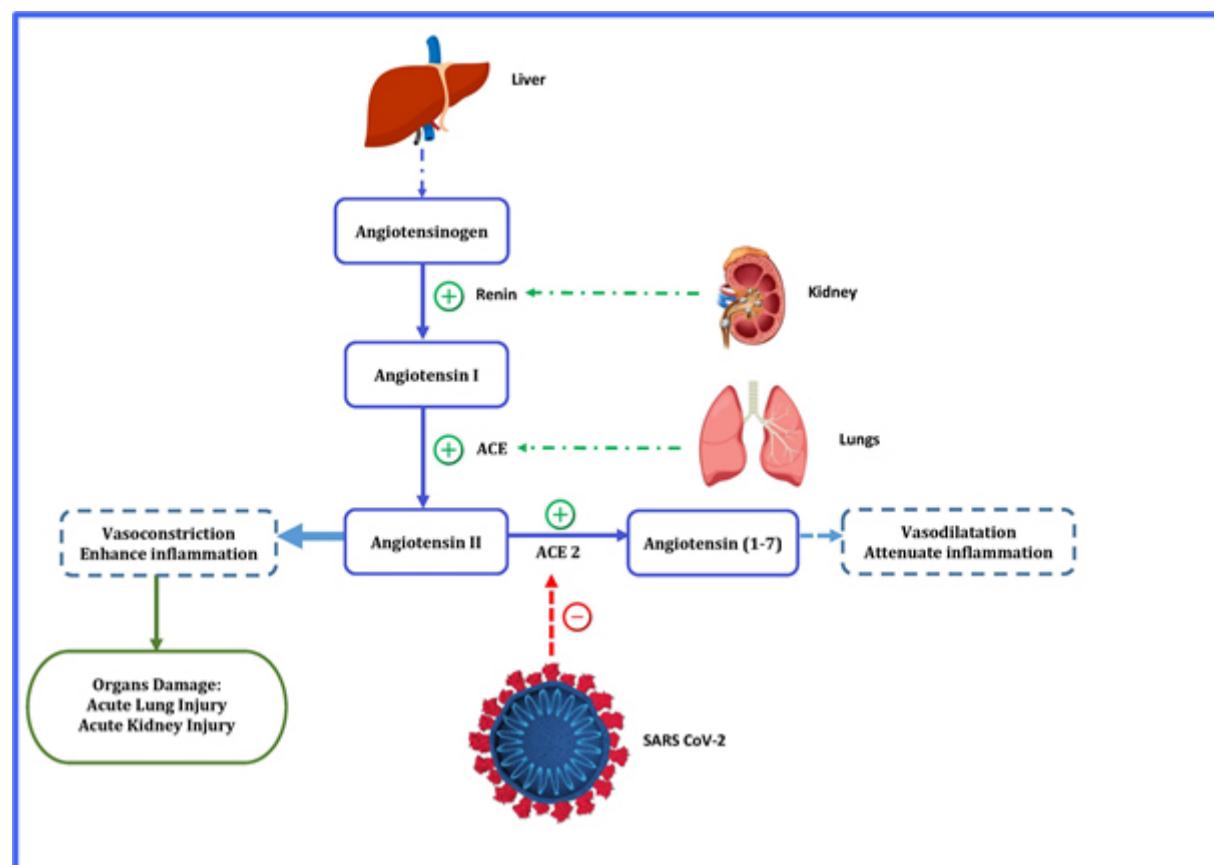


Figure2: SARS-CoV-2 infection could disrupt the physiological balance between ACE/ACE2 and Angiotensin-II/angiotensin-(1–7) and subsequently causing severe organ injury.

Drug	Mechanism of action	Dose in normal renal function	Dose adjustment in AKI	Dose adjustment in RRT	Remarks
Hydroxychloroquine	Immunomodulatory effects	400 mg once and then 200 mg bid	None	None	50-70% protein-bound
Tocilizumab	IL6 antagonist	8 mg/kg (max 800 mg)	None	None	
Lopinavir/Ritonavir	Protease inhibitors	400mg/100 mg bid	None	None	Highly protein-bound
Darunavir/Ritonavir	Protease inhibitors	800 mg/100mg daily	None	None	Highly protein-bound
Favipiravir	RNA polymerase inhibitor	1200 mg bid for two days and then 600 mg bid	? Yes	Potentially dialysable	50% protein-bound
Remdesivir	Nucleotide analogue inhibits viral replication	200 mg once and then 100 mg daily	Yes, excipient accumulates with eGFR < 30 ml/min	Potentially dialysable,	Excluded in most trial with eGFR < 30 ml/min

Table 1: Summary of drugs tried in COVID-19 treatment, dose adjustment with AKI and dialysis:

Drug	Dose in normal renal function	Dose adjustment in CKD	Interaction with transplant medications	Remarks
Hydroxychloroquine	400 mg once and then 200 mg bid	None	Increase Cyclosporine, Tacrolimus, and Sirolimus	50-70% protein-bound
Tocilizumab	8 mg/kg (max 800 mg)	None	Decrease Cyclosporine, Tacrolimus, and Sirolimus	
Lopinavir/Ritonavir	400mg/100 mg bid	None	Increase Cyclosporine, Tacrolimus, and Sirolimus	Highly protein-bound
Darunavir/Ritonavir	800 mg/100mg daily	None	None	Highly protein-bound
Favipiravir	1200 mg bid for two days and then 600 mg bid	? Yes	Not reported	50% protein bound
Remdesivir	200 mg once and then 100 mg daily	Yes, excipient accumulates with eGFR < 30 ml/min	Not reported	Excluded in most trial with eGFR < 30 ml/min

Table 2: Summary of drugs tried in COVID-19 treatment in kidney transplant recipients:**References:**

1. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020;39(5):405-7.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-62.
3. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. 2020;97(5):829-38.
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-13.
5. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395(10239):1763-70.
6. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalised with COVID-19. *Kidney Int*. 2020;98(1):209-18.
7. Fisher M, Neugarten J, Bellin E, Yunes M, Stahl L, Johns TS, et al. AKI in Hospitalised Patients with and without COVID-19: A Comparison Study. *J Am Soc Nephrol*. 2020;31(9):2145-57.
8. Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The Novel Coronavirus 2019 epidemic and kidneys. *Kidney Int*. 2020;97(5):824-8.
9. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020;181(2):271-80.e8.
10. Farouk SS, Fiaccadori E, Cravedi P, Campbell KN. COVID-19 and the kidney: what we think we know so far and what we don't. *J Nephrol*. 2020;33(6):1213-8.
11. Mohamed MMB, Lukitsch I, Torres-Ortiz AE, Walker JB, Varghese V, Hernandez-Arroyo CF, et al. Acute Kidney Injury Associated with Coronavirus Disease 2019 in Urban New Orleans. *Kidney360*. 2020;1(7):614-22.
12. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat Rev Nephrol*. 2020;16(6):308-10.
13. van den Akker JP, Egal M, Groeneveld AB. Invasive mechanical ventilation as a risk factor for acute kidney injury in the critically ill: a systematic review and meta-analysis. *Crit Care*. 2013;17(3):R98.

14. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, et al. Cytokine release syndrome. *J Immunother Cancer.* 2018;6(1):56.
15. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int.* 2020;98(1):219-27.
16. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? A Comprehensive Evaluation of Clinical and Basic Evidence. *J Clin Med.* 2020;9(5).
17. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(4):844-7.
18. Batlle D, Soler MJ, Sparks MA, Hiremath S, South AM, Welling PA, et al. Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology. *J Am Soc Nephrol.* 2020;31(7):1380-3.
19. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMP, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145-7.
20. Pan XW, Xu D, Zhang H, Zhou W, Wang LH, Cui XG. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. *Intensive Care Med.* 2020;46(6):1114-6.
21. Glowacka I, Bertram S, Herzog P, Pfefferle S, Steffen I, Muench MO, et al. Differential downregulation of ACE2 by the spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus NL63. *J Virol.* 2010;84(2):1198-205.
22. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA.* 2020;323(18):1843-4.
23. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural Evidence for Direct Renal Infection with SARS-CoV-2. *J Am Soc Nephrol.* 2020;31(8):1683-7.
24. Larsen CP, Bourne TD, Wilson JD, Saqqa O, Sharshir MA. Collapsing Glomerulopathy in a Patient With COVID-19. *Kidney Int Rep.* 2020;5(6):935-9.
25. Kudose S, Batal I, Santoriello D, Xu K, Barasch J, Peleg Y, et al. Kidney Biopsy Findings in Patients with COVID-19. *J Am Soc Nephrol.* 2020;31(9):1959-68.
26. Jhaveri KD, Meir LR, Flores Chang BS, Parikh R, Wanchoo R, Barilla-LaBarca ML, et al. Thrombotic microangiopathy in a patient with COVID-19. *Kidney Int.* 2020;98(2):509-12.
27. Kissling S, Rotman S, Gerber C, Halfon M, Lamoth F, Comte D, et al. Collapsing glomerulopathy in a COVID-19 patient. *Kidney Int.* 2020;98(1):228-31.
28. Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. *Kidney Int.* 2005;67(2):698-705.
29. Thomas G. Renin-angiotensin system inhibitors in COVID-19. *Cleve Clin J Med.* 2020.
30. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood.* 2014;124(2):188-95.
31. Porter D, Frey N, Wood PA, Weng Y, Grupp SA. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel. *J Hematol Oncol.* 2018;11(1):35.
32. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, et al. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. *N Engl J Med.* 2018;379(15):1431-42.
33. Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med.* 2008;359(1):7-20.
34. Burgner A, Ikizler TA, Dwyer JP. COVID-19 and the Inpatient Dialysis Unit: Managing Resources during Contingency Planning Pre-Crisis. *Clin J Am Soc Nephrol.* 2020;15(5):720-2.
35. Division of Nephrology CIUVCoP. Disaster Response to the COVID-19 Pandemic for Patients with Kidney Disease in New York City. *J Am Soc Nephrol.* 2020;31(7):1371-9.
36. Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomised controlled trial. *JAMA.* 2009;301(23):2445-52.
37. Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, et al. Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level: The EUPHRATES Randomized Clinical Trial. *JAMA.* 2018;320(14):1455-63.
38. Kellum JA, Song M, Venkataraman R. Hemoabsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-kappaB DNA binding, and improves short-term survival in lethal endotoxemia. *Crit Care Med.* 2004;32(3):801-5.
39. Peng ZY, Wang HZ, Carter MJ, Dileo MV, Bishop JV, Zhou FH, et al. Acute removal of common sepsis mediators does not explain the effects of extracorporeal blood purification in experimental sepsis. *Kidney Int.* 2012;81(4):363-9.
40. Schädler D, Pausch C, Heise D, Meier-Hellmann A, Brederlau J, Weiler N, et al. The effect of a novel extracorporeal cytokine hemoabsorption device on IL-6 elimination in septic patients: A randomised controlled trial. *PLoS One.* 2017;12(10):e0187015.
41. Ronco C, Reis T, De Rosa S. Coronavirus Epidemic and Extracorporeal Therapies in Intensive Care: si vis pacem para bellum. *Blood Purif.* 2020;49(3):255-8.
42. Ronco C, Bagshaw SM, Bellomo R, Clark WR, Husain-Syed F, Kellum JA, et al. Extracorporeal Blood Purification and Organ Support in the Critically Ill Patient during COVID-19 Pandemic: Expert Review and Recommendation. *Blood Purif.* 2021;50(1):17-27.
43. Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, et al. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. *ACS Cent Sci.* 2020;6(5):672-83.
44. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med.* 2017;9(396).
45. Kiser TH, Fish DN, Aquilante CL, Rower JE, Wempe MF, McLaren R, et al. Evaluation of sulfobutylether- β -cyclodextrin (SBED) accumulation and voriconazole pharmacokinetics in critically ill patients undergoing continuous renal replacement therapy. *Crit Care.* 2015;19:32.
46. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med.* 2020;383(19):1827-37.
47. Adamsick ML, Gandhi RG, Bidell MR, Elshaboury RH, Bhattacharyya RP, Kim AY, et al. Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19. *J Am Soc Nephrol.* 2020;31(7):1384-6.
48. Xiong F, Tang H, Liu L, Tu C, Tian JB, Lei CT, et al. Clinical Characteristics of and Medical Interventions for COVID-19 in Hemodialysis Patients in Wuhan, China. *J Am Soc Nephrol.* 2020;31(7):1387-97.
49. Kikuchi K, Nangaku M, Ryuzaki M, Yamakawa T, Hanafusa N, Sakai K, et al. COVID-19 of dialysis patients in Japan: Current status and guidance on preventive measures. *Ther Apher Dial.* 2020;24(4):361-5.
50. Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, et al. A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection. *Kidney Int.* 2020;98(1):20-6.
51. Keller N, Chantrel F, Krummel T, Bazin-Kara D, Faller AL, Muller C, et al. Impact of first-wave COVID-19 infection in patients on haemoDIALysis in Alsace: the observational COVIDIAL study. *Nephrol Dial Transplant.* 2020;35(8):1338-411.
52. Ng JH, Hirsch JS, Wanchoo R, Sachdeva M, Sakhya V, Hong S, et al. Outcomes of patients with end-stage kidney disease hospitalised with COVID-19. *Kidney Int.* 2020;98(6):1530-9.

53. Sachdeva M, Uppal NN, Hirsch JS, Ng JH, Malieckal D, Fishbane S, et al. COVID-19 in Hospitalised Patients on Chronic Peritoneal Dialysis: A Case Series. Am J Nephrol. 2020;51(8):669-74.
54. Dudreuilh C, Kumar N, Moxham V, Hemsley C, Goldenberg S, Moutzouris DA. De-isolation of COVID-19-positive hemodialysis patients in the outpatient setting: a single-center experience. Kidney Int. 2020;98(1):236-7.
55. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;324(8):782-93.
56. Thakare S, Gandhi C, Modi T, Bose S, Deb S, Saxena N, et al. Safety of Remdesivir in Patients With Acute Kidney Injury or CKD. Kidney Int Rep. 2021;6(1):206-10.
57. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalised Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020.
58. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med. 2020;8(7):738-42.
59. Cassat JE, Skaar EP. Iron in infection and immunity. Cell Host Microbe. 2013;13(5):509-19.
60. Drakesmith H, Prentice A. Viral infection and iron metabolism. Nat Rev Microbiol. 2008;6(7):541-52.
61. Liu W, Zhang S, Nekhai S, Liu S. Depriving Iron Supply to the Virus Represents a Promising Adjuvant Therapeutic Against Viral Survival. Curr Clin Microbiol Rep. 2020;1:7.
62. Fishbane S, Hirsch JS. Erythropoiesis-Stimulating Agent Treatment in Patients With COVID-19. Am J Kidney Dis. 2020;76(3):303-5.
63. Chawla LS, Krishnan M. Causes and consequences of inflammation on anemia management in hemodialysis patients. Hemodial Int. 2009;13(2):222-34.
64. Li SY, Tang YS, Chan YJ, Tarn DC. Impact of the COVID-19 pandemic on the management of patients with end-stage renal disease. J Chin Med Assoc. 2020;83(7):628-33.
65. Kliger AS, Silberzweig J. Mitigating Risk of COVID-19 in Dialysis Facilities. Clin J Am Soc Nephrol. 2020;15(5):707-9.
66. Basile C, Combe C, Pizzarelli F, Covic A, Davenport A, Kanbay M, et al. Recommendations for the prevention, mitigation and containment of the emerging SARS-CoV-2 (COVID-19) pandemic in haemodialysis centres. Nephrol Dial Transplant. 2020;35(5):737-41.
67. Kliger AS, Cozzolino M, Jha V, Harbert G, Ikizler TA. Managing the COVID-19 pandemic: international comparisons in dialysis patients. Kidney Int. 2020;98(1):12-6.
68. Roper T, Kumar N, Lewis-Morris T, Moxham V, Kassimatis T, Game D, et al. Delivering Dialysis During the COVID-19 Outbreak: Strategies and Outcomes. Kidney Int Rep. 2020;5(7):1090-4.
69. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. Predicting infectious SARS-CoV-2 from diagnostic samples. Clin Infect Dis. 2020.
70. van Kampen JJA, van de Vijver DAMC, Fraaij PLA, Haagmans BL, Lamers MM, Okba N, et al. Duration and key determinants of infectious virus shedding in hospitalised patients with coronavirus disease-2019 (COVID-19). Nat Commun. 2021;12(1):267.
71. Program CUKT. Early Description of Coronavirus 2019 Disease in Kidney Transplant Recipients in New York. J Am Soc Nephrol. 2020;31(6):1150-6.
72. Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney Int. 2020;97(6):1083-8.
73. Moore J, Middleton L, Cockwell P, Adu D, Ball S, Little MA, et al. Calcineurin inhibitor sparing with mycophenolate in kidney transplantation: a systematic review and meta-analysis. Transplantation. 2009;87(4):591-605.
74. Su VCh, Greanya ED, Ensom MH. Impact of Mycophenolate Mofetil Dose Reduction on Allograft Outcomes in Kidney Transplant Recipients on Tacrolimus-Based Regimens: A Systematic Review. Ann Pharmacother. 2011;45(2):248-57.
75. Caraballo-Lozoya J, Müller MA, Kallies S, Thiel V, Drosten C, von Brunn A. Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506. Virus Res. 2012;165(1):112-7.
76. British Transplantation Society. Guidance on the management of transplant recipients diagnosed with or suspected of having COVID-19. Updated January 22, Accessed January 31, 2021. <https://bts.org.uk/wp-content/uploads/2021/01/Clinical-management-of-transplants-and-immunosuppression-22nd-January-2021-FINAL.pdf>

[Home](#)[Forward message](#)[Introduction](#)[Chapters](#)[Editors team](#)[Contact us](#)



Search this site



Diabetes and Endocrinology

Diabetes and COVID-19 an Introduction

- Dr Muhammad Zaka Ul Haq (MZHaq)
- Dr Abdul Wajid Safi (AW Safi)
- Dr Ammar Abdeen (AAAbdeen)

Keywords :

Diabetes mellitus, diabetic ketoacidosis (DKA), hyperosmolar hyperglycaemic state (HHS), hyperglycemia, hypoglycemia, insulin resistance, Insulin titration, insulin infusion, T2DM (Type 2 Diabetes Mellitus), COVID-19, T1DM (Type 1 Diabetes mellitus), Glucocorticoid induce hyperglycemia, Basal insulin, Bolus insulin, Rapid-acting insulin, long-acting insulin, Correction doses.

Introduction

Diabetes mellitus (DM) is a chronic, complex metabolic disorder characterized by elevated blood sugars due to either lack of insulin, a relative ineffective function of insulin at the cellular level, or defective insulin release that over time lead to **macrovascular** (IHD, CVA, PVD) and **microvascular** complications(retinopathy, nephropathy, and neuropathy) causing significant morbidity and mortality. The prevalence of diabetes, primarily type 2, is gradually increasing globally.

This increased prevalence is mainly attributed to lack of physical activity, unhealthy food choices, and excessive dependence on machine-based luxuries.

Diabetes mellitus is characterized by a chronic low-grade inflammatory state.

It is vital to manage hyperglycemia effectively in hospitalized patients within stringent targets to aid the recovery process. A dedicated diabetes team is an essential part of multidisciplinary care while managing admitted patients. These teams are guided by local clinical pathways and protocols developed in line with clinical evidence and up-to-date practices.

DM is among the top 3 comorbidities that impact the clinical course and severity of illness in patients suffering from COVID-19. There is also a direct link between COVID-19 severity and prior glycemic control and glycemic control during the illness.

Many other comorbidities that significantly impact the clinical course of patients suffering from COVID-19, like ischemic heart disease, hypertension, and obesity, are all interlinked with diabetes.

The COVID-19 pandemic has affected people with existing diabetes adversely by disrupting clinical care continuity, diversion of clinical staff and resources towards dealing with a pandemic, lack of physical activity, relative difficult access to healthy food and medications.

The diabetes care plan allocates essential financial support, mass public education, provision of diabetes and other interlinked multidisciplinary services (service delivery, prevention, care, and monitoring for complications), individualized and patient-centered care, and empowering patients to self-manage their diabetes.

With evidence from **the RECOVERY** trial showing a benefit of high-dose glucocorticoids in people with severe COVID-19, physicians continue to face significant challenges managing these patients' hyperglycemia. At the same time, most of these require insulin least temporarily.

Epidemiology

9th edition of IDF world diabetes atlas recognizes diabetes as one of the fastest-growing global health emergencies of the 21st century. In 2019, it was estimated that 463 million people have diabetes, and this number is projected to reach 578 million by 2030 and 700 million by 2045.

The Middle East and North Africa situation are alarming, with a projected estimate of people with diabetes doubling by 2045 compared to the current number of 55 million.

This number is second-highest after Africa, projected to grow by 143% by 2045 (19 million present to 47 million by 2045).

Another cause for concern is the consistently high percentage of people with undiagnosed diabetes (overwhelmingly type 2 diabetes), currently over 50%. This reveals the urgent need to diagnose the 'undiagnosed diabetics' and provide appropriate and timely care for all as early as possible.

Annual global health expenditure on diabetes is estimated to be USD 760 billion. It is projected that expenditure will reach USD 825 billion by 2030 and USD 845 billion by 2045.

Type 2 diabetes accounts for over 90% of diabetes cases worldwide; thus, the upcoming discussion will mainly focus on type 2 diabetes.

Diabetes in COVID-19 patients

Clinical outcomes for hospitalized patients with any illness are directly linked to comorbidities. Diabetes mellitus is one of the most common comorbidities found in patients admitted with COVID-19 and is closely linked with the illness's severity.

A meta-analysis of comorbidities in COVID-19 patients admitted to the hospital showed hypertension to be the most common comorbidity (21.1%), followed by diabetes (9.7%), cardiovascular diseases (8.4%), and respiratory system disease being 1.4% of all the cases(1).

In the US, diabetes is one of the most common chronic conditions prevalent among those admitted with severe COVID-19, affecting mortality(2, 3).

A US study on 5700 patients admitted to the hospital with severe illness from COVID-19 showed that one in every third patient had diabetes (33%)(4).

Earlier observational data at the outset of the COVID-19 pandemic from a hospital in Wuhan has shown that length of stay and the case fatality rate is higher in those patients with diabetes and severe COVID-19 than those without diabetes (3).

Type 2 diabetes has a pooled odds ratio of 2.75 and 1.90 for severity and mortality of COVID-19, respectively, as shown by a meta-analysis from 33 studies (5).

Diabetes is an independent prognostic factor for patients admitted to critical care units with COVID-19 (6). Moreover, in patients with no previous diagnosis of diabetes, a multicentre retrospective study demonstrated fasting hyperglycemia to be an independent mortality predictor in patients with COVID-19(7).

Management of Hyperglycemia in Hospitalised patients with COVID-19

It is essential to achieve strict glycemic control within recommended targets for all the patients admitted to the hospital with any illness while avoiding hypoglycemic episodes. The aim is to maintain smooth glycemic control and transfer the benefit of strict diabetes control to outpatient care.

Diabetes and hyperglycemia are among the most common problems in hospitalized patients.

Management of Diabetes and hyperglycemia could be challenging, especially in the setting of a pandemic due to a high number of patients with diabetes and a limited number of specialty providers; this is further complicated by lack of COVID-19 specific knowledge and the relative paucity of guidelines, pathways, and protocols for managing diabetes in COVID-19(8).

Hypoglycemia and hyperglycemia are predictors of poor outcomes in patients admitted to the hospital, and measures need to be taken to avoid glucose variability in order to reduce complications (9).

Patients with COVID-19 and no previous history of diabetes should also be monitored for hyperglycemia. Many of these patients are started on high dose glucocorticoids to combat the cytokine storm and inflammation secondary to COVID-19. Glucocorticoids use is associated with an increased incidence of hyperglycemia, for which the mainstay of treatment is insulin therapy (8)

People with diabetes have worse outcomes in COVID-19, and controlling hyperglycemia is essential. Hyperglycemia can be controlled by either using oral hypoglycemic medications or using insulin.

In hospital settings, insulin is the most effective and mainstay treatment option to treat hyperglycemia. However, insulin safety can be a concern if not appropriately administered, and staff is ill-trained(8).

General Principles of management

- Random glucose and HbA1c should be routinely checked in all patients admitted to the hospital with COVID-19 irrespective of the previous history of diabetes.
- Type of diabetes should be documented, i.e., type 1 or type 2. An inquiry should be made about the duration of diabetes.
- Where possible, every effort should be made to document any diabetes treatment that patient is taking, including doses and types of insulin where applicable; this is important as invariably majority of COVID-19 patients initially will require insulin. Knowledge about pre-hospital diabetes treatment will help physicians switch therapy in appropriate cases.
- Where applicable and possible, arrangements should be made for diabetes multidisciplinary team inputs (inpatient or outpatients) depending upon clinical needs.

Glycemic targets in the hospital setting

Currently, there is no evidence to guide us in defining glycemic targets in a patient with diabetes who has COVID-19 in hospital settings (10), therefore, we can refer to general inpatient glycemic targets recommended by the American diabetes association (ADA) (7.8 to 10mmol/L) and diabetes UK. (6 to 10mmol/L) (11)

DUK	(6 to 10mmol/L) up to 12mmol acceptable
ADA	(7.8 to 10mmol/L)

Glycemic targets

Pharmacological therapies for hyperglycemia management

Insulin

Due to insulin's proven efficacy and safety profile in the clinical setting, insulin is the preferred treatment for glucose lowering in in-hospital settings (10).

During the COVID-19 pandemic, insulin, from clinical and physiological aspects, should be the mainstay and first-line treatment option for hyperglycemia and diabetes management as long as it is administered safely(10).

When to initiate insulin

Inpatient glycemic management includes frequent monitoring of blood glucose. If blood glucose reading is above 12 mmol/l, then it is suggested to give a correction dose of rapid-acting insulin (Novorapid, Humalog, and Apidra) (11).

Patients with diabetes and especially those on insulin treatment should have blood glucose monitoring on a 4-6 hourly basis.

Rapid-acting insulin

Rapid-acting insulins are insulin analogs. This insulin category's onset is about 10-20 minutes and reaches its peak in about 30-90 minutes. The duration of action of rapid-acting insulin is around 3-5 hours(12).

Insulin dose for rapid-acting insulin is calculated using one of the following factors shown in table-1.

1. Correction ratio: in patients already established on insulin therapy, the correction dose of insulin is calculated as per their total daily insulin dose/requirement as given in table 1.
2. For insulin-naive patients or those in whom total daily insulin dose/requirement is unknown, the correction dose of rapid-acting insulin can be calculated according to their body weight as given in table 1 (11)

Glucose (mmol/l)	CR=1 unit drop 4mmol/l	CR=1 unit drop 3mmol/l	CR=1 unit drop 2mmol/l
	TDD <50 units/Day	TDD 50-100 units/Day	TDD >100 units/Day
	Weight <50 kg	Weight 50-100 kg	Weight >100 kg
12.0-14.9	1	1	2
15.0-16.9	2	2	3
17.9-18.9	2	3	4
19.0-20.9	3	3	5
21.0-22.9	3	4	6
23.0-24.9	4	5	7
25.0-27.0	4	5	8
>27	5	6	9

Table-1 Titration of rapid-acting insulin according to body weight and/or blood sugar readings

CR = Correction ratio

TDD = Total daily dose

Initiation of long-acting insulin, when and how?

Long-acting insulin has a longer duration of action and no pronounced peak (12). Examples of long-acting insulin are glargin, detemir, and degludec.

If a patient is already using long-acting insulin, then it should be continued at the same dose and dose to be titrated as per blood sugar readings.

If a patient is not already using long-acting insulin and 2 or more glucose readings in the last 24 hours are >12 mmol/l and/or the patient required 2 or more corrective doses of rapid-acting insulin in the previous 24 hours, then add long-acting insulin as per patient weight.

Long-acting insulin is added at 0.25units/kg/day and given as once daily or twice daily dose depending on the choice of basal insulin use. If the patient is older (>70 years) or frail or serum creatinine is more than 175umol/l, guidelines suggest using a lower dose of 0.15 units/kg/day (11).

In the context of glucocorticoid therapy, basal insulin may be better administered at the time of glucocorticoid intake to match subsequent hyperglycemia.

Dose adjustment/titration for long-acting insulin

Once a patient is started on basal insulin, blood glucose needs to be monitored closely. Insulin dose may need adjustment due to either change in clinical status of the patient or a change in glucocorticoid dose(11).

Titration of basal insulin can be done daily, but basal insulin may take 48 to 72 hours to reach a steady state.

Dose adjustment of basal insulin is carried out according to fasting blood glucose levels for bedtime insulin administration and pre-meal glucose levels for morning insulin administration.

Fasting blood glucose level	
<4 mmol/L	Reduce insulin by 20%
4.1-6 mmol/L	Reduce insulin by 10%
6.1-12 mmol/L	No Change
12.1-18mmol/L	Increase insulin by 10%
>18mmol/L	Increase insulin by 20%

Table 2. Titration of basal insulin (bedtime) according to blood glucose levels.

Glucose level	Just before morning, insulin dose.	Just before evening, insulin dose
<4 mmol/L	Reduce evening insulin by 20%	Reduce morning insulin by 20%
4.1-6 mmol/L	Reduce evening insulin by 20%	Reduce morning insulin by 20%
6.1-12 mmol/L	No Change	No Change
12.1-18mmol/L	Increase evening insulin by 10%	Increase morning insulin by 10%
>18mmol/L	Increase evening insulin by 20%	Increase morning insulin by 20%

Table 3. Twice daily basal insulin titration.

Initiation of prandial insulin

Patients who are eating require mealtime bolus insulin dosing in addition to basal insulin. The recommended starting dose of mealtime insulin is 4 units, 0.1 units/kg, or 10% of the basal dose(12).

In insulin-naive patients, **prandial insulin** dose is calculated from the amount of insulin requirement over the last 24 hours. The total daily dose of insulin is calculated by adding a basal insulin dose and a rapid-acting insulin dose for correction. As per **ADA**.

50% of the total daily dose of insulin is given in once-daily long-acting insulin or twice daily intermediate-acting insulin.

50% of the total daily dose of insulin is given in three divided doses, with each meal as prandial insulin.

Correction dose of rapid-acting insulin needs to be continued and given as per table-1, especially in COVID-19 patients as most of them require glucocorticoids. There is growing evidence that COVID-19 itself causes insulin resistance (11). Patients with COVID-19 may require higher correction doses even if they are already established on basal and prandial insulin.

Adjustment of prandial insulin doses

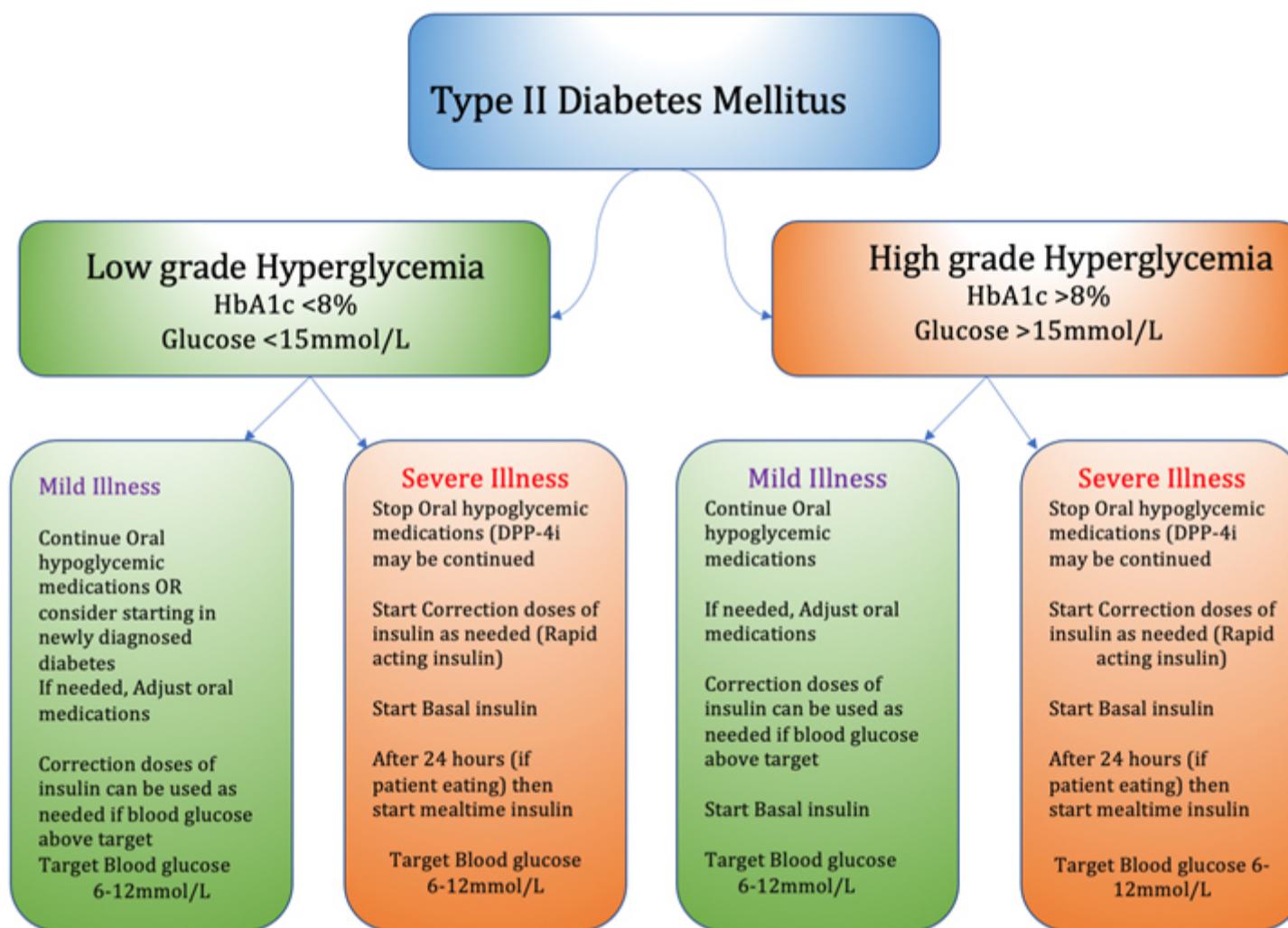
Once a patient is established on basal insulin and the patient's fasting blood sugar reading are with-in the target range, the next step is to adjust prandial insulin doses.

If pre-lunch blood glucose readings are above target, adjust the breakfast bolus of rapid-acting insulin.

If pre-dinner blood glucose readings are above target, adjust the lunchtime bolus of rapid-acting insulin.

If bedtime blood glucose readings are above target, adjust dinner time bolus of rapid-acting insulin (8).

Postprandial blood glucose	Action
<4 mmol/L	Reduce prandial insulin by 2-3 units
4.1-5.5 mmol/L	Reduce prandial insulin by 1-2 units
5.6 - 10 mmol/L	No Change
10.1-12.0 mmol/L	Increase prandial insulin by 1-2 units
>12 mmol/L	Increase prandial insulin by 2-3 units

Table-4 Adjustment of mealtimes (prandial) insulin

Overview of type 2 diabetes treatment in patients hospitalized with COVID-19

The transition of diabetes care from a hospital setting to ambulatory care

A structured discharge plan should be tailored to the individual patient with diabetes.

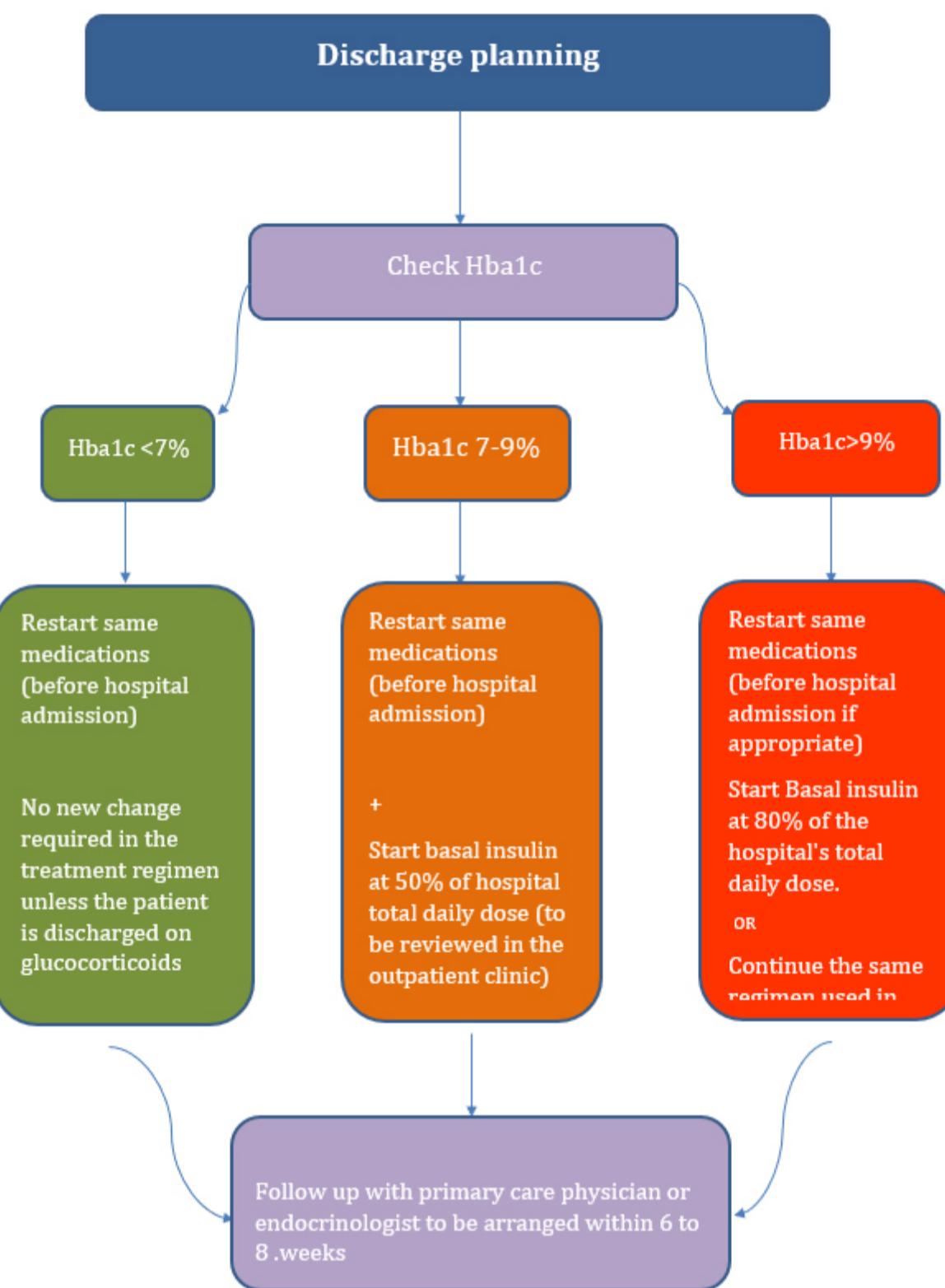
It is recommended to check HbA1c of all patients if not checked within the last 3 months (13).

If HbA1c is <7%, no change is required in treatment regimen, and home medication (before hospital admission) should be restarted.

If HbA1c is 7-9%, basal insulin at 50% of hospital dose is started, and restart non-insulin oral hypoglycemia agents.

If HbA1c is >9%, continue the same basal-bolus regimen as the patient was using in the hospital or add once-daily basal insulin at 80% of the hospital dose and restart non-insulin oral hypoglycemia agents.

An arrangement should be made to follow up with all patients with diabetes or hyperglycemia after discharge from the hospital with a primary care physician or diabetologist as per clinical need. Ideally, the patient should be reviewed within 4 to 6 weeks-time post-discharge(13).



Glucocorticoid use in COVID-19 and hyperglycemic management

High-dose **glucocorticoids** reduce mortality in people with COVID-19 who require ventilation or oxygen therapy. High-dose glucocorticoid regimens such as dexamethasone dose of 6 mg/d (oral or IV) used in the RECOVERY trial will be likely to affect glucose metabolism adversely (14).

COVID-19 increases insulin resistance and impairs insulin production from the pancreatic beta cells. High dose glucocorticoid therapy increases insulin resistance. This triple insult can precipitate hyperglycemia and life-threatening diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) in people with and without diabetes, leading to increased morbidity and mortality. Glucose levels above 10.0 mmol/L have been linked to increased mortality in people with COVID-19 (14).

Glucocorticoid type and duration of action must determine insulin treatment regimens (13).

Patients on morning glucocorticoid regimens have disproportionate hyperglycemia during the day, but they frequently reach normal blood glucose levels overnight regardless of treatment (13).

In patients on high doses of glucocorticoids, increasing doses of prandial insulin and frequent use of correction insulins may be required on top of basal insulin therapy (13).

Sulphonylureas are generally not recommended in COVID-19 as beta-cell function may be impaired, and insulin resistance is likely to be severe, making these agents ineffective(14).

For glucocorticoids induced hyperglycemia, management principles are generally the same as given above in the general section, but these patients require higher than usual insulin dosages to correct their hyperglycemia. Also, it is vital to escalate insulin therapy more rapidly.

Glucose (mmol/l)	TDD <50 units/day Weight <50 kg	TDD units/day 50-100 kg	TDD >100 units/day Weight >100 kg
		Weight 50-100 kg	
12.0-14.9	2	3	4
15.0-16.9	2	3	5
17.9-18.9	3	4	5
19.0-20.9	3	5	6
21.0-22.9	4	6	7
23.0-24.9	4	7	8
25.0-27.0	5	8	9
>27	6	9	10

Table 5 Titration of rapid-acting insulin according to body weight and/or blood sugar readings for patients on high dose glucocorticoids

As suggested by the **RECOVERY** trial, **dexamethasone** in COVID-19 patients with severe illness is usually continued for 10 days in the hospital and, in some cases, for longer. As metabolic effects of dexamethasone can last up to 36 hours, therefore, longer-acting insulins are the preferred choice over intermediate-acting insulin with similar experience in our practice.

For patients already on insulin therapy and started on glucocorticoids, insulin dosages may need to be increased by 20 to 40%.

End of glucocorticoid therapy

Once glucocorticoids are stopped, there is a sharp decline in insulin resistance, which leads to reduced insulin requirements in COVID-19 patients. The total daily dose may need to be reduced by 50% from day one after stopping glucocorticoids. Further reduction in insulin dosage is guided by blood glucose profile.

Management of type 1 diabetes in settings of COVID-19

The mainstay of type 1 diabetes mellitus management in COVID-19 patients is insulin. Patients already diagnosed with type 1 diabetes and established on insulin should be continued on their pre-hospital insulin regimen keeping in mind that they may require higher doses. Given the risk of DKA, basal insulin should not be stopped under any circumstances. The local diabetes team should review all people with type 1 diabetes upon admission to the hospital.

Oral hypoglycemic agents for the management of type 2 diabetes, literature review, and our local practice

Metformin

Metformin is the first-line pharmacological agent for managing hyperglycemia in people with type 2 diabetes mellitus (15), and it is the most frequently prescribed glucose-lowering agent (9).

Apart from exerting an effect on lowering blood glucose, metformin, via complex mechanisms, also leads to anti-inflammatory activity, and it may help reduce the severity of COVID-19 infection (15).

Metformin is usually well-tolerated and has a low rate of adverse effects (9). Nausea, dyspepsia, and diarrhea are the most frequently reported side effects, especially at therapy initiation (15).

Patients with severe COVID-19 infection are at an increased risk of developing multiple organ failure, particularly renal and/or hepatic impairment, dehydration, and hypoxic states. These conditions can lead to the development of lactic acidosis. Lactic acidosis is also a rare but severe side effect of metformin therapy (15).

The threshold to stop metformin should be kept low if a patient with COVID-19 infection exhibits gastrointestinal symptoms (15) and particularly in those who present with severe illness due to risk of lactic acidosis (16).

Metformin therapy could be continued in diabetic patients with asymptomatic or mild COVID-19. However, as a rule, metformin should be withdrawn in hospitalized patients with severe illness and in those particularly at risk of developing lactic acidosis as described above. Further studies are needed to prove or disprove this recommendation (9). However, a recent study from China showed significantly lower (2.9% vs. 12.3%) in-hospital mortality in diabetic patients who received metformin compared to those who did not receive metformin (17).

A firm conclusion about metformin in COVID-19 can only be obtained by a randomized controlled trial (RCT). However, such trials may be challenging to conduct in the context of the COVID-19 pandemic (15).

In conclusion, metformin therapy could be continued, provided no contraindications, especially in those with milder illness and in whom there is no increased risk of lactic acidosis. It is an excellent first-line oral hypoglycaemic agent in patients who recover from illness and are stepped down from insulin therapy.

DPP IV inhibitors:

DPP-IV inhibitors were introduced for the treatment of type 2 diabetes in 2006. They stimulate insulin secretion and inhibit glucagon secretion by elevating endogenous GLP-1 concentrations without an intrinsic hypoglycemia risk (18).

Commonly used DPP-IV inhibitors are alogliptin, linagliptin, saxagliptin, and sitagliptin. All DPP-IV inhibitors are usually well tolerated (16).

Common side effects include nasopharyngitis and skin lesions(18).

DPP-IV inhibitors alone or combined with basal insulin are considered safe and effective for patients with mild to moderate hyperglycemia during in-hospital admission. These recommendations are based on multiple RCTs (8).

Several small studies also demonstrated the safety and efficacy of DPP-IV inhibitors in selected type II diabetics admitted to the hospital with COVID-19 (19).

DPP-IV inhibitors have a potent anti-inflammatory effect by reducing pro-inflammatory cytokines, as evidenced by experimental and human studies. This may reduce the intensity of the inflammatory storm in COVID-19 (20).

The use of DPP-IV inhibitors in COVID-19 for type II diabetes showed no significant difference in in-hospital mortality. Also, there was no difference in ICU admissions or 30-day mortality in DPP-IV inhibitor users than in non-users(21).

CORONADO reported similar primary (tracheal intubation and or death evaluated within 7-days of admission) and secondary outcomes (death at day 7) in DPP-IV inhibitors users compared to non-users (22).

Further analysis of the CORONADO study showed that the rate of discharge from hospital was significantly higher in DPP-IV inhibitor users than in non-users. However, there was no difference in mortality within 28 days (22).

Hence, DPP-IV inhibitors are generally considered effective and safe oral hypoglycaemic agents in COVID-19 and are frequently used in our local practice.

Sulfonylurea

Sulfonylureas have been available since the 1950s for the treatment of type 2 diabetes. (23).Sulfonylureas are insulin secretagogues that stimulate pancreatic beta-cells to secrete insulin (24).

Sulfonylureas are the most commonly prescribed medication in treating type 2 diabetes after metformin (25), mainly due to their ability to achieve quick glycemic control, minimal cost, and years-long experience (25).

The most severe side effect of sulfonylurea is severe symptomatic hypoglycemia, especially with increasing age and impaired renal function (26).

Therefore these medications have to be used with caution due to the risk of hypoglycemia in patients with worsening renal functions and the elderly and best avoided in severe COVID-19 (20).

CORONADO study shows no association of the use of sulfonylureas in diabetes with tracheal intubation and/or death within 7 days.

In conclusion, SUs can be continued in patients with diabetes who have contracted mild to moderate COVID-19 infection, provided they are not elderly, have a normal renal function, and are not at increased risk of hypoglycemia.

Thiazolidinediones

Pioglitazone belongs to the **thiazolidinedione (TZD)** group of medications and acts as a peroxisome proliferator-activated receptor (PPAR)- γ agonist (27).

It promotes insulin sensitivity by reduction of hepatic triglycerides and visceral fat mass. It also stimulates lipogenesis, suppresses lipolysis in the adipose tissue, and reduces insulin resistance (28).

Pioglitazone downregulates certain enzymes and increases ACE2. ACE2 is the leading portal of entry for SARS-CoV-2 to cells. Due to this effect, some researchers suggested avoiding pioglitazone in a patient with diabetes and COVID-19 (20).

There is, unfortunately, no report of the outcome of pioglitazone users in people with T2DM and COVID-19 in recent studies, including **CORONADO**.

These medications are weak hypoglycaemic agents, and better treatment options are available to manage diabetes in COVID-19.

GLP-1 receptor agonists

GLP-1 agonists include albiglutide, dulaglutide, exenatide-extended release, liraglutide, lixisenatide, and semaglutide(8).

GLP-1 receptor agonists commonly cause nausea, vomiting, and dehydration; therefore, initiating and/or continuing GLP-1 therapy in an acute care setting is not recommended , especially in patients with COVID-19 infection as there is a chance of rapid deterioration(19).

CORONADO study did not find any beneficial effect of GLP-1 agonists on either discharge rate from the hospital or the mortality compared to non-users.

The vast majority of COVID-19 patients report nausea, either due to COVID-19 illness itself or due to the use of various medications given to treat COVID-19. On balance, GLP-1 analogs should be best avoided in these patients.

Once these patients recover fully, the GLP-1 therapy resumption should be overseen by the treating diabetologist.

SGLT2 inhibitors

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) inhibit the glucose absorption from the kidney's proximal tubule, leading to glycosuria. These medications are a recent addition to oral hypoglycaemic agents. SGLT2i have demonstrated cardioprotective effects and reduction in CV outcomes along with a reduction in HbA1c (29).

Medications in this class include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (16).

SGLT2i carry a risk of dehydration, diabetic ketoacidosis, and genitourinary infections, and the risk of these side effects increases further during any medical illness (16).

There is no specific data or guidelines about the use of SGLT2i in patients with diabetes and COVID-19 illness. SGLT2i are associated with euglycemic ketoacidosis and volume depletion; therefore, these should be avoided in patients with severe COVID-19 illness (20).

However, some studies have shown anti-inflammatory properties of SGLT2i, which can positively affect tissue hypoxia and oxidative stress (20) and no difference has been reported in the outcome of disease severity (OR 1.75; 95% CI, 0.23–13.50; p = 0.59) or deaths (OR 5.05; 95% CI, 0.48–53.26); p = 0.18) in patients with COVID-19 infection using SGLT2i compared to non-users (30).

Another study reported no difference in the primary outcome of ICU admissions or death within 30 days (OR 0.66; 95% CI, 0.30–1.52; p = 0.40) amongst SGLT2i users (24/337) compared to the non-users in COVID-19(21).

As the majority of COVID-19 patients with diabetes admitted to the hospital are unwell, and at risk of ketosis, therefore, it is preferable to stop SGLT2i in these circumstances. These can be reinstated upon recovery from COVID-19.

COVID-19 and Diabetes emergencies

This section will cover mainly diabetic ketoacidosis (DKA), hyperosmolar hyperglycaemic state (HHS), hypoglycemia in hospital, and management of hyperglycemia in critically ill patients with diabetes in an intensive care unit (ICU) during the COVID-19 pandemic.

DKA is an inflammatory state resulting from relative or absolute insulin deficiency, reduced glucose utilization, and unchecked lipolysis, leading to a large amount of ketone body production and metabolic acidosis (31).

Diabetic ketoacidosis is a severe complication of diabetes. During COVID-19, DKA can be the presentation of a new-onset DM.

DKA has been reported in COVID-19, as with other severe infections in patients with T1DM and T2DM(32).

Uncontrolled DM and other comorbidities, some oral hypoglycemic medications (SGLT-2 inhibitors), and pregnancy may trigger DKA.

COVID-19 infection is associated with ketone body production and ketosis in patients without DM. Hence the risk of diabetic ketoacidosis increases in patients with known DM (33).

As shown in some studies, patients in the older age group with diabetes are more vulnerable to COVID-19 (34).

Children with COVID-19 infection are less likely to have symptoms or develop severe presentations than adult patients (35).

Children exhibit normal physiological, metabolic acidosis, which may protect them against the COVID-19's severe form (36). However, type 1 diabetic children suffered from severe DKA during the pandemic (37). Low mortality among children with COVID-19 and DKA was noted.

High levels of HbA1C are associated with high mortality in patients with COVID-19 and potentiate DKA episodes and hyperosmolar hyperglycaemic state (HHS) (38).

Clinical presentation and management of DKA and HHS

There is variability in DKA and HHS presentation, ranging from euglycemia or mild hyperglycemia and acidosis to severe hyperglycemia, dehydration, profound ketoacidosis, and coma; therefore, careful individualization of management based on the laboratory as well as the clinical presentation is needed.

Management goals include the restoration of circulatory volume and tissue perfusion, hyperglycemia resolution, electrolyte imbalance, and acidosis correction.

It is also essential to treat any underlying correctable cause of **DKA**, such as sepsis, stroke, and myocardial injury. In critically ill and mentally obtunded patients with DKA or hyperosmolar hyperglycemia, continuous intravenous insulin infusion is the standard of care.

Successful transition of patients from intravenous to subcutaneous insulin requires administration of basal insulin, which should be initiated on admission to hospital to prevent recurrence of ketoacidosis and rebound hyperglycemia. This is in keeping with recommendations by most of the guidelines.

There is no significant difference in outcomes for intravenous human regular insulin versus subcutaneous rapid-acting analogs when combined with aggressive fluid management for treating mild or moderate **DKA**.

In our institution, **Hazm Mebaireek General Hospital** (which is the primary designated COVID-19 facility), we frequently treated patients with uncomplicated DKA (mild to moderate DKA) with subcutaneous insulin in the emergency department or step-down units and the medical wards, an approach that we found safer and more practical owing to the need to limit the frequency of contact of staff with patients. If subcutaneous insulin administration is used, it is crucial to provide an adequate fluid replacement as this can be easily overlooked in these situations. These patients need frequent bedside glucose testing and monitoring of electrolytes and fluid balance at regular intervals.

The management of DKA is guided by universal protocols as advocated by local and **international guidelines**.

The main difference which one might experience when dealing with DKA in patients with COVID-19 as compared to DKA in a patient without COVID-19 are as follows:

Patients may present with DKA despite reasonable diabetes control and euglycemic state (we, therefore, advise checking blood ketones/urine ketones as a screening test in every patient with diabetes who gets admitted with COVID-19)

The patient may require increasing amounts of insulin through intravenous infusions due to increased insulin resistance that may be contributed by multiple factors such as the pro-inflammatory state associated with COVID-19 and concomitant

glucocorticoid use.

Acute hypoglycemia

According to the American diabetes association (ADA), hypoglycemia in hospitalized patients is categorized by a low blood glucose concentration and clinical correlates (39).

Level 1 hypoglycemia is a glucose concentration 54–70 mg/dL (3.0–3.9 mmol/L).

Level 2 hypoglycemia is a blood glucose concentration <54 mg/dL (3.0 mmol/L), which is typically the threshold for neuroglycopenic symptoms.

Level 3 hypoglycemia is a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery. Levels 2 and 3 require immediate correction of low blood glucose.

Causes of hypoglycemia in hospital in the context of COVID-19

In addition to errors with insulin treatment, hypoglycemia may be induced by reduced oral intake, vomiting, inappropriate timing or dose calculation of short- or rapid-acting insulin with meals, reduced infusion rate of intravenous dextrose, unexpected interruption of enteral or parenteral feedings, delayed or missed blood glucose checks, the sudden reduction of glucocorticoids dose and altered ability of the patient to report symptoms.

During COVID-19, the common symptom of loss of smell and taste contributes to the reduced oral intake and precipitation of hypoglycemia. In contrast, many other patients may have reduced oral intake due to nausea and vomiting caused by various medications used for COVID-19 treatment.

Treatment of hypoglycemia

Hypoglycemia treatment principles are universal, including a range of measures depending on the level, cause, severity, and hypoglycemia duration. This includes modifying diet and timing of meals, modifying type and dose of insulin to prevent hypoglycemia recurrence. A standardized hospital-wide, nurse-initiated hypoglycemia treatment protocol is available on the intranet.

In the acute stage, the hallmark of treatment is the institution of rapid-acting carbohydrates followed by long-acting complex carbohydrates. Hypoglycemia treatment kits are available in each ward and clinical area, and they have essential preparations for unconscious patients. Apart from intravenous dextrose, which is often needed to treat severe or level 2 and 3 hypoglycemia, intramuscular glucagon is very useful in patients who don't have intravenous access. Glucagon may fail to produce the desired response in patients with poor nutritional status and chronic liver disease.

Individualized plans for preventing and treating hypoglycemia for each patient should be adopted. Patient education and continued support by diabetes educators and clinical dietitians are vital for these patients.

The ADA consensus statement recommends that a patient's treatment regimen be reviewed any time a blood glucose value of <70 mg/dL (3.9 mmol/L) occurs, as such readings often predict subsequent level 3 hypoglycemia (<https://doi.org/10.2337/dc09-9029>). Episodes of hypoglycemia in the hospital should be documented and tracked in the medical record (40).

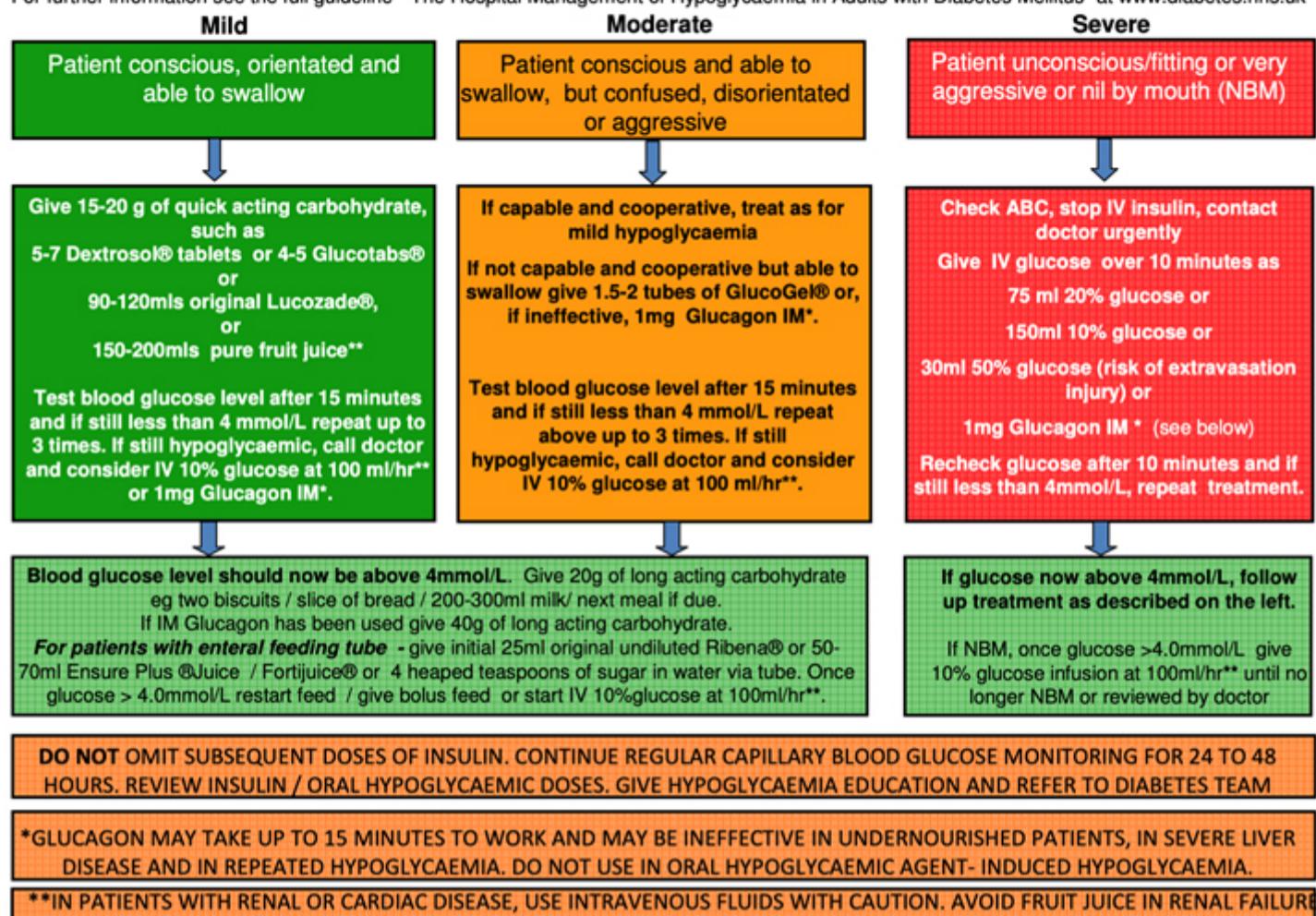
In the context of patients with COVID-19 and hypoglycemia, we need to be vigilant to avoid hypoglycemic episodes, particularly in the following situations.

- Tapering of glucocorticoids, as these patients need a reduction in oral hypoglycemic agents and insulin dosages.
- Switching from intravenous to subcutaneous insulin therapy.
- Elderly patients and those with chronic renal impairment.

Algorithm for the Treatment and Management of Hypoglycaemia in Adults with Diabetes Mellitus in Hospital

Hypoglycaemia is a serious condition and should be treated as an emergency regardless of level of consciousness. Hypoglycaemia is defined as blood glucose of less than 4mmol/L (if not less than 4mmol/L but symptomatic give a small carbohydrate snack for symptom relief).

For further information see the full guideline "The Hospital Management of Hypoglycaemia in Adults with Diabetes Mellitus" at www.diabetes.nhs.uk



Management of hyperglycemia of the critically ill diabetics in the ICU

Besides managing the underlying COVID-19 and other acute complications and comorbidities, Insulin therapy should be initiated to treat persistent hyperglycemia starting at a threshold of ≥ 180 mg/dL (10.0 mmol/L). Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is preferred for the majority of critically ill and noncritically ill patients (41).

Continuous intravenous insulin infusion is the most effective method for achieving glycemic targets in the critical care setting. Intravenous insulin infusions should be administered based on validated written or computerized protocols that allow for predefined adjustments in the infusion rate, accounting for glycemic fluctuations and insulin dose.

Insulin administration is based on frequent capillary or blood glucose levels. Additionally, we suggest using basal insulin subcutaneously once daily to decrease variability in the blood glucose profile and help in stepping down to subcutaneous insulin injections once the patient's condition improves.

Our Experience in Qatar

The prevalence of diabetes in Qatar's adult population is about 15%. ([9th edition of IDF world diabetes Atlas](#)). In our population with COVID-19 admitted to the hospital, the prevalence of diabetes was approximately 35-40%, including younger patients under 40 years. A significant proportion of these patients had their diabetes diagnosed first on admission to the hospital.

Role of Cerner/ electronic patient record

Qatar's healthcare system is well equipped with electronic patient records and databases. This enabled us to manage our patients' diabetes control and their insulin adjustment remotely, making it possible to carry out virtual rounds and adjustments to their medications. This helped us to manage our patients' diabetes effectively while minimizing unnecessary contact with the patient.

A dedicated consultant-led diabetes team was available for diabetes consultations, advice, review, and medication adjustment.

Post-discharge arrangements were made to follow these patients in diabetes and allied clinics, especially those discharged from the hospital on glucocorticoids or insulin treatment.

Subcutaneous insulin injections for correcting hyperglycemia (Table-1) were used frequently in most patients, especially in those who were started on glucocorticoids Table-5.

This strategy was of particular help for patients managed in field hospitals, newly diagnosed diabetes cases with poor control, and incorrect or doubtful information about their diabetes medications.

This was also used as a bridging therapy until patients reviewed the diabetes team.

Qatar has done exceptionally well during this pandemic and is one of the top countries with the lowest COVID-19 related mortality and highest recoveries from an intensive care unit.

Our local strategy to manage diabetes has been very effective and fruitful in achieving good outcomes for our COVID-19 patient population.

Future challenges from a Diabetes perspective

1. On one hand, this pandemic challenged our health care system, but at the same time, it has presented us with an opportunity to diagnose many new cases of diabetes that otherwise were unknown to us. Now, this is our chance to step forward and make a difference to these newly diagnosed type 2 diabetes patients who otherwise would have remained undiagnosed.
2. The long-term effects of COVID-19 on pancreatic health need to be determined. The primary concern is an unknown autoimmune or inflammatory trigger for pancreatic beta cells, which are very sensitive to viral illnesses.
3. In Qatar, we have a substantial expatriates population with dynamic population inflow and outflow, poor socioeconomic conditions, and low literacy rate in this group, adding to our challenges in meeting their health needs.
4. There is a need to come up with a pathway to follow up our newly diagnosed patients, educate them and provide essential follow-up and multidisciplinary inputs along with keeping an eye on their long-term health holistically.
5. Finally we need to equip our patients with the necessary education and provide them with appropriate and effective care models so that they are well prepared to face any future challenges, pandemics, etc.
6. In summary, the COVID-19 pandemic has exerted a significant impact on the health status of our diabetes patients, be it use of glucocorticoids for severely ill patients, weight gain due to multiple reasons, poor access in and around pandemic to health care facilities, disruption to medication supply and multidisciplinary team services. On top of this, there is an economic loss equal to all society sections and the healthcare facilities and structure. We need to look at different cost-effective ways and develop mechanisms and strategies to rehabilitate our diabetes population's health. This is achievable with hard work, commitment, and motivation.

Reference:

1. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis.* 2020;94:91-5.
2. Team CC-R. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12-March 28, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(13):382-6.
3. Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical Characteristics and Risk Factors for Mortality of COVID-19 Patients With Diabetes in Wuhan, China: A Two-Center, Retrospective Study. *Diabetes Care.* 2020;43(7):1382-91.
4. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA.* 2020;323(20):2052-9.
5. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr.* 2020;14(4):535-45.
6. Dennis JM, Mateen BA, Sonabend R, Thomas NJ, Patel KA, Hattersley AT, et al. Type 2 Diabetes and COVID-19-Related Mortality in the Critical Care Setting: A National Cohort Study in England, March-July 2020. *Diabetes Care.* 2021;44(1):50-7.
7. Wang S, Ma P, Zhang S, Song S, Wang Z, Ma Y, et al. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. *Diabetologia.* 2020;63(10):2102-11.
8. Aljehani FA, Funke K, Hermayer KL. Inpatient Diabetes and Hyperglycemia Management Protocol in the COVID-19 Era. *Am J Med Sci.* 2020;360(4):423-6.
9. Longo M, Caruso P, Maiorino MI, Bellastella G, Giugliano D, Esposito K. Treating type 2 diabetes in COVID-19 patients: the potential benefits of injective therapies. *Cardiovasc Diabetol.* 2020;19(1):115.
10. Wallia A, Prince G, Touma E, El Muayed M, Seley JJ. Caring for Hospitalized Patients with Diabetes Mellitus, Hyperglycemia, and COVID-19: Bridging the Remaining Knowledge Gaps. *Curr Diab Rep.* 2020;20(12):77.
11. Rayman G, Lumb A, Kennon B, Cottrell C, Nagi D, Page E, et al. New Guidance on Managing Inpatient Hyperglycaemia during the COVID-19 Pandemic. *Diabet Med.* 2020;37(7):1210-3.
12. Silver B, Ramaiya K, Andrew SB, Fredrick O, Bajaj S, Kalra S, et al. EADSG Guidelines: Insulin Therapy in Diabetes. *Diabetes Ther.* 2018;9(2):449-92.
13. American Diabetes A. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S193-S202.
14. Rayman G, Lumb AN, Kennon B, Cottrell C, Nagi D, Page E, et al. Dexamethasone therapy in COVID-19 patients: implications and guidance for the management of blood glucose in people with and without diabetes. *Diabet Med.* 2021;38(1):e14378.
15. Scheen AJ. Metformin and COVID-19: From cellular mechanisms to reduced mortality. *Diabetes Metab.* 2020;46(6):423-6.
16. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol.* 2020;8(6):546-50.
17. Luo P, Qiu L, Liu Y, Liu XL, Zheng JL, Xue HY, et al. Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis. *Am J Trop Med Hyg.* 2020;103(1):69-72.
18. Gallwitz B. Clinical Use of DPP-4 Inhibitors. *Front Endocrinol (Lausanne).* 2019;10:389.
19. Korytkowski M, Antinori-Lent K, Drincic A, Hirsch IB, McDonnell ME, Rushakoff R, et al. A Pragmatic Approach to Inpatient Diabetes Management during the COVID-19 Pandemic. *J Clin Endocrinol Metab.* 2020;105(9).
20. Singh AK, Singh R, Saboo B, Misra A. Non-insulin anti-diabetic agents in patients with type 2 diabetes and COVID-19: A Critical Appraisal of Literature. *Diabetes Metab Syndr.* 2021;15(1):159-67.
21. Izzi-Engbeaya C, Distaso W, Amin A, Yang W, Idowu O, Kenkre JS, et al. Adverse outcomes in COVID-19 and diabetes: a retrospective cohort study from three London teaching hospitals. *BMJ Open Diabetes Res Care.* 2021;9(1).
22. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salamah A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia.* 2020;63(8):1500-15.
23. Zimmerman BR. Sulfonylureas. *Endocrinol Metab Clin North Am.* 1997;26(3):511-22.
24. Ashcroft FM. Mechanisms of the glycaemic effects of sulfonylureas. *Horm Metab Res.* 1996;28(9):456-63.
25. Singh AK, Singh R. Is gliclazide a sulfonylurea with difference? A review in 2016. *Expert Rev Clin Pharmacol.* 2016;9(6):839-51.
26. Robertson DA, Home PD. Problems and pitfalls of sulphonylurea therapy in older patients. *Drugs Aging.* 1993;3(6):510-24.
27. Jagat JM, Kalyan KG, Subir R. Use of pioglitazone in people with type 2 diabetes mellitus with coronavirus disease 2019 (COVID-19): Boon or bane? *Diabetes Metab Syndr.* 2020;14(5):829-31.
28. Katsiki N, Ferrannini E. Anti-inflammatory properties of antidiabetic drugs: A "promised land" in the COVID-19 era? *J Diabetes Complications.* 2020;34(12):107723.

29. Tentolouris A, Vlachakis P, Tzeravini E, Eleftheriadou I, Tentolouris N. SGLT2 Inhibitors: A Review of Their Antidiabetic and Cardioprotective Effects. *Int J Environ Res Public Health.* 2019;16(16).
30. Kim MK, Jeon JH, Kim SW, Moon JS, Cho NH, Han E, et al. The Clinical Characteristics and Outcomes of Patients with Moderate-to-Severe Coronavirus Disease 2019 Infection and Diabetes in Daegu, South Korea. *Diabetes Metab J.* 2020;44(4):602-13.
31. Stentz FB, Umpierrez GE, Cuervo R, Kitabchi AE. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. *Diabetes.* 2004;53(8):2079-86.
32. Stratigou T, Vallianou N, Vlassopoulou B, Tzanela M, Vassiliadi D, Ioannidis G, et al. DKA cases over the last three years: has anything changed? *Diabetes Metab Syndr.* 2019;13(2):1639-41.
33. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metab.* 2020;22(10):1935-41.
34. Ma WX, Ran XW. [The Management of Blood Glucose Should be Emphasized in the Treatment of COVID-19]. *Sichuan Da Xue Xue Bao Yi Xue Ban.* 2020;51(2):146-50.
35. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics.* 2020;145(6).
36. Olson RM, Woods JE, Soule EH. Regional lymph node management and outcome in 100 patients with head and neck melanoma. *Am J Surg.* 1981;142(4):470-3.
37. Rafique S, Ahmed FW. A Case of Combined Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State in a Patient With COVID-19. *Cureus.* 2020;12(7):e8965.
38. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020;8(5):475-81.
39. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 2020;43(Suppl 1):S14-S31.
40. Bogun M, Inzucchi SE. Inpatient management of diabetes and hyperglycemia. *Clin Ther.* 2013;35(5):724-33.
41. Yamada T, Shojima N, Noma H, Yamauchi T, Kadokawa T. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. *Intensive Care Med.* 2017;43(1):1-15.

[Home](#)[Forward message](#)[Introduction](#)[Chapters](#)[Editors team](#)[Contact us](#)

Copyright © 2022 Ministry of Public Health. All rights reserved.



Search this site



Oncology and Haematology

Chapter: Oncology and Hematology:

Authors: Dr Kakil Rasul ,Dr Harith Al Khater, Dr Salha Bujassoum, Dr Javid Gaziev, Dr Amna Gameil and Dr Harman Saman.

Keywords: COVID-19, chemotherapy, immunosuppression, cancer, hematological malignancy, hematopoietic stem cell transplantation, allogeneic stem cell transplantation, autologous stem cell transplantation, EBMT, recommendations

Medical and Radiation Oncology:

Introduction:

Patients with cancer, especially those receiving cytotoxic therapies with the potential to cause immunosuppression, are considered a high-risk group to suffer from COVID-19 disease complication (1).

The mortality rate caused by SARS-CoV-2 in cancer patients is higher compared to general population (1). Risk stratification remains a challenging aspect of managing these patients during the pandemic.

The UK Coronavirus Cancer Monitoring Project (UKCCMP) studied different tumour types and showed different primaries as having differing susceptibility to SARS-CoV-2 infection and COVID-19 phenotypes (2).

Table 1 from UKCCMP shows the effect of different primary, age and gender on COVID-19 case mortality. One of the priorities of oncology services worldwide during the pandemic is to protect patients and staff alike and to maintain a high quality of care in the face of the challenges posed by a considerable stretch on resources and restrictions against individual's movement due to the pandemic.

Outpatient visits for cancer patients should be reduced to the safest and most feasible level without jeopardising patient care. Important aspects of preventative measures within oncology services include patient's education and promotion of hand washing, social distancing and reporting symptoms that might suggest COVID-19 infection, such as cough, fever or new onset of poorly explained malaise and myalgia.

The services need to adapt to minimize direct social contact for example, the oncology services in the state of Qatar started and implements a wide scale campaign through which virtual clinics via telephone consultation and video conferencing with patient and their largely replaced traditional outpatient appointments and physical attendance.

A special helpline service was established allowing patients to call their health care providers without the need to attend clinics in person.

Our service adapted itself by replacing parenteral systemic treatment to oral alternative that requires no hospital attendance and by setting up home delivery of medications services to our patients.

Whenever physical attendance is required, our service ensured safe clinical environment through setting up check desks that triage patients for their symptom's priority to their entry to the clinical areas.

Patient's prioritisation during pandemic:

The focus of care should shift to supporting and treating patients of high medical needs, such as patients with active cancer and/or patients receiving active treatment.

One of the key [European Society for Medical Oncology \(ESMO\)](#) recommendations is for hospitals to identify specific pathways in order to guarantee timing of treatment for patients with curative intent and, when possible, patients receiving palliative treatment.

ESMO identified priorities to high, medium and low, table 2.

As it can be seen in table 2, high priority is given to patients who receive curative therapies, for example for tumour types of high (more than 50%) curative rate such as germ cell tumors or Ewing sarcoma. Medium priority group includes patients who are not critical but delaying their treatment by more than six weeks might potentially adversely affect their overall outcomes. Low priority group encompasses patients on palliative treatment whose life expectancy is less than one year.

For low priority patients, the delivery of care can be delayed to accommodate the need of the higher priority groups during the pandemic.

Further adjustment might involve making alteration in treatment schedules without compromising the care to patients. For example, in certain patients with breast or colon cancer, surgery can be delayed by giving neoadjuvant chemotherapy.

Other alteration might include shortening the course of radiotherapy through delivering intensified courses with less fractions.

Delaying the start of adjuvant chemotherapy without compromising the benefit can be offered under certain conditions.

Another example is giving maintenance or therapy holidays in certain patients in remission, whenever such an intervention is justifiable (3).

Specific oncology challenges during COVID-19 pandemic:

Adverse effects among patients who receive immune checkpoint inhibitors (such as for severe myocarditis and pneumonitis) are more challenging to diagnose and might not be treated promptly, therefore would adversely affect patient' survival. (4)

Description of Initiative / Intervention / Service - including what is being provided and the intended benefits:

Cancer centres worldwide including National Center for Cancer Care and Research (NCCCR) have adopted certain measures to minimize the risk to patients with active cancer especially those receiving immunosuppressant therapies. NCCCR have introduced and implemented the following measures:

1. We patients requiring outpatient review and assessment were diverted into a separate building outside NCCCR, called the Ambulatory Care Centre, this to reduce the risk of exposure of patients of different risk factors and to comply with the rules surrounding social distancing.
2. Virtual clinics were established in order to monitor and treat selected patients remotely without the need for attendance physically to the outpatient facilities in the horseshoe hello
3. Show patients returning from overseas and who are on active chemotherapy treatment we are managed at a separate unit called the dental care centre.
4. Catering facilities and food hygiene NCCCR was reviewed and appropriate measures were introduced to optimize infection control.
5. All walk-in consultations were discontinued and patients were referred to the virtual helpline to assess and manage.
6. Staff distribution and rotation at different sites were reviewed and restricted to the same areas as previously allocated, this with the view of minimizing and containing the risk of inter-staff transmission of infection.
7. To continue effective management of patients with a diagnosis of cancer all the multidisciplinary team meetings continued to operate virtually. This allowed the existing MDTs structures to continue functioning as before without causing interruption to patients' care and management.
8. Morning handover meetings and educational activities within NCCCR continued regularly and maintaining the highest quality through virtual meetings and conferences.
9. **Patients' information leaflets** providing information about cancer and COVID-19 infection were introduced and provided to the patients.
10. All newly diagnosed cancer patients' referrals, chemotherapy and radiotherapy continued in order to prevent delay in initiation or interruption to ongoing treatment protocols.
11. Patients who were identified to have risk of acute viral respiratory infections such as common seasonal flu or COVID-19 infection were advised to refrain from visiting NCCCR. A drawback of this intervention was some patients either did not respond to telemedicine or failed to report their symptoms correctly. Trained medical staff assigned to control the entry points to NCCCR, checking all arrivals temperatures, screening them for their symptoms and inspecting the status of mobile application Ehteraz, prior granting admission to NCCCR.
12. All patients were admitted to the facilities within NCCCR, had their COVID-19 swab tested for PCR; only patients with negative results were allowed admission and to continue in patient care.
13. The appointment times of visiting outpatient facilities for selected patients were controlled in order to prevent overcrowding and ensure social distancing.
14. Patients and their companions were briefed at outpatient facilities by trained staff regarding infection control, transmission risk and early detection and reporting of COVID-19 infection.

Management of common and important cancer primaries:

NCCCR is aiming to produce specific guidelines to come in and important Cancer primary is such as lung, breast, colorectal, prostate and germ-cell tumors as well as hematological malignancies. Currently breast cancer management guidelines during COVID-19 pandemic is published, see appendix 1.

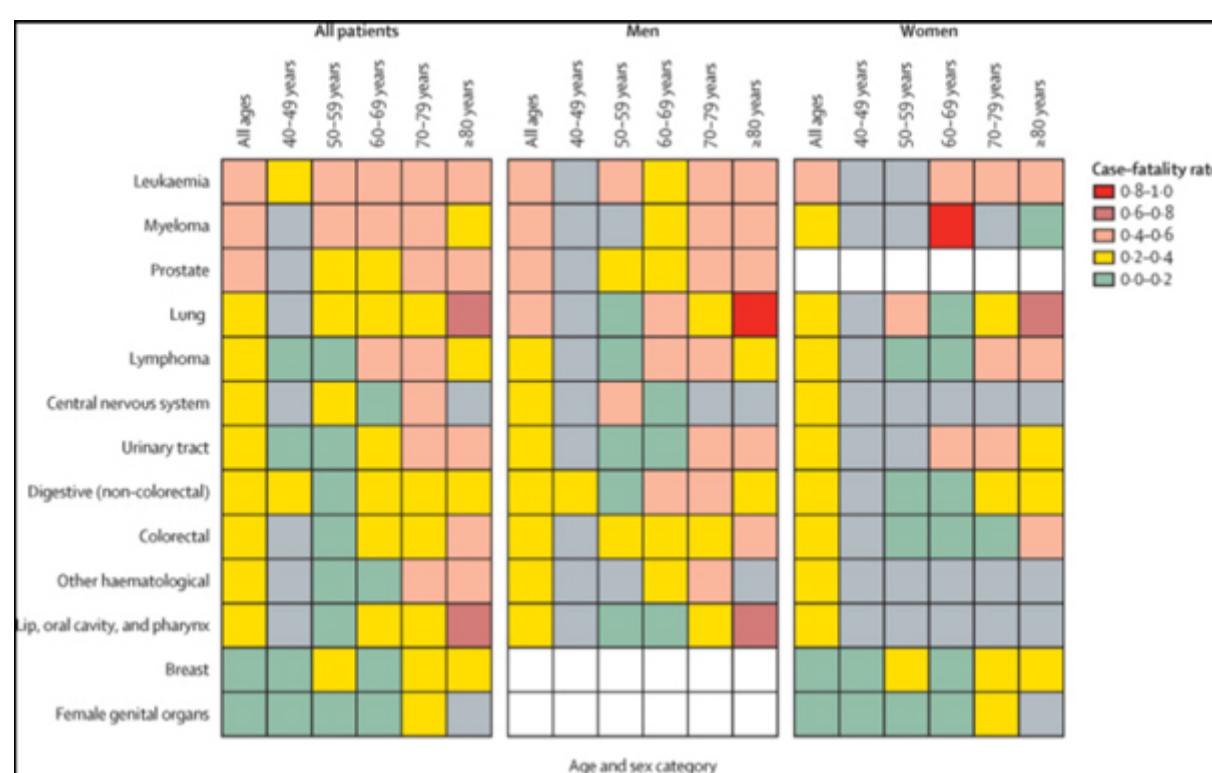
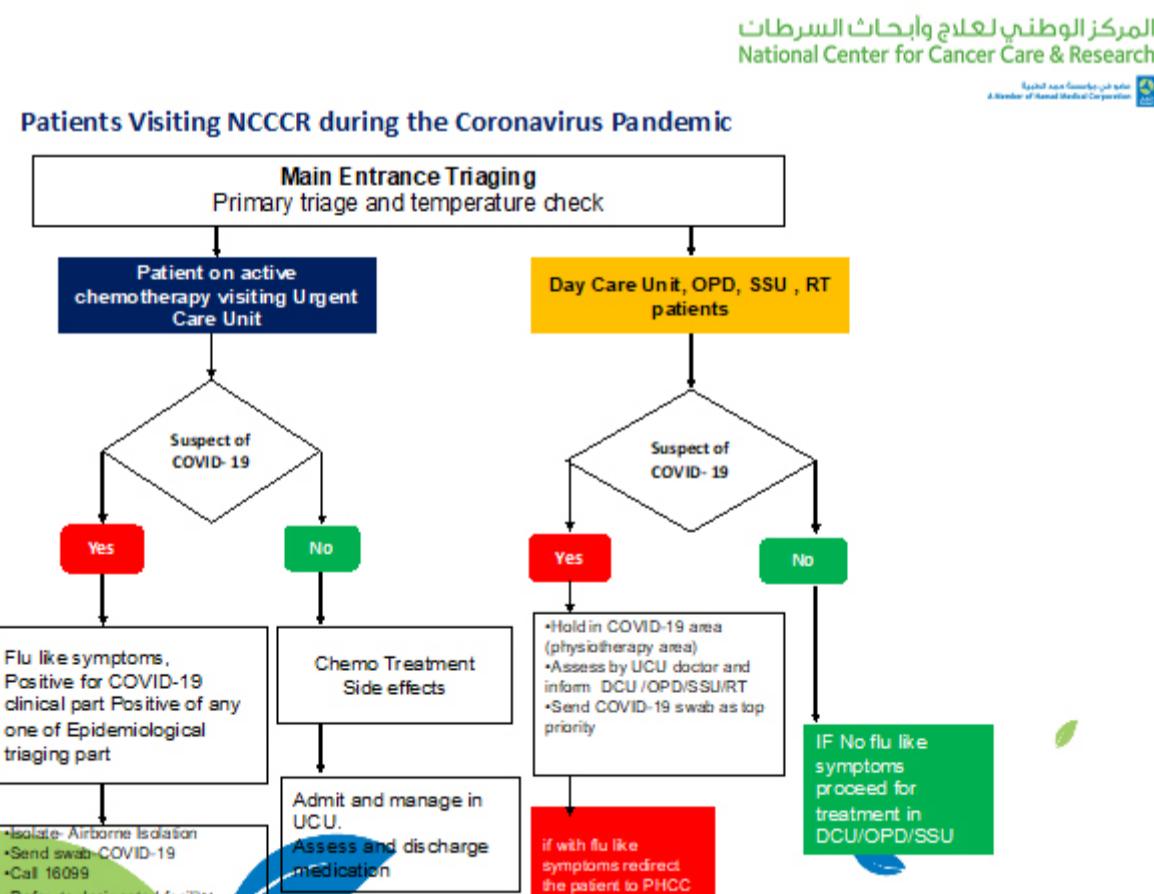


Table 1: COVID-19 case fatality rate by tumor subtype, age and sex (2)

High priority	Patient's condition is immediately life threatening, clinically unstable, and/or the magnitude of benefit qualifies the intervention as high priority (e.g. significant overall survival [OS] gain and/or substantial improvement in quality of life [QoL]);
Medium priority	Patient's situation is non-critical but delay beyond 6 weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for intermediate priority
Low priority	Patient's condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of benefit (e.g. no survival gain with no change nor reduced QoL).

Table 2: patients' prioritization as per ESMO recommendations:

**Appendix 1: HMC Guidelines for Treatment and Triage of Patients with Breast Cancer during COVID 19 Pandemic**

- The COVID-19 pandemic poses challenges for patients, clinicians and health care systems. We created these recommendations to develop guidance to mitigate the negative effects of the COVID-19 pandemic on the treatment of breast cancer patients with no impact on patient's survival and quality of life.

- The points mentioned below are intended to provide guidance for clinicians involved in breast cancer care during this time.
- Due to the urgency and the rapidly evolving situation, further updates to this guidance are possible and likely.
- Breast Cancer Patients Treatment decisions will be according to the MDT recommendations.

High priority	Patient's condition is immediately life threatening, clinically unstable, and/or the magnitude of benefit qualifies the intervention as high priority (e.g. significant overall survival [OS] gain and/or substantial improvement in quality of life [QoL]);
Medium priority	Patient's situation is non-critical but delay beyond 6 weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for intermediate priority
Low priority	Patient's condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of benefit (e.g. no survival gain with no change nor reduced QoL).

The tiered approach of HMC in delivering a guidance during COVID-19 for breast cancer patients is designed across three levels of priorities, namely: tier 1 (high priority intervention), 2 (medium priority) and 3 (low priority).

The Medical Oncology goals within NCCCR:

- Minimize patient interaction with health center
- Maintain patient safety
- Conserve resources while providing effective patient care
- Close monitoring of symptoms of infection to promptly withdraw the treatment and call 16000 / refer to COVID-19 diagnostic pathway

Priority	Patient Description	COVID-19 Treatment Considerations
Priority A		
A	Patients with oncologic emergencies (e.g. febrile neutropenia, hypercalcemia, intolerable pain, symptomatic pleural effusions or brain metastases, etc.)	Patient should be admitted to Inpatient unit for initiation of the necessary management
Priority B (All newly diagnosed early breast cancer cases should be discussed in the Breast Cancer MDT Meeting for individualized patient care)		
B1	Patients with inflammatory BC	Neoadjuvant chemotherapy
B1	Patients with HER2+ BC	<p>Neo/adjuvant chemotherapy</p> <ul style="list-style-type: none"> Neoadjuvant chemotherapy for tumor \geq 3cm / depending on breast tumor ratio / N1. Upfront surgery for tumor <3cm / depending on breast tumor ratio / N0, then consider adjuvant chemotherapy (trastuzumab + paclitaxel) Paclitaxel every 3 weeks x 4 can be considered. In addition, concurrently with trastuzumab every 3 weeks x 18 cycles.
B1	Patients with TNBC	<p>Neo/adjuvant chemotherapy</p> <ul style="list-style-type: none"> Neoadjuvant chemotherapy for \geq T2 or N+. Upfront surgery for < T2 and N0, then consider adjuvant chemotherapy (cyclophosphamide + docetaxel x 4 cycles). Consider AC (adriamycin + cyclophosphamide x 4 cycles) chemotherapy as second choice.
B1	Patients with clinical anatomic Stage 1 or Stage 2 ER+/HER2- BCs	<ul style="list-style-type: none"> Neoadjuvant endocrine therapy for 6 to 12 months to defer surgery (may consider Oncotype DX on core biopsy) Luminal B cancer to be decided by MDT
B1	Patients who already started neo/adjuvant chemotherapy	Continue therapy until complete
B1	Patients who have residual disease after surgery	Depending on patient response to neoadjuvant chemotherapy, continuation of adjuvant;

		<ul style="list-style-type: none"> Capecitabine treatment in high-risk triple-negative breast cancer patients T-DM1 in high-risk HER2-positive breast cancer patients (in the post-neoadjuvant setting)
B1	Patients progressing on neoadjuvant therapy	Refer to surgery or change systemic therapy
B1	Patients on oral adjuvant endocrine therapy	Continue therapy
B1	Premenopausal patients with ER+ BC receiving LHRH agonists (adjuvant or metastatic)	<ul style="list-style-type: none"> If on aromatase inhibitor, continue LHRH agonist and consider long acting 3 month dosing If on tamoxifen, consider deferring LHRH agonist
B1	Pregnancy-associated breast cancer	To be dealt according to MDT recommendation
B1	Patients with mBC for whom therapy is likely to improve outcomes	Initiate chemotherapy, endocrine, or targeted therapy
B1	Patients with mBC, ER / PR positive, Her 2 neu negative	<ul style="list-style-type: none"> The choice of postponing the incorporation of a CDK4/6 inhibitor in the first line, for patients presenting with special patterns of disease (e.g. bone only, low-burden, de novo metastatic disease) could be an option, especially in the elderly population Consider discussing case by case in Breast Cancer MDT, endocrine therapy with CDK 4- 6 inhibitors in ER-positive/HER2-negative breast cancer Close monitoring for symptoms of infection is recommended, to promptly withdraw the treatment and possibly refer to COVID-19 diagnostic pathway
B1	Patients with mBC and triple negative	<ul style="list-style-type: none"> Consider discussing case by case in Breast Cancer MDT, chemotherapy plus atezolizumab in PD-L1-positive TNBC. Close monitoring for specific symptoms, pneumonitis or infection is recommended, to promptly withdraw the treatment and possibly refer to COVID-19 diagnostic pathway
B2	Patients receiving adjuvant treatment for Stage 1 (T1N0) HER2+ breast cancer	Docetaxel Q 3 weeks x 3 cycles + Trastuzumab Q 3 weeks x 18 cycles
B2	Patients with mBC	When chemotherapy is recommended, prefer oral treatments / Q 3 weeks schedules in order to reduce access to hospital
B3	Patients with ER + DCIS	Consider neoadjuvant endocrine therapy to defer surgery
B3	Patients with mBC for whom therapy is unlikely to improve outcomes	Consider deferring chemotherapy, endocrine, or targeted therapy (best supportive care)
B3	Patients with HER2+ mBC beyond 2 years of maintenance antibody therapy (trastuzumab, pertuzumab) with minimal disease burden.	Consider stopping antibody therapy with monitoring for progression every 3-6 months
B3	Patients with mBC Second-, third-, beyond third-line treatment when therapy may provide clinical benefit and impact on outcome	Avoid or delay the addition of mTOR or PIK3CA inhibitors (still not approved in European Union) to endocrine therapy, particularly in elderly patients with comorbidities

B3	PATIENTS WITH HER2+ DC WITH T1a (tumor ≤ 1 cm and N0) receiving adjuvant antibody treatment	Consider trastuzumab for 7 months instead of 12 months
B3	Patients with ongoing adjuvant trastuzumab alone in quarantine / at high risk of complicated COVID-19 infection	Consider postponement by 6-8 weeks
B3	Patients with ongoing oral chemotherapy (palliative) in quarantine / at high risk of complicated COVID-19 infection	Swab for COVID-19 should be done as per protocol. Chemotherapy should be put on hold until negative result. Patient to be evaluated or assessed by oncologist through telemedicine / virtual clinic. Notes should be documented in Cerner. Risks and benefits of continuation of treatment should be discussed with the patient. If deemed necessary, new order should be put in Cerner. Pharmacist should be informed.
Priority C (Follow-up imaging, restaging studies, echocardiograms, ECGs and bone density scans can be delayed if patient clinically asymptomatic or clinical signs of response in the neoadjuvant setting)		
C	Patients receiving zoledronic acid, denosumab	Switch bone antiresorptive therapy frequency from monthly to Q 3 month unless for hypercalcemia
C	Patients with stable mBC	Interval for routine follow-up restaging studies can be delayed and use telemedicine / phone consultation for follow-up or monitoring of disease activity
C	Patients with mBC	Following Breast Cancer MDT discussion and according to patient preference, in later lines may discuss drug holidays, best supportive care and delayed regimens or de-escalated maintenance regimens, wherever appropriate.
C	Patients with lower risk imaging findings needing follow-up (e.g., small pulmonary nodules)	Interval follow-up can be delayed to Q 6 months and use telemedicine / phone consultation for follow-up or monitoring of disease activity
C	Patients who are candidates for prevention measures (e.g. family history, LCIS or ADH, BRCA1/2+)	Consider chemoprevention (endocrine therapy) as appropriate and delay risk-reducing surgery and high-risk surveillance imaging
C	Patients in long term follow up for early BC (survivors)	Defer routine in-person visit (use telemedicine / phone consultation for follow-up or monitoring of disease activity)
C	Patients on aromatase inhibitors	Defer bone density testing (baseline and follow up)

Priority Categories for Medical Oncology (NCCCR)

ADH, atypical ductal hyperplasia; BC, breast cancer; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LCIS, lobular carcinoma in situ; LHRH, luteinizing hormone releasing hormone; mBC, metastatic BC; TNBC, triple negative breast cancer.

RADIATION ONCOLOGY

During the COVID-19 pandemic, exposure to its causative virus, SARS-CoV-2, may confer an increased mortality risk in breast cancer patients, so minimizing infectious risk without compromising oncologic outcome becomes fundamental.

As Radiation Therapy (RT) has a major role in the treatment of breast cancer, it is vital to adopt strategies aimed at reducing the risk of infection for our Patients. This may be achieved through implementing several strategies, as already adopted by several Institutions, as well as by NCCCR(3).

These include hypofractionation; delaying treatment starts by 2-3 months in those cases where this would have no impact on outcome; or consider omission of treatment or omission of boost, wherever appropriate.

Since 2018, NCCCR adopted hypofractionation, following the data presented by ASTRO task force in.

The below details describe the current RT methodology used in our Department.

Fractionation

This document confirms that as a Department we are advocating fractionation schedules that reduce overall time spent in the department, favoring high level of evidence hypofractionated regimens in the curative, as well as in the palliative setting (2(4)).

All cases of post-operative breast cancer, referred from the Breast MDT for adjuvant radiation are treated with hypofractionation:

Residual whole breast receives a dose of 4000 cGy in 15 fractions;

When there is indication to include regional nodal sites (i.e. axilla, supraclavicular region, internal mammary nodes) for RT, these areas will be receiving:

- 4000 cGy in 15 fractions;

Patients, who underwent breast-conserving surgery, or a mastectomy without reconstruction, will all receive a boost to the lumpectomy cavity, or to the mastectomy scar site:

- In the absence of strong risk factors for local recurrence: 1000 cGy in 4 to 5 fractions
- In the presence of strong risk factor(s) for local recurrence, such as positive margins: 1250 cGy in 5 fractions.

Accordingly, the above Patients will be receiving radiotherapy to an overall treatment time of 4 weeks, as opposed to standard fractionation regimen of 6-6.5 weeks.

Patients who underwent mastectomy and a reconstruction will also receive adjuvant RT to the reconstructed chest wall and regional nodes with hypofractionation, however they will not be receiving a boost: hence, overall treatment time will be reduced to 3 weeks.

In the event of treating Patients with metastatic breast cancer, use of hypofractionation, or ideally single fraction treatments should be adopted in most palliative cases (except whole brain metastases), and possibly in SRS/SRT/SBRT .

Deferral

With our current staffing levels, there is no indication to defer the treatment of any Patient referred for Breast RT.

During the pandemic, we recognize that Patients who are already on treatment will be prioritized to complete their radiation courses already commenced, as an interruption of therapy is clinically unacceptable.

However, depending on the evolution of the pandemic, staffing numbers may be significantly reduced, with the necessity at one point in time to review treatment schedules and potentially defer Patients'.

This process should be based on a clear stratification of Patients, centered on intent and priority.

The objective of these actions would be a reduction in number of treatment slots, to an amount compatible with current staffing levels, ultimately guaranteeing safe and effective running of essential radiotherapy-related activities.

Several international oncology organizations have proposed Patient stratification, dividing them into priority groups, to aid in the decision of which Patients can be safely delayed to start RT, when this should become necessary.

In line with several Institutions and with the Multidisciplinary Team for breast cancer in HMC, priority categories were defined based on the severity of an individual patient's condition (including patient co-morbidities):

Omission of Radiotherapy

Currently, our Department does not recommend omission of RT to the whole breast, regional nodal areas or to the chest wall, for any case of Breast cancer, where adjuvant RT would normally be indicated.

However, Patients who underwent mastectomy and an immediate reconstruction will receive adjuvant RT to the reconstructed chest wall and regional nodes with hypofractionation, however they will not be receiving a boost: hence, overall treatment time will be reduced to 3 weeks.

Hematology and Bone Marrow Transplantation:

Hematological Malignancies and COVID- 19 infection

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-the causative agent of COVID -19 infection - is a cause of a significant mortality rate in patients with hematological malignancies who are a unique patients' population and are highly susceptible to infection due to the nature of the disease which affects the immune system alongside the use of myelosuppressive and lymphodepleting agents in the treatment protocols. As a result, inferior outcome was observed in patients with hematological malignancies compared to general population (5)

COVID -19 infection characterized by a wide spectrum of disease severity ranging from asymptomatic and mild illness to a very severe disease and potentially life threatening respiratory failure requiring ICU admission.

COVID -19 severity in hematological malignancies was attributed to several factors including advanced age, multiple comorbidities, the specific type of hematological malignancies and the treatment protocol used.(6)

Hospital admission and Non-white race but not recent therapy tend to be associated with increased risk of death. (7)A validated risk stratification model to predict disease severity in hematological malignancies is not yet been established.

Furthermore, patients with hematological malignancies tend to have persistent infection for a long period that extends beyond documented viral clearance By PCR in manner similar to chronic infection. Hence, long-term follow up is required.

Management of common hematological disorders during COVID-19 pandemic General measures:

- Special attention should be directed towards hygienic measures specially hand hygiene and social distancing in the hospital setting as well as in the community.

- Limiting outpatient visit to specific conditions and to specific times to avoid patient -to-patient contact.
- Adoption of telemedicine approach to address patients' concern without direct contact.
- Screening all patients prior to chemotherapy by COVID-19 PCR as well as chest high resolution computed tomography prior to intensive chemotherapy.
- Considering repeating the test before each cycle.
- In cases of positive PCR, therapy should be individualized and might be deferred based of patients' general condition and type of hematological malignancies and type of therapy. (8)

Acute leukemias

Acute leukemia patients require intensive chemotherapy causing profound myelosuppression that necessitates prolonged hospital admission and hence increased risk for infectious complication including COVID-19 infection.

Tailored treatment strategies were proposed by different hematology societies with a goal to reduce admission to ICU related to COVID -19 infection while receiving the appropriate leukemia therapy.

Acute myeloid leukemia (AML):

- Standard induction chemotherapy should be considered in fit patients.
- For asymptomatic patients with positive COVID-19 PCR, treatment might be postponed for 7-14 days till negative PCR is achieved.
- If chemotherapy is needed urgently, standard therapy should be commenced in a COVID-19 dedicated facility.
- Growth factors can be considered to minimize the duration of neutropenia.
- For high-risk AML in remission, allogenic stem cell transplant should be considered after obtaining PCR negativity.
- For patients with relapsed or refractory AML, individualized approach should be considered based on goal of therapy (curative vs palliative intent.)
- Acute promyelocytic leukemia is hematological emergency, treatment should be commenced without delay. (8)

Acute lymphoblastic leukemia (ALL)

- In ALL, Glucocorticoid therapy is a cornerstone in all treatment protocols, hence protocol -based doses should be followed.
- Drugs that carry survival advantage like blinatumomab or Inotuzumab should also be considered.
- Asparaginase therapy can be given with special attention to the risk of thrombosis and bleeding and to consider the use of appropriate prophylactic anticoagulation.
- Tyrosine kinase inhibitors in Philadelphia- positive ALL need to be continued due to survival advantage. (8)

Chronic myeloid leukemia (CML)

- The recommendation is to continue TKI to be continued in asymptomatic patient and patients with mild disease who does not require COVID-19 directed therapy.
- Prolongation of QTc interval and torsade de pointe are one of the major side effect of TKI and some of the COVID-19 directed therapy , temporary interruption of therapy needs to be considered till achieving PCR negativity.(9)

Chronic lymphocytic leukemia (CLL)

Due to the intrinsic nature of the disease, advanced age at diagnosis and the presence of comorbidities, CLL considered a potentially high risk for infectious complication including COVID -19.

Mortality rate reaching 33% in both treatment naïve and treated patients with CLL with symptomatic COVID -19 infection necessitating hospital admission. (10)

At the peaks of the pandemic, the recommendations are:

- To delay treatment for stable patients requiring treatment.
- To consider oral therapy if feasible to avoid frequent hospital visits and laboratory testing.
- The use of Monoclonal antibodies (rituximab, Obinutuzumab) to be limited as much as possible.

Local and international management guidelines should be followed once virus transmission is limited.(11)

Myeloproliferative Neoplasms (MPN)

Despite the increased incidence of thrombotic events in BCR-ABL negative myeloproliferative neoplasms (MPN) specifically Essential thrombocythemia (ET), there is little evidence of a higher thrombotic event when ET patients had COVID-19 infection.

Disease control through venesection, anti-platelets therapy and cytoreduction is crucial in reducing thromboembolic events in patient with COVID -19 infection.

Prophylactic anticoagulation therapy as per local guidelines are added to critically ill MPN patients with close observation specifically at the extreme of platelets count due to the risk of bleeding. (12)

There is no data to support stopping JAK inhibitors (Ruxolitinib) in patients infected with COVID-19. In fact, cessation of therapy might result in significant side effect including cytokine storm which is expected to worsen the outcome of COVID

-19 infection .(13)

Multiple myeloma (MM)

MM patients are severely immunocompromised and are at increased risk of severe COVID-19 infection. However, therapy should be initiated without delay in patient with organ involvement and myeloma emergencies. Individualized therapy based on risk stratification and consideration of less intense regimen and extended induction period with postponing of autologous stem cell transplant is considered at the peak of the pandemic. Temporary discontinuation of therapy in symptomatic COVID-19 disease is recommended till complete recovery. (14)

National centre for cancer care and research (NCCCR) Response to COVID -19 (haematological malignancies)

- Physical distancing: minimizing the patient -physician interaction through
 - Telemedicine for most of the outpatient's visits.
 - Physical visit is considered for newly diagnosed patients, patients on active therapy or patients with disease complication.
 - Reduce imaging and laboratory tests for patient on surveillance program
- Multidisciplinary approach in patient care with individualization of therapy after appropriate risk stratification and postponing certain therapy in stable disease.
- Screening all patient prior to initiation of each cycle chemotherapy with COVID -19 PCR, deferral of positive cases based on the clinical context.
- During cytopenic nadir and in the immediate period post intensive chemotherapy, patients who had COVID-19 negative PCR will be shifted to patient recovery centre (PRC) a controlled and monitored area to avoid contact with the community.
- Vaccination program to all patients to reduce or prevent the COVID-19 infection.

Hematopoietic Stem Cell Transplantation in Covid-19 pandemic.

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for a wide variety of blood cancers and inherited blood disorders. Stem cell transplants may be derived from the patient's own blood (autologous) or from a healthy donor who can be related or unrelated to the patient (allogeneic)(15).

The Qatar National Blood and Marrow Stem Cell Transplant Program at the National Center for Cancer Care and Research (NCCCR) offers both autologous and allogeneic stem cell transplants for patients with hematologic malignant and nonmalignant disorders. Our Program has performed 107 autologous and allogeneic stem cell transplants with excellent results.

The covid-19 pandemic has spread worldwide and poses immense pressure on healthcare system including Hemato-oncologists and stem cell transplant services.

Hematopoietic stem cell transplantation (HSCT) is a high-risk procedure. Patients with cancer have at least a two-times higher risk of Covid-19- associated intensive care unit admission, invasive ventilation, and death compared with the general population. Hematopoietic stem-cell transplantation recipients considered vulnerable group due to nascent immune systems and organs' function impairment from treatment-related toxicities(5).

They are prone to various infections including respiratory tract infections(5) .

Data on outcomes of HSCT recipients with Covid-19 in Qatar are limited due to the small number of cases in a single-centre experience. In a study from Italy, of 82 patients who developed Covid-19 after HSCT mortality rate was 35% in allogeneic (11/31) and 33% in autologous (17/51) transplant patients. Increasing age, progressive disease status and diagnosis of acute myeloid leukemia, non-Hodgkin lymphoma, or plasma cell neoplasms were associated with worse survival (16).

The Spanish HSCT and Cell Therapy Group reported on 65 patients underwent HSCT A 45-day overall mortality rate was 17% for 65 allogeneic and 18% for 58 autologous HSCT recipients.

Age above 70 years and hypertension were associated with a doubling of the risk of mortality (17). In another two studies from two North American cohorts comprising of 111 HSCT recipients (allogeneic n=55, autologous n=51, chimeric antigen receptor T-cell therapy n=5) had Covid-19 infection. In this study 15% of the patients (n=17) required intubation and mechanical ventilation and 19 (17%) of the patients died. Most of them had received an allogeneic HSCT within one year from transplantation (18)Patients with active GVHD and patients receiving steroids were more likely to have poor outcome.

Recently the Center for International Blood and Marrow Transplant Research (CIBMTR, USA) has reported the largest cohort of 318 HSCT recipients diagnosed with Covid-19 (7).

The median time from diagnosis to allogeneic HSCT was 8 months (IQR 5–19). In allogeneic HSCT patients 140 (76%) of 184 grafts were peripheral blood stem cells (PBSCs), 66 [36%] of 184 patients received grafts from HLA-matched siblings, and 49 [27%] of 184 from matched unrelated donors. Plasma cell disorders (86 [64%] of 134) or lymphoma (41 [31%] of 134) were the most common indications for autologous HSCT.

The median time from HSCT to the diagnosis of COVID-19 was 17 months (IQR 8–46; range 1–243) for allogeneic HSCT recipients and 23 months (IQR 8–51; range 1–169) after autologous HSCT. 60 (33%) of 184 allogeneic HSCT recipients had grade 2–4 acute GVHD, 66 (36%) had evidence of chronic GVHD before COVID-19. However, only 34 (18%) of 184 patients had received immunosuppression within 6 months of Covid-19 diagnosis. Upon last follow-up, the infection was considered resolved in 126 (40%) of 318 patients, 30 (9%) of them were improving, and infection was ongoing for 49 (15%) of the recipients 66 (21%) of 318 HSCT recipients reported to the registry had died and infection resolution status was unknown or not reported for another 48 (15%) patients. Among the allogeneic HSCT recipients group, 40 (22%) of 184 died. Except in 3 cases who passed away due to their underlying diseases, the rest are considered death related to Covid-19. 26 patients (19%) of 134 in the autologous HSCT group died. Covid-19 was the primary cause of death in 19 cases (73%) and other causes of death were related to relapse of the disease in four cases, one organ failure, and new malignancy in two cases. Overall probability of survival at 30 days after diagnosis of Covid-19 was 68% (95% CI 58–77) for recipients of allogeneic HSCT and 67% (55–78) for recipients of autologous HSCT.

Factors associated with higher mortality risks after contracting Covid-19 are age 50 and above, male and contracting Covid-19 within 12 months of transplantation in allogenic recipient group.. Disease indication of lymphoma was associated with a higher risk of mortality compared with plasma cell disorder or myeloma in autologous HSCT recipients. Worth to mention that ethnic background, hematopoietic cell transplantation-comorbidity index at the time of HSCT and immunosuppression within 6 months before being infected with Covid-19 were not associated with increase mortality. Absolute lymphocyte count of 0.3×10^9 cells per L or less at time of Covid-19 diagnosis was associated with worse survival (56% [95% CI 34–76] vs 85% [78–90]; p=0.003).

In transplant programs across the globe, physicians are trying to prevent Covid-19 infection in transplanted recipients and their respective donors so that HSCT could be conducted smoothly and risk-free.

The European Blood and Marrow Transplant (EBMT) and the American Society for Transplantation and Cell Therapy (ASTCT) have issued guidelines for recipients, and donors of HSCT.

The EBMT regularly updates their recommendations for stem cell transplant recipients or patients treated with CAR T cells. Herein, we have summarized the EBMT guidelines for HSCT patients.

Healthcare workers

Staff with any symptoms of infection should stay at home o Testing for SARS-CoV-2 is strongly recommended since symptoms can be uncharacteristic and very mild. PCR is the test recommended in this document.

Return to work by staff members who have recovered from Covid-19 should follow national guidelines, usually requiring the resolution of symptoms and two negative PCR results Testing asymptomatic healthcare workers: there are no general recommendations to regularly test asymptomatic healthcare workers.

Training of staff in proper procedures, including caring for those with suspected or confirmed infection, ensuring adequate access to personal protection equipment and planning for possible staff shortage are critical.

Staff should preferably be dedicated to a Covid-19 free transplant unit and not used interchangeably to care for Covid-19 positive patients.

It is critical that proper protective equipment is used as recommended by national and international competent authorities.

Outpatient visits and visitors

Outpatient visits should be substituted with telemedicine visits if deemed appropriate and feasible. For necessary out-patient visits, it is important that appropriate measures to reduce the risk for nosocomial transmission continue to be applied. When there is substantial Covid-19 activity, it is recommended to maintain visitor restrictions to transplant units. There might be exceptions for parents to transplanted children. Testing for SAR-CoV-2 should then be considered before entering the ward. Repeated testing might then be necessary.

Transplant patients

Patients planned to be admitted for a transplant or to undergo CAR T-cell therapy should try to minimize the risk by home isolation 14 days before the start of the transplant conditioning. Unnecessary clinic visits should be avoided

Transplant candidates that become infected by SARS-CoV-2

The decision to defer or not the transplant must be made taking into several factors. If a transplant candidate is diagnosed with COVID-19, a deferral of the transplant procedure is recommended. However, this is not always possible due to the risk for progression of the underlying disease.

In patients with high-risk disease

SCT should be deferred until the patient is asymptomatic and has two negative virus PCR swabs taken at least 24 hours apart.

In patients with low-risk disease

Who were asymptomatic or only mildly symptomatic with upper respiratory tract symptoms, deferral of 14 days after first negative PCR is a minimum but should preferably be 21 days and a new PCR is recommended before the start of conditioning.

For those with moderate to severe COVID-19 disease, it is recommended to defer the transplantation for at least three months

In case of close contact with a person diagnosed with COVID-19

Any transplant procedures (PBSC mobilization, BM harvest, and conditioning) shall not be performed within at least 14, days from the last contact.

Patient should be closely monitored for the presence of COVID-19, with confirmed PCR negativity before any transplant procedure is undertaken

Before starting the transplant procedure

Patients should be adequately informed that the risk for severe complications can be higher if the patient get infected with SARS-CoV-2 during or after the transplantation.

Availability of adequately trained staff, ICU beds, ventilators, as well as availability of the stem cell product should be ensured. All patients, including those without symptoms, should be triaged and tested before being admitted to a transplant ward.

Adequate space for symptomatic patients while awaiting the results of COVID-19 testing should be allocated preferably separate from the transplant unit.

All patients should be tested for SARS-CoV-2 by PCR and the test results should be negative before start of the conditioning regardless of whether any symptoms are present

Patients after HCT or CAR T cell therapy.

Those being regarded as immunosuppressed or having significant organ dysfunction should limit their risk of exposure to infected individuals as much as possible and strictly adhere to prevention practices such as hand hygiene and social distancing.

Refrain from travel and if travel is deemed necessary, travel by private car instead of any public transportations system is recommended if feasible.

DONORS

Social isolation before donation: donors within 28 days of donation should practice good hygiene and be as socially isolated as feasible during this period. Unnecessary travel should be avoided.

Donors with close contact or diagnosed with COVID-19

Diagnosed with COVID-19: Collection should be deferred for at least 28 days after recovery.

In case of close contact with a person diagnosed with COVID: the donor shall be excluded from donation for at least 28 days after the last contact.

If the patient's need for transplant is urgent, the donor is completely well, a test is negative for SARS-CoV-2 and there are no suitable alternative donors, earlier collection may be considered subject to careful risk assessment.

Testing before stem cells collection

It is recommended that donors are tested for COVID-19 and that results are available prior to starting the collection procedure, in order to protect the staff of the pheresis unit and other patients that can be at the unit at the same time from an infected donor

Cryopreservation of stem cells

If there is concern that the donor is at high risk of community-acquired infection between work-up and collection, pre-planned cryopreservation is recommended since it will allow patient conditioning to be withheld until successful donation and delivery are confirmed.

Stem cell products can also be frozen at the harvest site if prolonged transport time is expected

DIAGNOSIS AND GENERAL MANAGEMENT OF COVID-19 PATIENTS

Diagnostic procedures for COVID-19 should follow national or local guidelines.

Test for SARS-CoV-2 in nasopharyngeal swab can be falsely negative and needs to be repeated if there is a strong clinical suspicion of COVID-19.

The performance of testing is better in samples from the lower than from the upper respiratory tract (sputum or bronchoalveolar lavage.)

It is also important to test for other respiratory viral pathogens including influenza and RSV preferably by multiplex PCR.

SARS-CoV-2 infected patients

Patients, who are positive for SARS-CoV-2 should not be treated in rooms with laminar air flow or other rooms (HEPA) with positive pressure unless the ventilation can be turned off.

All patients positive for SARS-CoV-2 in an upper respiratory tract sample should undergo chest imaging, preferably by CT, and evaluation of oxygenation impairment.

Routine bronchoalveolar lavage (BAL) is not recommended if a patient tested positive for SARS-CoV-2.

It is recommended to perform spirometry in HCT patients, who have resolved COVID-19.

TREATMENT OF COVID-19 POSITIVE HCT AND CAR T CELL PATIENTS

Supportive care is crucial especially anti-coagulants to prevent thrombo-embolic events. Co-pathogens should be evaluated and treated.

At this point no clear recommendations can be made on specific therapies in HCT patients due to limited data or unclear risk vs benefit. Both antivirals and non-antiviral drugs have shown a significant impact in the death rate of COVID-19.

Remdesivir has been approved in the EU for treatment of severe COVID-19

Recently a monoclonal antibody, bamlanivimab, received an emergency use authorization by the FDA for mild to moderate COVID-19

Convalescent plasma: In randomised trials, no effect on mortality was observed (except in one very small trial with 21 patients). Nonetheless, convalescent plasma significantly reduce mortality in subgroups of patients: those who received convalescent plasma with higher antibody levels, and those who received plasma within three days of COVID-19 diagnosis.

Corticosteroid: Short-term corticosteroid therapy (7-10 days) was associated with lower mortality in immunocompetent patients with severe and critical COVID-19, was shown to be effective in randomized trials and is endorsed by the WHO

guideline.

Tocilizumab: no effect on mortality was observed in 5 randomized trial

VACCINATION

Two vaccines are currently approved by the FDA for emergency use in the USA (Moderna/National Institutes of Health, Pfizer/BioNTech) both based on mRNA technology. The British competent authority has approved the Pfizer/BioNTech vaccine for use in the UK. The EMA has approved the Pfizer/BioNTech vaccine December 21.

The FDA and CDC have presented advice for the use of this vaccine and it is recommended for immunosuppressed patients although no specific data has been presented.

It is recognized that the protection efficacy might be lower in immunosuppressed individuals.

More information can be obtained at the FDA (www.fda.gov) and CDC (www.cdc.gov) websites.

Currently our assumptions and recommendations are.:

1. HCT patients could be vaccinated with whatever vaccine is made available considering the results of the phase III trials in the healthy population, we can assume that the HCT patient population is among the ones, who should have the highest benefit/risk ratio of the vaccination.
2. This message is important to explain to patients and their relatives.
3. If the transmission rate in the surrounding society is high, vaccination could be initiated at the earliest three months after HCT and take priority over the regular vaccinations program. With the currently approved two-dose vaccines, this means a postponement of approximately 6 – 8 weeks for other vaccines.
4. If transmission in the surrounding society is well controlled, it would be logical to wait until six months after transplantation to initiate vaccination.
5. Studies with other vaccines with good immunogenicity potential have shown efficacy also in patients with ongoing moderately severe GVHD without obvious risks to result in worsening of the GHVD. These patients should therefore not be excluded. Although side effects are expected as with any vaccine, there is no example of a non-live vaccine having more frequent or more severe side effects in HCT recipients than in the healthy population of the same age range.
6. So far, there is no data suggesting immune activation of underlying conditions making the likelihood that COVID-19 vaccines will exacerbate GVHD low.
7. Reasonable exclusion criteria from COVID-19 vaccination based on our current knowledge are: severe, uncontrolled acute GVHD grades III – IV; recipients, who have received anti-CD20 antibodies such as rituximab during the past six months; CAR T cell patients with B-cell aplasia earlier than six months after treatment; recent therapy with ATG or alemtuzumab; children < 16 since there is no information regarding vaccination of this group in any of the studies. It can be justified to vaccinate adolescents ages 16 – 18 years old.
8. Studies of safety, efficacy and immunogenicity of COVID-19 vaccines are recommended, but positive antibody testing (both to spike or nucleocapsid proteins) is not equivalent with sufficient protection; and general preventive practices should be continued.
9. Healthcare workers should be vaccinated to protect the patients.
10. House-hold contacts should be vaccinated, especially when the HCT recipient is early after transplant or receiving intensive immunosuppression, as such patients are unlikely to respond to COVID-19 vaccine.
11. The duration of protection is unknown, but it is possible that it will be shorter in immunocompromised patients than in healthy individuals as has been shown with other vaccines. Thus, booster doses as most likely needed but it is unclear when such should be given.

References

1. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7.
2. Lee LYW, Cazier JB, Starkey T, Briggs SEW, Arnold R, Bisht V, et al. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. Lancet Oncol. 2020;21(10):1309-16.
3. de Azambuja E, Trapani D, Loibl S, Delaloge S, Senkus E, Criscitiello C, et al. ESMO Management and treatment adapted recommendations in the COVID-19 era: Breast Cancer. ESMO Open. 2020;5(Suppl 3).
4. McDowell L, Goode S, Sundaresan P. Adapting to a global pandemic through live virtual delivery of a cancer collaborative trial group conference: The TROG 2020 experience. J Med Imaging Radiat Oncol. 2020;64(3):414-21.
5. Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. Lancet Haematol. 2020;7(10):e737-e45.
6. Garcia-Suarez J, de la Cruz J, Cedillo A, Llamas P, Duarte R, Jimenez-Yuste V, et al. Impact of hematologic malignancy and type of cancer therapy on COVID-19 severity and mortality: lessons from a large population-based registry study. J Hematol Oncol. 2020;13(1):133.
7. Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood. 2020;136(25):2881-92.
8. Brissot E, Labopin M, Baron F, Bazarbachi A, Bug G, Ciceri F, et al. Management of patients with acute leukemia during the COVID-19 outbreak: practical guidelines from the acute leukemia working party of the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant. 2020.
9. Rea D. CML, TKI treatment and COVID-19 disease [Available from: <https://ehaweb.org/covid-19/covid-19-recommendations/recommendations-for-specific-hematologic-malignancies/>.
10. Mato AR, Roeker LE, Lamanna N, Allan JN, Leslie L, Pagel JM, et al. Outcomes of COVID-19 in patients with CLL: a multicenter international experience. Blood. 2020;136(10):1134-43.
11. M S. COVID-19 and CLL: Frequently Asked Questions. Feb 2021.
12. COVID-19 and Myeloproliferative Neoplasms: Frequently Asked Questions: ASH; Jan 2021 [Available from: <https://www.hematology.org/covid-19/covid-19-and-myeloproliferative-neoplasms>.

13. Kamaz B, Mullally A. COVID-19 and myeloproliferative neoplasms: some considerations. Leukemia. 2021;35(1):279-81.
14. Terpos E, Engelhardt M, Cook G, Gay F, Mateos MV, Ntanasis-Stathopoulos I, et al. Management of patients with multiple myeloma in the era of COVID-19 pandemic: a consensus paper from the European Myeloma Network (EMN). Leukemia. 2020;34(8):2000-11.
15. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323(20):2052-9.
16. Shah GL, DeWolf S, Lee YJ, Tamari R, Dahi PB, Lavery JA, et al. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. J Clin Invest. 2020;130(12):6656-67.
17. Sharma A, Bhatt NS, St Martin A, Abid MB, Bloomquist J, Chemaly RF, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. Lancet Haematol. 2021;8(3):e185-e93.
18. Ljungman P, Mikulska M, de la Camara R, Basak GW, Chabannon C, Corbacioglu S, et al. The challenge of COVID-19 and hematopoietic cell transplantation; EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. Bone Marrow Transplant. 2020;55(11):2071-6.

[Home](#)[Forward message](#)[Introduction](#)[Chapters](#)[Editors team](#)[Contact us](#)

Copyright © 2022 Ministry of Public Health. All rights reserved.



Search this site



Neurology

Chapter: Neurological manifestation of the Novel Coronavirus (COVID-19)

Chapter Editor:

Yahia Z. Imam MBBS, MD, FRCP(Edin), MSc, FAAN, FESO

Hamad Medical Corporation, Doha, Qatar

Chapter contributors:

Stroke Section:

Yahia Z. Imam MBBS, MD, FRCP(Edin), MSc, FAAN, FESO

Hamad Medical Corporation, Doha, Qatar

Epilepsy section:

Lubna Ebn Omar Elsheikh MBBS, MD

Boulenouar Mesraoua MD, FAAN

Hamad Medical Corporation, Doha, Qatar

Miscellaneous neurological disorders section:

Salman K Al Jerdi MD

Weil Cornel Medicine-Qatar, Doha, Qatar

Tahira Thekkupurath MD

Hamad Medical Corporation, Doha, Qatar

Word count (without references) =4792

Contents

Chapter: Neurological manifestation of the Novel Coronavirus (COVID-19)

[**1. Introduction**](#)

[**2. Pathogenesis:**](#)

[**3. Stroke and COVID-19**](#)

3.1. Introduction:

3.2. Incidence of stroke in COVID19 patients:

3.3. Effect of COVID 19 on stroke care and stroke epidemiology:

3.4. Characteristics of Stroke in COVID-19 patients:

3.4.1 COVID-19-induced Acute Ischemic Stroke (AIS):

3.4.1.1 Clinical characteristics of COVID-19 patients with AIS:

3.4.1.2 Outcome

3.4.2 Cerebral venous thrombosis:

3.4.3 Intracerebral Hemorrhage with COVID-19

3.5. COVID-19 Stroke in Qatar:

[**4. Epilepsy and COVID-19**](#)

4.1. Introduction

4.2. COVID-19 and seizure disorders:

4.3. Teleneurology: Caring for patients with epilepsy during the COVID pandemic:

4.4. Drug consideration:

- 4.5 Electroencephalography- (EEG) related problems:
- 4.6 Social impact of COVID-19 in patients with epilepsy:
- 4.7 Management of seizures in patients with COVID-19:
- 4.8. Epilepsy and COVID-19 in Qatar:

5. Miscellaneous Neurological Manifestations

- 5.1.2 Critical illness polyneuropathy/myopathy
- 5.1.3 Myositis
- 5.2 Mononeuritis and Mononeuritis Multiplex
- 5.2.1 Cranial Neuropathies
 - 5.2.1.1 Anosmia and Agusia
 - 5.2.1.2 Isolated Cranial Neuropathies
- 5.3 Meningoencephalitis
- 5.4 Demyelinating disorders
- 5.5 Generalized myoclonus
- 5.6 Posterior reversible encephalopathy syndrome (PRES)
- 5.7 Long term neurological sequela of COVID-19
- 5.8. Patients with premorbid neurologic disease

6.Challenges and future directions

7.References

1.Introduction

Neurological manifestations are not uncommon in COVID-19, occurring in 25%-84% of patients depending on severity of disease(1).

These can range from mild symptoms, similar to any upper respiratory virus, such as headache and muscle aches, to more serious debilitating conditions such as large vessel ischemic stroke, Guillain Barre syndrome, critical illness myeloneuropathy-like illnesses and encephalopathy(2) .

2.Pathogenesis:

The neuroinvasive and neurotropic potential of SARS-CoV-2 is documented in humans(3).

Additionally, it has a propensity to incite inflammation, endothelial dysfunction and thrombosis, key to the development of other neurological manifestations such as stroke (3).

The COVID-19 virus can directly infect motor or sensory neurons or gain entry to the Central Nervous System (CNS) through anterograde transport machinery using kinesin and dynein.

(Kinesins are a group of related motor proteins that use a microtubule track in anterograde movement, while Dyneins are microtubule motors capable of retrograde sliding movement) (4).

This mechanism induces the production of pro-inflammatory cytokines (TNF- α , IL-6, IL-1B), nitric oxide, prostaglandin E2 and free radicals, and causes chronic inflammation, neuronal hyper-excitability, seizures and death(5).

Retro-neuronal (particularly through the olfactory or vagus nerves), transcribral and hematogenous spread have all been hypothesised to be valid virus entry routes into the CNS (6) .

For a comprehensive review on the pathogenesis of COVID-19, please refer to this review (Pathogenesis)(3).

Possible mechanisms and manifestations for COVID-19 are depicted in Figure 1 (adapted from Nannoni et al (7))

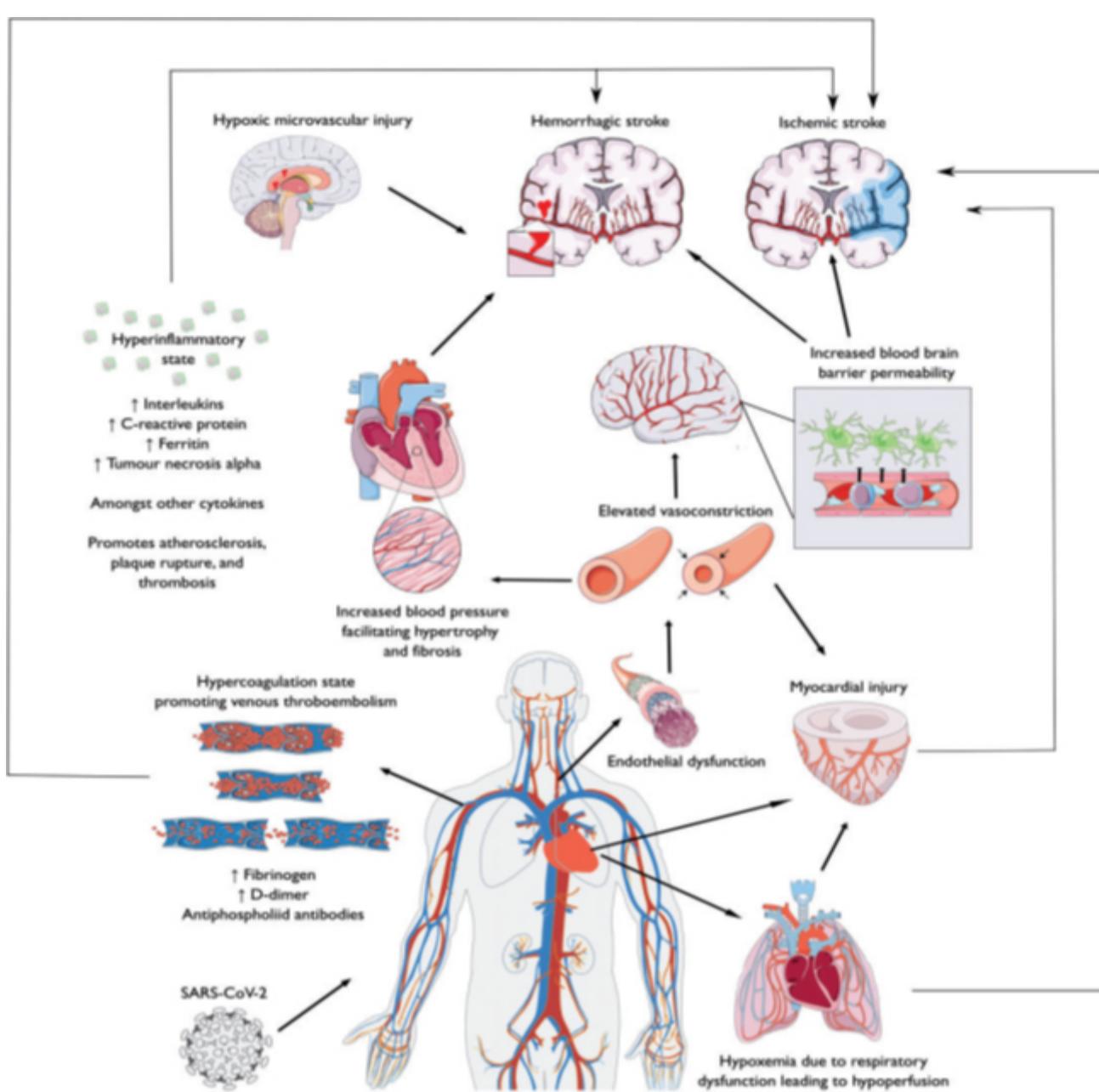


Figure 1: Possible mechanism and manifestation are illustrated (adapted from Nannoni et al (5))

3. Stroke and COVID-19

Yahia Z. Imam MBBS, MD, FRCP(Edin), MSc, FAAN, FESO

Keywords: Stroke, Acute ischemic stroke (AIS), Intracerebral haemorrhage (ICH), Cerebral venous thrombosis (CVT), Incidence, Characteristics, Outcome

3.1. Introduction:

Stroke causes mortality and morbidity worldwide (8).

Conditions such hypertension, diabetes, atherosclerosis and heart disease are common risk factors(8). Another underappreciated trigger for thrombotic events and vasculopathy is viral infections (8).

Indeed viruses such as HIV, CMV, VZV and seasonal influenza viruses(9) have been associated with an increased short term risk of stroke.

While the Novel coronavirus pandemic has coincided chronologically with a rising incidence of stroke, it is now understood that the virus in particular is associated with an increased risk of stroke, even in younger patients without typical risk factors, and at a rate that exceeds that of seasonal flu(9).

3.2. Incidence of stroke in COVID19 patients:

Earlier reports from Wuhan, the epicentre of the virus, reported 5 ischemic strokes in 214 consecutive COVID-19 patients (2.3%) (10).

Similarly, a case series from the hard-hit Lombardy region in Italy showed a 2.5% ischemic stroke rate among COVID-19 proven cases (11).

On the other hand, reports from New York, another epicentre, and across the United States health system, showed a lower reported stroke incidence of 0.9%(12).

It is now understood that stroke rates among COVID-19 patients are around 1.2% (0.9-2.7%) (13).

The discrepancies in these observational studies may be due to method of ascertainment, variable access to neuroimaging, selection bias, silent strokes or strokes in non-eloquent areas or concealed by more dramatic peripheral or global manifestations of the disease.

Additionally, ethnic and racial variation among these study populations might be a contributing factor. Thus, it is likely that these rates overall underestimate the true incidence of stroke in COVID-19 patients.

3.3. Effect of COVID 19 on stroke care and stroke epidemiology:

Multiple reports around the globe have shown that the number of non-COVID hospital admissions have decreased. This was also reflected in the number of stroke and TIA admissions(14).

One reason might be that people with minor symptoms refrained from visiting hospitals due to fear of the virus, or may have been turned away or overlooked due to scarcity of resources or bed capacity (15).

This phenomenon has serious ramifications in terms of stroke recurrence and creating bottlenecks for service delivery, impacting door-to-needle times, decreasing use of reperfusion therapies, and risking possible failure of the stroke chain of survival (15, 16).

3.4. Characteristics of Stroke in COVID-19 patients:

According to Akhtar et al(17), strokes occurring during the COVID-19 pandemic can be classified as follows:

1. Stroke without COVID-19 infection: these patients have the usual risk factors for stroke and present during the pandemic. They are otherwise asymptomatic and have tested negative for SARS-CoV-2.
2. Stroke with incidental COVID-19 infection: Patients are asymptomatic and have normal chest x-rays. They present with a stroke and test positive for SARS-CoV-2 upon routine screening.
3. COVID-19-induced prothrombotic cerebrovascular event (which could be arterial or venous in origin): these patients are symptomatic and have positive COVID-19 swabs or suggestive chest imaging and an ischemic stroke or cerebral venous thrombosis.

We will discuss the last category in further detail below.

3.4.1 COVID-19-induced Acute Ischemic Stroke (AIS):

3.4.1.1 Clinical characteristics of COVID-19 patients with AIS:

A systematic review with COVID-19 induced stroke included 135 patients, with 80% being from the USA/Europe, reported a mean age of 63.4+13.1 years, with 62.3% of patients being male (13).

Another systemic review found COVID-19-induced stroke patients to be 6 years younger on average than those that had non-COVID-19 related strokes. However, the former were about 5 years older than non-stroke COVID-19 patients. COVID-19 stroke patient were also reported to more likely have typical vascular risk factors such as hypertension, diabetes mellitus and coronary artery disease (7).

Most COVID-19 stroke patients manifested typical COVID-19 symptoms, such as fever (63.7%) or acute respiratory symptoms (76 %).

The mean duration of AIS from COVID-19 symptom onset was 10 ± 8 days. D-dimer was elevated with a mean value of $(9.2 \pm 14.8 \text{ mg/L})$ (13).

Strokes were reported to be generally 'severe' on the National Institute of Health Stroke Scale (NIHSS), with a median value of 19 ± 8 , and were 5 points higher on average compared to non-COVID-19 strokes(7).

This is consistent with the higher prevalence of large vessel occlusion (LVO), which was seen in more than half of the COVID-19 stroke patients. Simultaneous multiple LVOs of different vascular territories were reported in 14.9% of COVID-19 LVO cohort.

Small vessel pattern infarctions were relatively infrequently reported on imaging (8.7%) (13).

3.4.1.2 Outcome

Strokes in COVID-19 patients confer additional morbidity and mortalitydespite receiving acute stroke therapy (thrombolysis and thrombectomy) in similar proportions to non -COVID-19 strokes(7). Increased stroke severity, large vessel occlusion and presence of already severe COVID infection are important contributing factors (17, 18).

3.4.2 Cerebral venous thrombosis:

Cerebral Venous Sinus Thrombosis (CVST) remains a relatively rare manifestation of the COVID-19 prothrombotic state, with reports limited to case reports and case series of previously healthy young to middle-aged patients(19). This emphasizes the importance of a heightened clinical index of suspicion given the associated morbidity and mortality. The treatment of choice is anticoagulation, and salvage thrombectomy might be rarely required in severe cases(19).

3.4.3 Intracerebral Haemorrhage with COVID-19

Intracerebral Haemorrhage (ICH) appears to be less common than the thrombotic pathology, with an incidence around 11.6-17.2% of total stroke cases (7, 20).

A causal relationship is yet to be established as the ICH may occur incidentally due to underlying hypertensive or cerebral amyloid pathology, or may be aggravated by the COVID-19 infection(7).

Proposed mechanisms for such induction of haemorrhage include depletion of angiotensin converting enzyme 2 (ACE2) receptors or neurovascular injury due to an overactive immune response(21).

3.5. COVID-19 Stroke in Qatar:

The number of confirmed cases of COVID-19 in Qatar increased exponentially since the first cases were reported in February 2020 to 150,000 almost a year later. Qatar boasts one of the lowest fatality rates in major outbreak countries (<0.2%), reflecting its young healthy demographics(22).

Stroke admissions declined significantly when compared to the 6 months immediately prior to COVID-19 ($p=0.024$) (14). This reduction in admissions was driven by a decrease in functional stroke mimics.

While there were no significant differences in stroke subtypes, there was a relative decrease in small vessel disease strokes, with an increase in large vessel occlusive infarctions observed(14).

Additionally, in a case series of 32 COVID-19 stroke patients compared to historical non-COVID-19 strokes, the former were younger with significantly lower rates of hypertension, diabetes and dyslipidemia.

They had more cortical infarctions, a higher risk of moderate-to-severe presentation (NIHSS >10), prolonged hospitalization and poorer outcomes, in keeping with global trends (14, 17).

Several cases of CVST have also been encountered, such as the one reported by Hussain et al(23).

4.Epilepsy and COVID-19

Lubna Ebn Omar Elsheikh MBBS, MD

Boulenouar Mesraoua MD, FAAN

Keywords: Seizure, Epilepsy, antiseizure Medications (ASMs), Sudden Unexpected death in epilepsy (SUDEP)in patients with epilepsy (PWE), Electroencephalogram (EEG)

4.1. Introduction

Seizure is one of the well-documented neurological complications of COVID-19, occurring either indirectly as part of a systemic illness or directly as a consequence of central nervous system infection.

At the beginning of the pandemic, due to lack of sufficient data, many questions were left unanswered, such as: are patients without epilepsy more vulnerable to epileptic attacks if they contract COVID-19? Are patients with epilepsy (PWE) more prone to COVID-19 infection? (24).

With more accumulating knowledge about the mechanism of central nervous system impact of the virus, the possibility of having seizures in patients with COVID-19 has been confirmed.

In addition, awareness regarding the special precautions that should be taken for PWE with COVID-19 infection became more clear, for instance pertaining to the potential interaction between the antiseizure Medications (ASMs) and previously commonly prescribed COVID treatments such as hydroxychloroquine (25).

PWE with COVID-19 infection may develop seizures because of fever, which decreases the seizure threshold. Anxiety-related problems during the pandemic and physical confinement, and drug non-adherence due to difficulty securing medication refills may also be contributing factors(26). In general, COVID-19 cumulative incidence was higher in patients with active epilepsy, while epilepsy was associated with increased fatality during hospitalization (27).

4.2. COVID-19 and seizure disorders:

One study reported about new-onset acute symptomatic seizures in patients with COVID-19 (4). The study involved 304 patients, none with a prior history of epilepsy, of which 108 patients had severe disease.

Patients presented with acute cerebrovascular disease and systemic disorders which could provoke seizures. Two patients had seizure-like events, due to acute stress reaction and hypocalcemia.

The study concluded that COVID-19 may have a role in increasing the risk for acute symptomatic seizures. It is notable that electroencephalography (EEG) was not used to investigate these seizure-like attacks.

Another study reported neurologic features in severe COVID-19 with acute respiratory distress syndrome in 58 patients. Eight patients underwent EEG, and only nonspecific findings without epileptiform discharges were reported (28). A similar study(29) reported 28 patients under investigation for COVID-19 who underwent routine or continuous EEG. Twenty-two patients tested positive for COVID-19 and 6 were found to be negative.

In the first group, 14 patients experienced seizure-like events (63.6%) vs 2 (33.3%) patients in the second group. "Seizure-like" events were seen in patients without a history of seizures (11/17, 64.7%; 2/6, 33.3%).

Epileptiform discharges such as frontal sharp waves were present in 40.9% of COVID-19 positive and 16.7% of COVID-19 negative patients. No electrographic seizures were reported.

Reports describing seizures and other paroxysmal events in association with COVID-19 have been published. These include new-onset generalized tonic clonic seizures (30), focal status epilepticus, seizures in critically ill patients(31, 32) and COVID-19 presenting with paroxysmal events (possibly seizures) in a 6-week-old boy (33).

The concept that seizures and epilepsy are worsened by COVID-19 has been raised despite the lack of population-based studies.

Although potential interaction between epilepsy and COVID-19 was lacking in many studies, seizure may be one of the initial presentations during the infection in some patients.

Seizure frequency increased in patients with higher baseline seizure frequency, PWE taking multiple ASMs, PWE showing nonadherence, patients with increased self-reported stress and in PWE presenting with sleep pattern changes(34).

Moreover, patients with autoimmune epilepsy, those taking immunosuppressants and patients with Tuberous Sclerosis might have a higher risk of contracting the COVID-19 infection because of their impaired immunity and reduction of lung function.

On the other hand, Dravet syndrome patients might experience a drop in their seizure threshold during COVID-19 infection due to their fever sensitivity (35, 36).

One study examined 30 patients with the diagnosis of epilepsy admitted with COVID-19 infections.

It demonstrated that patients with recurrent epileptic seizures had more underlying neurological disease than patients who had an epilepsy history but without seizures during the COVID-19 illness.

Patients with new-onset and recurrent epileptic seizures suffered a more severe/critical COVID-19 disease course, and a worse outcome when compared to patients without seizures.

The study emphasized that the risk of recurrent seizures may be reduced, with an overall good prognosis for PWE who continue using ASMs during COVID-19 infections(37).

4.3. Teleneurology: Caring for patients with epilepsy during the COVID pandemic:

The COVID-19 crisis has stretched all health systems to the limit. Some systems have fortunately managed to cope but the majority were somewhat overwhelmed.

Telemedicine was introduced actively early last year to decrease the exposure of patients and staff to the infection and to help drive down the cost of the clinical visit. There is no doubt that Telemedicine was beneficial during the pandemic.

However, clinicians have faced some issues treating some patients who required a physical visit for an examination to establish a working diagnosis or to plan a specific diagnostic test or treatment approach.

Selected patients in need of physical evaluation were allowed to present to the clinic physically to while applying necessary precautions as shown by Table 1 below (5).

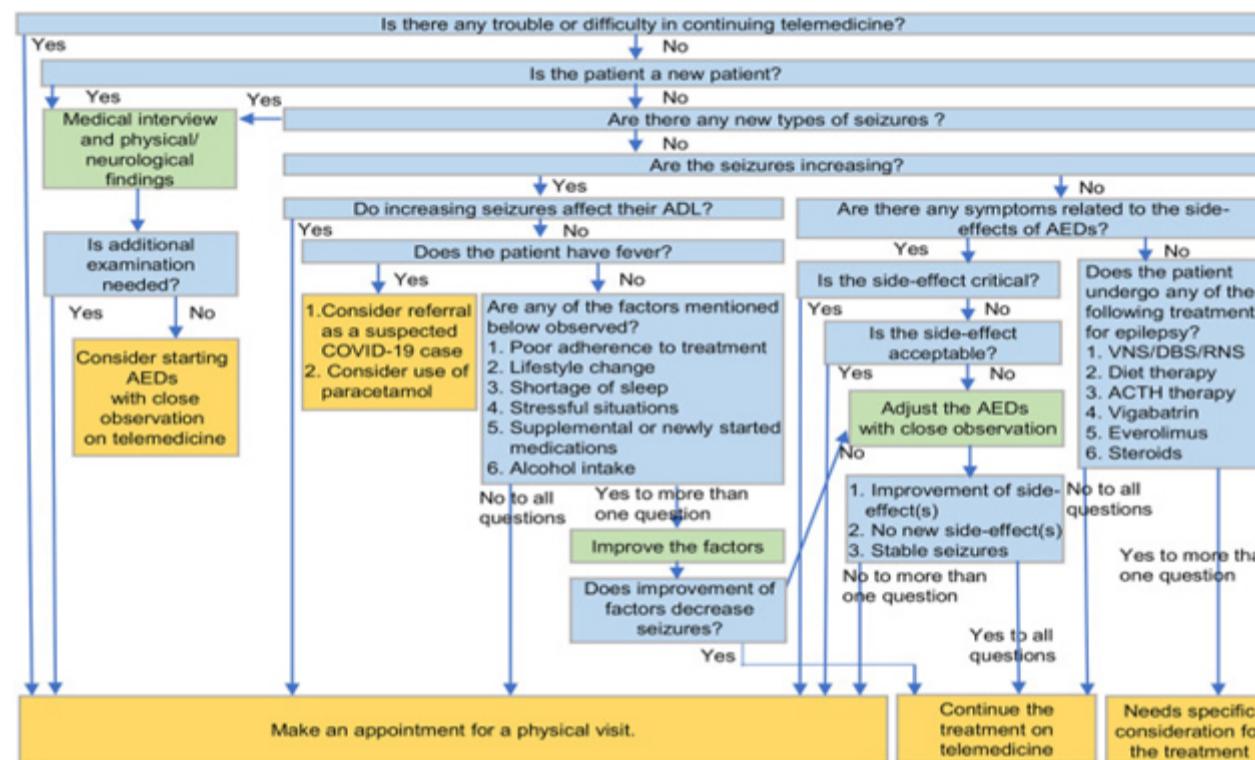


Table 1. Proposed algorithm for selecting patient for Telemedicine adopted from Huang et al.(5).

One study from Spain aimed to establish the impact of the COVID-19 pandemic on PWE in terms of seizure control, and to determine the subjective perception of telemedicine as a remote resource during the pandemic.

Two hundred fifty-five patients were recruited.

An increase in seizure frequency was reported by 25 (9.8%) patients. Confinement-related anxiety was reported by 68 patients (26.7%), depression in 22 (8.6%), and both in 31 (12.2%), while insomnia was reported in 72 (28.2%).

Finally, A reduction in income was reported in 73 (28.6%) patients(38).

Interestingly, tumor-related epilepsy etiology [OR = 7.36 (95% CI 2.17-24.96)], drug-resistant epilepsy [OR = 3.44 (95% CI 1.19-9.95)], insomnia [OR = 3.25 (95% CI 1.18-8.96)], fear of epilepsy [OR = 3.26 (95% CI 1.09-9.74)], and income reduction [OR = 3.65 (95% CI 1.21-10.95)] were associated with an increased seizure frequency.

Two hundred and fourteen patients found telemedicine satisfactory (83.9%).

Five patients who tested positive for COVID-19 did not show any change in seizure frequency(38).

4.4. Drug consideration:

As most of the ASMs are metabolized by the liver, their drug plasma level is highly affected by concomitant use of other enzyme inhibitors or inducers (39). These include medications used to treat COVID-19 Infection.

Carbamazepine, lacosamide, oxcarbazepine, lamotrigine, phenobarbital, and phenytoin drug efficacy may be lowered when used in combination with chloroquine derivatives (24, 40, 41). Cannabidiol, carbamazepine, cenobamate, clonazepam, ethosuximide, lacosamide, perampanel, and zonisamide plasma levels were reported to increase when used with ritonavir(24, 42, 43).

4.5 Electroencephalography- (EEG) related problems:

For PWE or patients suspected of having epilepsy, EEG is used as a vital diagnostic test. During the COVID-19 outbreak, elective EEGs were performed sparingly. However, there was a relative increase in the frequency of use of continuous EEG monitoring, especially in COVID-19 positive and critically ill patients(44). Recommendations were to reduce EEG duration and electrode montages by using single-use subdermal EEG needle electrodes(44).

4.6 Social impact of COVID-19 in patients with epilepsy:

The social impact of the COVID-19 infection was one of the main concerns for most people worldwide. particularly in view of the financial crisis and travel bans. Moreover, epilepsy as a chronic disease has its own impact on the patient as discussed below. One study reported the impact of the pandemic on the well-being and the virtual care of PWE (45). Decreased social engagement and activity cessation of PWE resulted in increased anxiety and stress. However, Virtual care was well-received. Securing employment, burnout, and fear from stigma were the main concerns of PWE as society adapted to the situation. This study highlights the tenacity of PWE during this pandemic.

4.7 Management of seizures in patients with COVID-19:

Patients with COVID-19 presenting with a single seizure and no evidence of encephalitis, excluded clinically and by lumbar puncture, or structural brain lesion (after CT or MRI head) were not started on ASMs. However, infected patients in a critically ill state with altered mental status and seizures were treated as early as possible given their risk of developing convulsive and non-convulsive status epilepticus, and the associated increased mortality and morbidity (45).

Epilepsy related sudden unexpected death (SUDEP) is the most common cause of death in PWE, with an incidence of 1 to 2 per 1000 patient-years. There is, to date, no documented direct association between SUDEP and COVID-19 in PWE despite stress being one of the prominent risk factors for SUDEP(46).

4.8. Epilepsy and COVID-19 in Qatar:

In Qatar, during the peak of the COVID -19 pandemic in 2020, special measures were taken by authorities at the Ministry of Public Health to maintain an adequate, efficient continuity of care for all patients and protect them and health care workers from the infection.

These recommendations included specifics pertaining to all emergency departments, all inpatient services, and elective procedures such as electroencephalography and epilepsy monitoring unit admissions.

Some PWE with COVID-19 developed seizures due to their health status and their underlying chronic medical illness. Most of these patients were critically ill.

Limited access and adherence to ASM during the initial lockdown has resulted in some PWE suffering from breakthrough seizures.

In addition, the introduction of telemedicine was slow and some PWE were not familiar with its purpose.

Many failed to attend phone calls from the outpatient clinic, which resulted in a heightened risk of lapses in seizure control.

In such situations, Hamad Medical Corporation neurologists/epileptologists were instructed to automatically renew ASMs and schedule new follow up appointments

for PWE. The need for physical attendance, EEG and starting ASMs was left to the clinical judgement of the epileptologists during the telemedicine sessions.

Priority was given to PWE and COVID -19 that has already started on anti-COVID -19 Medications.

Seizure disorders in COVID-19 patients with no previous history of epilepsy were variable depending on the underlying mechanism of the seizure. The hypercoagulable state-induced by COVID-19 infection is reported to induce seizures secondary to cortical venous thrombosis(47).

A case report from Hamad General Hospital describes the case of a young COVID-19 patient who was admitted to with new onset seizure. His magnetic resonance imaging demonstrated cerebral venous thrombosis with venous infarction and hemorrhagic transformation. Vasculitis and thrombophilia work up were unrevealing in his case, while his workup revealed a prolonged prothrombin time and elevated D-Dimer(23).

Anecdotally, we did not notice significant COVID-19-related complications in PWE compared to other neurological conditions during the pandemic, with the exception of critically ill patients who remain vulnerable to developing uncontrolled seizures and status epilepticus due to multiple causes, including COVID-19-induced encephalitis, cerebral venous thrombosis or systemic infection.

5. Miscellaneous Neurological Manifestations

Salman K Al Jerdi MD

Tahira Thekkupurath MD

Keywords: Guillain-Barre syndrome (GBS), Critical illness polyneuropathy/myopathy, mononeuritis, myasthenia gravis, myositis, Meningoencephalitis, demyelination

Keywords: Guillain-Barre syndrome (GBS), Critical illness polyneuropathy/myopathy, mononeuritis, myasthenia gravis, myositis, Meningoencephalitis, demyelination

5.1 Peripheral Nervous system manifestation

5.1.1Guillain-Barre syndrome (GBS)

Guillain-Barre syndrome is an immune- mediated disorder affecting the peripheral nervous system and nerve roots that is triggered by infections(48).While a causal relationship is yet to be determined with COVID-19,existing evidence from other viral infections such as the Zika and Epstein Bar viruses as well as a suspiciously increasing incidence in COVID-19 population may suggest a stronger relation (49, 50).

it is a potentially fatal condition and should be an important consideration in patient developing flaccid paralysis.

The onset of GBS in the context of COVID-19 is variable.

It can be the initial manifestation of the disease or can occur later in the course of the illness (para-infectious presentation) or even after it has concluded (post-infectious presentation).

On average GBS manifest 5-14 days (mean of 11.5 days(51)) after respiratory symptoms. The classical presentation of GBS of acute demyelinating inflammatory polyneuropathy(AIDP) is the commonest type occurring in more than 2/3 of the patients(51).

It is clinically evident with commonly ascending lower limb weakness loss of deep tendon reflexes with variable sensory abnormalities. Virtually all other GBS variants presentation were also described(51, 52).

Classical cytoalbuminmic dissociation is present in most patients, however viral PCR is not detected in the CSF(51). Early recognition and treatment with intravenous immunoglobulin (IVIG) or plasma exchange/plasmapheresis (PLEX), along with supportive care remains the mainstay of therapy in COVID-19 patient as well as non-COVID 19 patients and lead to short term favorable outcome in over 60% of cases(51).

5.1.2 Critical illness polyneuropathy/myopathy

Intensive Care Unit Acquired Weakness (ICUAW) is a well-described complication of systemic infections, including Severe Acute Respiratory Syndrome (SARS) and COVID.

ICUAW may be related to Critical Illness Neuropathy or Myopathy (CIN/CIM).

The identification of this weakness is an important prognostic factor for functional recovery and provides direction for the need for aggressive physical and occupational therapy(10).

A prospective observational study by Frithiof and colleagues, performed at Uppsala University Hospital in Sweden(53), found that 11 out of 111 patients admitted to their ICU with PCR confirmed COVID-19 infections developed CIN/CIM.

In their study, a positive PCR test for COVID-19, in addition to a prolonged ICU stay (>11 days) was found to correlate with an increased risk for developing ICUAW.

5.1.3 Myositis

Patients with COVID-19 infections frequently report diffuse muscle pain and fatigue. Although clinical case series have reported these symptoms frequently, documentation of laboratory- or imaging-confirmed myositis is rare.

Beydon and colleagues in France (54) reported an MRI-confirmed case of myositis in a patient who presented with body aches and proximal muscle weakness upon awakening.

The patient had a fever, lymphocytopenia, elevated CRP and markedly elevated CK levels.

He underwent an MRI on day 7 of his admission, which confirmed the diagnosis. The patient remained in critical condition at the time of publication.

In other clinical series, the incidence of muscle weakness ranges from 11-50%, with elevated CK levels documented or reported in <1% of cases(5, 55, 56).

5.2 Mononeuritis and Mononeuritis Multiplex

COVID19 patients have also been reported to experience mononeuropathies and multifocal neuropathies. In a case series published by Needham and colleagues(57), 11 out of 69 patients with severe COVID-19 who were discharged from the ICU were found to have mononeuritis multiplex. In their series, the patients had an average of 3 nerves affected, with the most common being the proximal sciatic (57).

5.2.1 Cranial Neuropathies

5.2.1.1 Anosmia and Agusia

Both loss of sensation and loss of taste have been heavily advertised presenting symptoms of COVID-19.

In fact, both the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) list it as a symptom on their websites. In a series of 141 patients from Qatar (58) almost 25% of PCR-confirmed COVID-19 patients presented with loss of smell, taste or both.

They identified an association with more severe disease but indicated that most of their patients regained their sensory abilities within a mean of approximately 7 day. A recent systematic review and meta-analysis (59) examined loss of smell and taste in 8438 patients with PCR-confirmed COVID-19.

In their analysis, 41% of patients presented with olfactory dysfunction, while 38% presented with dysgeusia.

They also established an inverse correlation between advancing age and incidence of these symptoms.

5.2.1.2 Isolated Cranial Neuropathies

Other isolated cranial neuropathies have also been reported in COVID-19 patients(60). A report by Gutierrez-Ortiz et al(52) described two patients with COVID19 presenting with cranial neuropathies.

These mostly affected extraocular movements, with one of the patients receiving a diagnosis of Miller Fischer Syndrome (MFS) after testing positive for Anti-GD1b ganglioside antibodies and responding to Intravenous Immunoglobulin IVIG.

Dinkin et al (61)also reported about two patients with extraocular movement abnormalities, one with an isolated sixth nerve palsy, in the setting of COVID19.

They hypothesized leptomeningeal invasion of the cranial nerves as the underlying mechanism of the cranial neuropathies, despite an unremarkable CSF analysis. However, they were able to demonstrate cranial nerve enhancement on MRI, supporting their hypothesis.

5.3 Meningoencephalitis

Meningoencephalitis has been one of the more reported and more serious complications of COVID-19. In a systematic review by Mondal et al(62), 61 patients with positive nasopharyngeal swab PCR COVID-related meningoencephalitis were reviewed. the CSF profile was consistent with meningoencephalitis.

They present with fever, chills, headache, neck stiffness, and seizures. However, only < 10% of patients had detectable virus using PCR or antibodies in the CSF.

These patients tended to be middle-aged, with several previous comorbidities.

They were typically hospitalized after a week of symptom onset and remained in the hospital an average of 2 weeks.

Most of these patients had received antibiotics and antivirals, with a survival rate >80% for those who had been discharged by the time of publication. Similarly, case reports of apparent autoimmune meningoencephalitis with COVID-19 infection mimicking autoimmune encephalitis and responding to immune therapy has also been reported(63).

5.4 Demyelinating disorders

Demyelinating disease has been previously reported in patients with MERS and SARS-CoV-1(64). With SARS-CoV-2, studies have postulated several mechanisms behind crossing the blood-brain-barrier (BBB) and causing acute or delayed demyelination(65).

Poyiadji et al (66)described a case of Acute Hemorrhagic Necrotizing Encephalitis (AHNE) in a 58-year-old airline worker who presented with fever, cough and altered mental status.

In this case, a proposed mechanism for demyelination is activation of glial cells through cytokines induced by a cytokine storm related to the acute viral infection(67).

Other demyelinating disorders, such as multiple sclerosis (MS), Acute Disseminated Encephalomyelitis (ADEM), transverse myelitis and Neuromyelitis Optica (NMO) have all been described in the context of acute or subacute COVID19 infections(68-72).

5.5 Generalized myoclonus

Rabano-Suarez et al (73) reported on three patients, aged 63-88, who presented with generalized myoclonus following an initial symptom of anosmia in the setting of COVID-19.

The patients had an extensive work-up, which did not reveal any cause to their myoclonus, which involved mainly the face and upper half of the body and was extremely sensitive to stimuli. The patients responded well to immune therapy.

5.6 Posterior reversible encephalopathy syndrome (PRES)

Several case reports and case series have documented the occurrence of PRES in the setting of acute SARS-CoV-2 infection. In a case series published by Parauda et al(74), four patients presenting to the hospital with acute respiratory distress syndrome (ARDS) and requiring mechanical ventilation developed changes consistent with PRES on neuroimaging. This was obtained after alteration of mental status or development of seizures. All four patients had elevated blood pressure, renal injury, and evidence of systemic inflammation and hypercoagulability prior to the diagnosis. Although most case reports document the presence of hypertension or kidney injury prior to the diagnosis, one case reports suggest the possible implication of anti-interleukin treatment in the development of vasogenic edema on neuroimaging(75-77).

5.7 Long term neurological sequela of COVID-19

It has been over a year since the first case of COVID-19 has been report, yet people who contracted and recovered from the acute phase of the infection continue to experience symptoms weeks and months after recovery. The terms "Chronic COVID syndrome" and "COVID-Long Haulers" were recently coined (78).

Most of these patients have an initially mild to moderate disease course(79). Most, with lingering symptoms resembling chronic fatigue. However, several neurological manifestations such as headaches, prolonged loss of taste or smell, and brain Fog have been reported (79). These symptoms contribute to significant morbidity, are associated with anxiety and a delayed return to work(80) .

5.8. Patients with premorbid neurologic disease

It is not yet known whether the illness per se exacerbates preexisting neurologic illness, hence the need for further real-world data is important with several registries on the way(81-83). Initial reports suggests that the infection may trigger or exacerbate some conditions such as myasthenia gravis due drug access issues ,weakness of muscles due to infection or due to the effect of treatment of COVID-19 drugs such as macrolide antibiotics and hydroxychloroquine for the treatment of COVID-19(81).

On a different note, discontinuing immunosuppressive therapy or disease modifying treatment in patients with multiple sclerosis is associated with poor outcomes, without clear evidence to suggest that they confer an increased risk of severe infection. Such medications should most likely be continued unless severe infection occurs, (81, 84) and restarting treatment should be tailored to the individual patient's condition.

Furthermore, it is essential for those with disabling neurological conditions and those receiving immunosuppressive therapy to protect themselves by strictly adhering to infection control measures and social distancing practices.

6. Challenges and future directions

Neurological manifestation of COVID-19 are common,. The reporting of several new variant mutations (85) and anticipation for a longer pandemic course, in addition to long-term manifestations of the virus present continued challenges in the management of neurologic manifestations. Increased screening, widespread uptake of effective vaccines, and worldwide collaboration on clinical registries and research are essential in the continued treatment and control of COVID-19 and its neurologic manifestations.

7. References

1. Rahman A, Niloofa R, De Zoysa IM, Cooray AD, Kariyawasam J, Seneviratne SL. Neurological manifestations in COVID-19: A narrative review. SAGE Open Medicine. 2020;8:2050312120957925.

2. Nepal G, Rehrig JH, Shrestha GS, Shing YK, Yadav JK, Ojha R, et al. Neurological manifestations of COVID-19: a systematic review. *Critical Care*. 2020;24(1):421.
3. Yachou Y, El Idrissi A, Belaparov V, Ait Benali S. Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. *Neurol Sci*. 2020;41(10):2657-69.
4. Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study. *Epilepsia*. 2020;61(6):e49-e53.
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*. 2020;395(10223):497-506.
6. Keyhanian K, Umeton RP, Mohit B, Davoudi V, Hajighasemi F, Ghasemi M. SARS-CoV-2 and nervous system: From pathogenesis to clinical manifestation. *J Neuroimmunol*. 2020;350:577436-.
7. Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. *International journal of stroke : official journal of the International Stroke Society*. 2020;1747493020972922.
8. Nagel MA, Mahalingam R, Cohrs RJ, Gilden D. Virus vasculopathy and stroke: an under-recognized cause and treatment target. *Infect Disord Drug Targets*. 2010;10(2):105-11.
9. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza. *JAMA Neurology*. 2020;77(11):1366-72.
10. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA neurology*. 2020;77(6):683-90.
11. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9-14.
12. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS-CoV-2 and Stroke in a New York Healthcare System. *Stroke*. 2020;51(7):2002-11.
13. Tan Y-K, Goh C, Leow AST, Tambyah PA, Ang A, Yap E-S, et al. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. *J Thromb Thrombolysis*. 2020;50(3):587-95.
14. Akhtar N, Al Jerdi S, Mahfoud Z, Imam Y, Kamran S, Saqqur M, et al. Impact of COVID-19 pandemic on stroke admissions in Qatar. *BMJ Neurology Open*. 2021;3(1):e000084.
15. Perry R, Banaras A, Werring DJ, Simister R. What has caused the fall in stroke admissions during the COVID-19 pandemic? *Journal of Neurology*. 2020;267(12):3457-8.
16. Montaner J, Barragán-Prieto A, Pérez-Sánchez S, Escudero-Martínez I, Moniche F, Sánchez-Miura JA, et al. Break in the Stroke Chain of Survival due to COVID-19. *Stroke*. 2020;51(8):2307-14.
17. Akhtar N, Abid FB, Kamran S, Singh R, Imam Y, AlJerdì S, et al. Characteristics and Comparison of 32 COVID-19 and Non-COVID-19 Ischemic Strokes and Historical Stroke Patients. *Journal of Stroke and Cerebrovascular Diseases*. 2021;30(1):105435.
18. Perry RJ, Smith CJ, Roffe C, Simister R, Narayananamoothi S, Marigold R, et al. Characteristics and outcomes of COVID-19 associated stroke: a UK multicentre case-control study. *Journal of Neurology, Neurosurgery & Psychiatry*. 2020;jnnp-2020-324927.
19. Tu TM, Goh C, Tan YK, Leow AS, Pang YZ, Chien J, et al. Cerebral Venous Thrombosis in Patients with COVID-19 Infection: a Case Series and Systematic Review. *J Stroke Cerebrovasc Dis*. 2020;29(12):105379-.
20. Siow I, Lee KS, Zhang JJY, Saffari SE, Ng A, Young B. Stroke as a Neurological Complication of COVID-19: A Systematic Review and Meta-Analysis of Incidence, Outcomes and Predictors. *Journal of Stroke and Cerebrovascular Diseases*. 2021;30(3).
21. Pavlov V, Beylerli O, Gareev I, Torres Solis LF, Solís Herrera A, Aliev G. COVID-19-Related Intracerebral Hemorrhage. *Frontiers in Aging Neuroscience*. 2020;12(352).
22. COVID-19 pandemic in Qatar 2021 [Available from: https://en.wikipedia.org/wiki/COVID-19_pandemic_in_Qatar.
23. Hussain S, Vattoth S, Haroon KH, Muhammad A. A Case of Coronavirus Disease 2019 Presenting with Seizures Secondary to Cerebral Venous Sinus Thrombosis. 2020. p. 260-5.
24. Asadi-Pooya AA, Attar A, Moghadami M, Karimzadeh I. Management of COVID-19 in people with epilepsy: drug considerations. *Neurol Sci*. 2020;41(8):2005-11.
25. Badyal DK, Mahajan R. Chloroquine: Can it be a Novel Drug for COVID-19. *International journal of applied & basic medical research*. 2020;10(2):128-30.
26. Parihar J, Tripathi M, Dhamija RK. Seizures and Epilepsy in Times of Corona Virus Disease 2019 Pandemic. *Journal of epilepsy research*. 2020;10(1):3-7.
27. Cabezudo-García P, Ciano-Petersen NL, Mena-Vázquez N, Pons-Pons G, Castro-Sánchez MV, Serrano-Castro PJ. Incidence and case fatality rate of COVID-19 in patients with active epilepsy. *Neurology*. 2020;95(10):e1417-e25.
28. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in Severe SARS-CoV-2 Infection. 2020. p. 2268-70.
29. Galanopoulou AS, Ferastraoraru V, Correa DJ, Cherian K, Duberstein S, Gursky J, et al. EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: A small case series preliminary report. *Epilepsia open*. 2020;5(2):314-24.
30. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-CoV-2. 2020. p. 55-8.
31. Vollono C, Rollo E, Romozzi M, Frisullo G, Servidei S, Borghetti A, et al. Focal status epilepticus as unique clinical feature of COVID-19: A case report. *Seizure*. 2020;78:109-12.
32. Provencio JJ, Hemphill JC, Claassen J, Edlow BL, Helbok R, Vespa PM, et al. The Curing Coma Campaign: Framing Initial Scientific Challenges-Proceedings of the First Curing Coma Campaign Scientific Advisory Council Meeting. *Neurocritical care*. 2020;33(1):1-12.
33. Dugue R, Cay-Martínez KC, Thakur KT, Garcia JA, Chauhan LV, Williams SH, et al. Neurologic manifestations in an infant with COVID-19. *Neurology*. 2020;94(24):1100-2.
34. Alkhotani A, Siddiqui MI, Almuntashri F, Baothman R. The effect of COVID-19 pandemic on seizure control and self-reported stress on patient with epilepsy. *Epilepsy & behavior : E&B*. 2020;112:107323-.
35. Kuroda N. Epilepsy and COVID-19: Associations and important considerations. 2020. p. 107122-.
36. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, behavior, and immunity*. 2020;87:18-22.
37. Sun M, Ruan X, Li Y, Wang P, Zheng S, Shui G, et al. Clinical characteristics of 30 COVID-19 patients with epilepsy: A retrospective study in Wuhan. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. 2020.
38. Fonseca E, Quintana M, Lallana S, Luis Restrepo J, Abraira L, Santamarina E, et al. Epilepsy in time of COVID-19: A survey-based study. *Acta Neurologica Scandinavica*. 2020;142(6):545-54.
39. Asadi-Pooya A, Sperling M. Antiepileptic DrugsA Clinician's Manual: A Clinician's Manual. Oxford, UK: Oxford University Press; 2016.
40. Kuroda N. Decision Making on Telemedicine for Patients With Epilepsy During the Coronavirus Disease 2019 (COVID-19) Crisis. *Frontiers in neurology*. 2020;11:722-.

41. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic acids research. 2018;46(D1):D1074-D82.
42. Gélisse P, Rossetti AO, Genton P, Crespel A, Kaplan PW. How to carry out and interpret EEG recordings in COVID-19 patients in ICU? Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2020;131(8):2023-31.
43. Nguyen T, McNicholl I, Custodio JM, Szwarcberg J, Piontowsky D. Drug Interactions with Cobicistat- or Ritonavir-Boosted Elvitegravir. AIDS reviews. 2016;18(2):101-11.
44. Subotic A, Pricop DF, Josephson CB, Patten SB, Smith EE, Roach P. Examining the impacts of the COVID-19 pandemic on the well-being and virtual care of patients with epilepsy. Epilepsy & behavior : E&B. 2020;113:107599-.
45. Ch'ang J, Claassen J. Seizures in the critically ill. Handbook of clinical neurology. 2017;141:507-29.
46. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: A nationwide population-based case-control study. Neurology. 2020;94(4):e419-e29.
47. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. Journal of thrombosis and haemostasis : JTH. 2020;18(6):1421-4.
48. Leonhard SE, Mandarakas MR, Gondim FAA, Bateman K, Ferreira MLB, Cornblath DR, et al. Diagnosis and management of Guillain–Barré syndrome in ten steps. Nature Reviews Neurology. 2019;15(11):671-83.
49. Carrillo-Larco R, Altez-Fernandez C, Ravaglia S, Vizcarra J. COVID-19 and Guillain-Barre Syndrome: a systematic review of case reports [version 2; peer review: 2 approved]. Wellcome Open Research. 2020;5(107).
50. Filosto M, Cotti Piccinelli S, Gazzina S, Foresti C, Frigeni B, Servalli MC, et al. Guillain-Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. Journal of Neurology, Neurosurgery & Psychiatry. 2020;jnnp-2020-324837.
51. Uncini A, Vallat J-M, Jacobs BC. Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic. Journal of Neurology, Neurosurgery & Psychiatry. 2020;91(10):1105-10.
52. Gutiérrez-Ortíz C, Méndez-Guerrero A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Mañas R, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. Neurology. 2020;95(5):e601-e5.
53. Frithiof R, Rostami E, Kumlien E, Virhammar J, Fällmar D, Hultström M, et al. Critical Illness Polyneuropathy and Myopathy in COVID-19 Patients: A Prospective Observational Intensive Care Unit Cross-Sectional Cohort Study2020.
54. Beydon M, Chevalier K, Al Tabaa O, Hamroun S, Delettre A-S, Thomas M, et al. Myositis as a manifestation of SARS-CoV-2. Annals of the Rheumatic Diseases. 2020:annrheumdis-2020-217573.
55. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. 2020;382(18):1708-20.
56. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
57. Needham E, Newcombe V, Michell A, Thornton R, Grainger A, Anwar F, et al. Mononeuritis multiplex: an unexpectedly frequent feature of severe COVID-19. Journal of Neurology. 2020.
58. Al-Ani RM, Acharya D. Prevalence of Anosmia and Ageusia in Patients with COVID-19 at a Primary Health Center, Doha, Qatar. Indian J Otolaryngol Head Neck Surg. 2020:1-7.
59. Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis. Mayo Clin Proc. 2020;95(8):1621-31.
60. Costello F, Dalakas MC. Cranial neuropathies and COVID-19: Neurotropism and autoimmunity. Neurology. 2020;95(5):195-6.
61. Dinkin M, Gao V, Kahan J, Bobker S, Simonetto M, Wechsler P, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. Neurology. 2020;95(5):221-3.
62. Mondal R, Ganguly U, Deb S, Shome G, Pramanik S, Bandyopadhyay D, et al. Meningoencephalitis associated with COVID-19: a systematic review. J Neurovirol. 2020:1-14.
63. Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain : a journal of neurology. 2020;143(10):3104-20.
64. Dessau RB, Lisby G, Frederiksen JL. Coronaviruses in brain tissue from patients with multiple sclerosis. Acta neuropathologica. 2001;101(6):601-4.
65. Desforges M, Le Coupanec A, Dubeau P, Bourguin A, Lajoie L, Dubé M, et al. Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? Viruses. 2019;12(1).
66. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features. Radiology. 2020;296(2):E119-E20.
67. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4.
68. Mislin D. COVID-19-associated CNS Demyelinating Diseases Department of Neuroscience Faculty Papers. Paper 48: the Jefferson Digital Commons; 2020 [Available from: https://jdc.jefferson.edu/department_neuroscience/48.
69. Sarma D, Bilello LA. A Case Report of Acute Transverse Myelitis Following Novel Coronavirus Infection. Clin Pract Cases Emerg Med. 2020;4(3):321-3.
70. Zanin L, Saraceno G, Panciani PP, Renisi G, Signorini L, Migliorati K, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. Acta Neurochir (Wien). 2020;162(7):1491-4.
71. Zhang T, Hirsh E, Zandieh S, Rodricks MB. COVID-19-Associated Acute Multi-infarct Encephalopathy in an Asymptomatic CADASIL Patient. Neurocritical Care. 2020.
72. Zhao K, Huang J, Dai D, Feng Y, Liu L, Nie S. Acute myelitis after SARS-CoV-2 infection: a case report. medRxiv. 2020:2020.03.16.20035105.
73. Rábano-Suárez P, Bermejo-Guerrero L, Méndez-Guerrero A, Parra-Serrano J, Toledo-Alfocea D, Sánchez-Tejerina D, et al. Generalized myoclonus in COVID-19. Neurology. 2020;95(6):e767-e72.
74. Parauda SC, Gao V, Gewirtz AN, Parikh NS, Merkler AE, Lantos J, et al. Posterior reversible encephalopathy syndrome in patients with COVID-19. J Neurol Sci. 2020;416:117019.
75. Conte G, Avignone S, Carbonara M, Meneri M, Ortolano F, Cinnante C, et al. COVID-19-Associated PRES-like Encephalopathy with Perivascular Gadolinium Enhancement. American Journal of Neuroradiology. 2020;41(12):2206-8.
76. Djellaoui A, Seddik L, Cleret De Langavant L, Cattan S, Bachoud-Lévi AC, Hosseini H. Posterior reversible encephalopathy syndrome associated with SARS-CoV-2 infection. Journal of Neurology, Neurosurgery & Psychiatry. 2021;92(1):113-4.
77. Llansó L, Urri X. Posterior Reversible Encephalopathy Syndrome in COVID-19 Disease: a Case-Report. SN Compr Clin Med. 2020;1-3.
78. Baig AM. deleterious Outcomes in Long-Hauler COVID-19: The Effects of SARS-CoV-2 on the CNS in Chronic COVID Syndrome. ACS chemical neuroscience. 2020;11(24):4017-20.
79. Simoneaux R, Shafer SL. Long-Term Effects of SARS-CoV-2 in 'Long-Haulers'. ASA Monitor. 2021;85(2):1-4.

80. Rubin R. As Their Numbers Grow, COVID-19 "Long Haulers" Stump Experts. *JAMA*. 2020;324(14):1381-3.
81. Muppidi S, Guptill JT, Jacob S, Li Y, Farrugia ME, Guidon AC, et al. COVID-19-associated risks and effects in myasthenia gravis (CARE-MG). *Lancet Neurol*. 2020;19(12):970-1.
82. Peeters LM, Parciak T, Walton C, Geys L, Moreau Y, De Brouwer E, et al. COVID-19 in people with multiple sclerosis: A global data sharing initiative. *Multiple Sclerosis Journal*. 2020;26(10):1157-62.
83. Sanchez-Larsen A, Gonzalez-Villar E, Díaz-Maroto I, Layos-Romero A, Martínez-Martín Á, Alcahit-Rodriguez C, et al. Influence of the COVID-19 outbreak in people with epilepsy: Analysis of a Spanish population (EPICOVID registry). *Epilepsy & Behavior*. 2020;112:107396.
84. Brownlee W, Bourdette D, Broadley S, Killestein J, Ciccarelli O. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. *Neurology*. 2020;94(22):949-52.
85. Wise J. Covid-19: The E484K mutation and the risks it poses. *BMJ*. 2021;372:n359.

[Home](#)[Forward message](#)[Introduction](#)[Chapters](#)[Editors team](#)[Contact us](#)

Copyright © 2022 Ministry of Public Health. All rights reserved.



Search this site



Rheumatology

Chapter: COVID 19 in patients with Autoimmune Rheumatic diseases (ARDs)

Authors:

Dr. Samar Al Emadi

Division Chief of Rheumatology/Sr. Consultant

SAlEmadi@hamad.qa**Dr. Eman Satti**

Consultant, Rheumatology

EElsayed1@hamad.qa**Dr. Omar Alsaed**

Associate Consultant

OAAlsaed@hamad.qa

Content:

- Introduction and definitions.
- Prevalence & susceptibility to infection.
- The outcome of COVID-19 in patients with ARDs
- Current guidelines on the management of ARDs during the pandemic
- Spotlight on APLS in COVID-19
- COVID-19 vaccine in patients with ARDs.
- Qatar experience
- Recommendations

Key words: Autoimmune rheumatic diseases, immunosuppression, rheumatological diseases.

Introduction:

Autoimmune rheumatic diseases; aetiology and epidemiology:

Autoimmune rheumatic diseases (ARD) comprise diverse conditions that affect multiple organ systems. ARD associated with significant morbidity and mortality. These conditions' aetiology is poorly understood but is generally attributed to an altered immune response involving the innate and adaptive immune systems that eventually result in an uncontrolled inflammatory reaction.

Although ARD shares many typical features and clinical presentations, it is vital to accurately diagnose each disease using the available criteria. Rheumatologist plays a crucial role in ascertaining ARD's diagnostic process accuracy. This diagnostic accuracy is crucial for appropriate management and predicting prognosis.

Defining the prevalence of different ARD is a significant challenge. The disease presentation is heterogeneous, and the biochemical diagnostic markers are missing in several cases. The non-specific disease presentation makes the process of early accurate diagnosis onerous.

The financial and socioeconomic burden of established diseases is of great concern. Rheumatoid arthritis is the most known ARD and is ranked as the 42nd highest contributor to disabilities just after malaria(1).

The Global Burden of Disease 2010 estimated its prevalence to be around 0.24%.

Over the last few decades, the research in rheumatology focused on developing effective treatments for different diseases. The research resulted in a revolution in managing autoimmune rheumatic diseases and translated to improved prognosis and survival in many diseases(2, 3).

These agents combat the disease by altering the immune system, which increases susceptibility to infections. Due to the nature of these diseases and the widespread use of the new biologic therapies, patients with ARD are considered an established group of the immune-compromised population susceptible to serious infections and life-threatening complications(4).

COVID-19 pandemic and ARD; background and challenges:

Early in the pandemic, various international rheumatology societies raised considerable concerns regarding the potentially deleterious impact of COVID-19 in patients with rheumatic illnesses.

It was a legitimate concern to consider these patients at higher risk of the COVID-19 infection and its complications due to their immune-compromised status.

Surprisingly COVID-19 manifestations were widely variable and in its severe form resembled a well-established complication of autoimmune diseases called a cytokine storm(5).

Many therapeutic options for COVID-19 were known anti-rheumatic agents used to treat ARD. Few examples are hydroxychloroquine, tocilizumab, steroids, intravenous immune globulins, TNF-inhibitors, JAK-inhibitor, etc (6).

The overlap in therapeutic options made it unclear if patients with ARD are at higher risk of COVID-19 infection or are paradoxically protected due to these agents' long-term use.

The virus's interaction with these diseases, their prognosis, and management of the underlying ARD during the infection were among many challenging questions raised during the pandemic.

Many research initiatives and guidelines were developed worldwide to resolve these uncertainties and guide clinicians during this challenging time.

COVID-19 Global Rheumatology Alliance (GRA) registry is an international effort launched in March 2020 to collect information pertinent to SARS-CoV-2 infection in patients with rheumatologic disease.

Qatar actively participates in this alliance to help register de-identified patients' information about COVID-19 in patients with ARD.

The accumulated knowledge in this registry revealed considerable information mentioned below.

Risk of contracting the infection: Patients with rheumatic diseases are not at increased risk of infection.

The pandemic heavily impacted Europe and China. Most of the data addressing the risk and prevalence of COVID-19 in patients with rheumatic diseases was extrapolated from research in these regions(7).

Large cross-sectional studies are widely used as the most preferred method in establishing robust and quick answers related to infection risk.

Favalli and colleagues reviewed 955 patients with various autoimmune rheumatic diseases. This survey revealed an incidence of 0.62%, comparable to the general population incidence of COVID-19 (0.66%)(8).

A population-based study was performed in Italy during the first two months of the outbreak. It examined patients with rheumatic diseases treated with biological agents or small molecules. Out of 1051 patients, 47 tested positive for SARS-CoV-2 PCR (4.7%) compared to 4.35 in the general population during the same period.

The comparative numbers reassured patients on these agents to continue taking them during the pandemic(9).

Similarly, a large multicenter retrospective study conducted in China involving more than 6000 subjects with ARD found a prevalence of 0.43%.

This study was performed early in the pandemic and thus estimated the prevalence between Dec 2019 and March 2020. Interestingly, this study also examined the families residing with ARD patients. Forty- two families were identified (43 patients). Within these families, sixty-three per cent of patients with ARDs and 34% of their family members were diagnosed with COVID-19 (adjusted odds ratio [OR] 2.68), indicating higher susceptibility to infection with ARD at comparable exposure risk. This finding was based on a small data set and cannot be generalized(10).

Regardless of the variability in the prevalence across the different countries, prevalence studies conclude that patients with ARD on anti-rheumatic have a comparable risk of COVID-19 to the general population(11, 12).

Outcome and complications:

Despite the analogous susceptibility to infection, determining the risk of "severe infection" is paramount.

A systematic review observed a statistically non-significant trend towards increased hospitalization and death in ARD (hospitalization (OR) 1.17; 95% (CI) 0.6 to 2.29; mortality rate: OR 1.53; 95% CI 0.33 to 7.11). Furthermore, these patients were at an increased risk of critical care admission and invasive mechanical ventilation (OR 3.72; 95% CI 1.35 to 10.26)(13).

In a comparative study of COVID-19 patients with or without ARD, D'Silva KM et al. found a similar rate of hospitalization ((23 (44%) vs 42 (40%), p=0.50) and mortality (3 (6%) vs 4 (4%), p=0.69). The rate of critical care admission and mechanical ventilation was higher in patients with rheumatic diseases with an adjusted odds ratio of 3.11 (95% CI 1.07 to 9.05)(14).

In May 2020, the Global Rheumatology Alliance (GRA) reported its first publication on the outcome of COVID-19 in patients with rheumatic diseases. GRA is a multicenter collaboration in 40 countries and included around 600 patients.

Forty-six per cent of patients required hospitalizations, with a mortality rate of 9 %. In the multivariate analysis, the risk of hospitalization was not increased with conventional disease-modifying agents (cDMARDs) and was inversely associated with TNF blockers' use.

Steroid use at a dose of more than 10 mg was associated with increased odds of hospitalizations (OR 2.05, 95% CI 1.06 to 3.96), while hydroxychloroquine and NSAIDs intake did not affect hospitalization(15).

CONTROL 19, an Italian study during the pandemic's peak, reported a high hospitalization rate, invasive mechanical ventilation, and mortality in 232 patients with rheumatic disease.

The risk of these adverse outcomes was associated with steroid use and decreased in patients with biologic or targeted synthetic DMARDs. However, this association was not statistically significant when adjusted for age and gender(16).

Hydroxychloroquine (HCQ) received substantial attention during the pandemic, with studies suggesting contradictory results and a controversial role in the treatment/prevention of SARS-CoV-2.

Thus, it was imperative to observe its role in patients with rheumatic diseases on long-term use of HCQ.

In conclusion, patients with rheumatic diseases seem to be at higher risk of COVID-19 adverse outcomes, particularly those on long-term steroid use.

International guidelines and recommendations for the management of rheumatic diseases in the context of COVID-19 infection:

ACR COVID-19 clinical guidance:

In September 2020, the American College of Rheumatology (ACR) released updated guidance on managing patients with autoimmune rheumatic diseases during the pandemic.

These guidelines intended to integrate the available evidence with experts' opinions from rheumatologists and infectious disease specialists in North America.

They are not meant to dictate practice in different countries or individual patients' care(17).

The guidance statements were designed to address everyday situations, as follows:

The general guidance for patients with rheumatic diseases:

- General measures of social distancing and hand hygiene should be emphasized with patients.
- Measures to reduce patients' exposure to infection secondary to health care encounters should be addressed. Examples: reduce blood extraction frequencies, optimize telehealth, spacing intravenous medications as possible...etc.
- Glucocorticoids should be used at the lowest dose possible and should not be stopped abruptly regardless of exposure or infection status.

Guidance of ongoing treatment for patients with stable disease in the absence of known exposure or infection with SARS-CoV-2:

- Ongoing treatment with conventional DMARDs (hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide), immune suppressants (tacrolimus, cyclosporin, mycophenolate, azathioprine), biologics, JAK-inhibitors, and NSAIDs may be continued.
- Denosumab dose can be extended to no longer than eight months if necessary.
- In newly diagnosed patients with SLE, hydroxychloroquine should be started at full dose.
- In pregnant women with SLE, hydroxychloroquine should be continued.
- Immune suppressants should not be reduced in patients with a vital organ-threatening disease history.

Guidance for the management of newly diagnosed or active diseases in the absence of infection or known exposure:

- Management should be initiated and switched according to the patient's clinical condition as per the guidelines before the pandemic.

Guidance of the management of rheumatic diseases following known exposure of infection with SARS-CoV-2:

Following exposure:

- HCQ, sulfasalazine, and NSAIDs may be continued.
- Immune suppressants, non-IL-6 biologics, and JAK inhibitors should be held while awaiting a negative COVID 19 PCR test or two weeks of symptom observation.
- IL-6 may be continued.

Following confirmation of COVID-19 infection:

- HCQ may be continued.
- Sulfasalazine, methotrexate, leflunomide, immune suppressants, non- IL-6 biologics, and JAK-inhibitors should be stopped.
- NSAIDs should be stopped in patients with severe respiratory symptoms.
- IL-6 biologics may be continued.

Re-starting treatment following infection:

- In patients with uncomplicated COVID-19 infection, all treatments can be resumed after 7-14 days of symptom resolution.
- In patients recovering from severe COVID-19 infection, resumption of anti-rheumatic drugs should be managed case by case.

Spotlight on APLS & COVID-19

Antiphospholipid syndrome (APLS) is a hypercoagulable disease that can lead to arterial or venous thrombosis or pregnancy morbidities. Its severe form can lead to a catastrophic, life-threatening disease that carries a high mortality rate.

Concerning COVID-19, patients with severe respiratory failure and death were found to have widespread pulmonary thrombosis and microangiopathy on postmortem specimens(18).

This fact has generated substantial research efforts looking for this phenomenon's potential pathophysiology. Given that APLS is a highly thrombogenic disease and is theoretically triggered by infections, it became a focus for study in patients with severe COVID-19 with and without thrombotic events.

COVID-19 vaccination in patients with autoimmune diseases

With the urgent need for comprehensive measures to combat the pandemic, global efforts have collaborated to develop effective and safe vaccines against COVID-19 in an unprecedented short duration.

The mRNA vaccine technology is relatively untested, with some experts anxious about the possibility of triggering autoimmunity.

There is a paucity of data related to the different diseases and conditions in patients with deranged immunity or on immune suppressants.

To date, all inactivated vaccines are used when appropriate in patients with autoimmune diseases without significant safety concerns. Holding immune suppressants is sometimes used to improve these vaccines' potential efficacy(19).

Considering the low potential of side-effects associated with COVID-19 mRNA vaccines (Pfizer/BioNTech and Moderna), vaccinating ARD patients becomes a priority.

Furthermore, mRNA vaccine technology is a promising modality for managing certain autoimmune diseases (e.g., scleroderma)(20).

Efforts will continue to observe vaccinated patients with ARD to ensure their safety meticulously.

Qatar Experience:

COVID-19 pandemic has affected the rheumatology service in many aspects. This section will address all the new raised issues related to rheumatology service during the peak of COVID-19 infection in Qatar. Also, we will mention how we can overcome some of these issues.

1. There was a significant drop in the number of rheumatologists as many volunteered to work in the dedicated COVID-19 facilities. This led to an interruption in the continuity of patient care. Other rheumatologists followed patients following with the volunteering doctors during the peak of the COVID-19 outbreak. We found the patients exhibited a considerable understanding, and no dissatisfaction was reported. On the other hand, the rheumatologists who covered their colleagues felt stressed and over-worked during their absence. They had to deal with almost double the number of patients they used to have during regular days. This overwork may have affected the quality of patient care.
2. Since the ministry of public health and COVID-19 steering committee's decision regarding outpatient service to be run virtually, many patients were not reachable for various reasons. Some of them had an outdated phone number on records; others could not pick up the phone due to work, amongst other reasons. These patients were unable to get their medications within the required time frame. We partially resolved this problem via the 16000 hotline number. The helpline played a crucial role in connecting the patients with their rheumatologists through our rheumatology coordinator number. We are expecting that several patients ran out of their medication supply. In the future, we suggest having better communication with patients through social media and traditional media tools.
3. Pneumococcus vaccination was interrupted for the newly diagnosed rheumatic disease patient during the COVID-19 outbreak as clinics were done virtually. Patients had difficulty going to the outpatient clinics' area to get their vaccinations. All these patients will get their pneumococcal vaccination once regular clinic duties are resumed.
4. During the pandemic, some patients stopped their immunosuppressive medications without consulting their rheumatologist. The international rheumatic disease society recommendations advised not to stop immunosuppression unless COVID-19 is confirmed. Some of these medications are safe during COVID-19. The rheumatology division created a short video and social media posts, advising people on continuing immunosuppressants during the pandemic. The advice was also disbursed on what to do if the COVID-19 infection is confirmed. These messages were published through Qatar's rheumatology society, social media platforms.
5. The immunosuppressive medications in many rheumatic disease patients diagnosed with SARS-CoV-2 infection and quarantined or admitted to a COVID-19 facility were stopped due to the admitting physicians' insufficient expertise. Immunosuppressants vary in terms of mechanism of action and degree of immunosuppression. Like steroid and IL-6 inhibitors, some of these immunosuppressions were used to treat catastrophic COVID-19 complications like cytokine storm. There was a communication gap between frontline physicians dealing with COVID-19 cases and rheumatologists. In the future, we plan on a dedicated hotline distributed to all COVID-19 facilities to take a quick opinion from a rheumatologist, followed by an in-person assessment if needed.
6. During the pandemic, many rheumatic medications were used to treat COVID-19 infection, like hydroxychloroquine and IL-6 inhibitor—these medications are now controlled to avoid any shortage of these essential rheumatic diseases medications.
7. Elderly osteoporotic patients are the group of patients at the highest risk for COVID-19 mortality. This group was shielded at their homes and did not receive anti-osteoporotic injections. The rheumatology division facilitated some of the anti-osteoporotic injections administered during home care visits.

To date, we have two studies of COVID-19 in ARD in Qatar run by the rheumatology division in Hamad Medical Corporation (HMC). These two studies gave us an insight into the interaction between COVID-19 infection and ARD.

One of the studies is a part of the COVID-19 global rheumatology registry, an ongoing project.

We plan to present the data of the first 108 ARD patients infected with COVID-19 shortly.

This data will give us insight into ARD interaction with SARS-CoV-2 infection and how disease-modifying anti-rheumatic disease drugs (DMARDs), including biological agents, played a role in the outcomes. The second study is designed to test whether ARD patients are at more risk for COVID-19 infection than the general population.

COVID-19 rheumatology registry

Cohort characteristics:

108 ARD patients confirmed to be infected with COVID-19 by the throat and nasal PCR swab. Around 55% were females, with a mean age was 44.5 years (std 11.3). Asian and Arab were the predominant ethnicities in this cohort, 48.1% and 43.5%, respectively. Around one-fourth of the cohort were diabetic, and 18.5% were hypertensive. Four patients had cardiovascular disease. Table 1 demonstrates the patients' baseline characteristics.

	n (%)
Age, Mean (std) years	44.5 (11.3)
Gender, Female n (%)	44.5 (11.3)
Race/ethnicity n (%)	
- Arab	47 (43.5)
- Black	2 (1.9)
- Asian	52 (48.1)
- West Asian and middle east	7 (6.5)
Comorbidities N (%)	
- Interstitial lung disease	3 (2.8)
- Obstructive lung disease	4 (3.7)
- Other lung diseases	3 (2.8)
- Diabetes	25 (23.1)
- Morbid obesity (BMI >=40)	3 (2.8)
- Hypertension	20 (18.5)
- Cardiovascular disease	4 (3.7)
- Cerebrovascular disease	1 (0.9)
- Pulmonary hypertension	1 (0.9)
- Chronic renal insufficiency or end-stage renal disease	4 (3.7)
- Cancer	3 (2.8)
Smoking status: n (%)	
- Current smoker	7 (6.5)
- Former smoker	8 (7.4)
- Never smoked	85 (78.7)
- Unknown	8 (7.4)

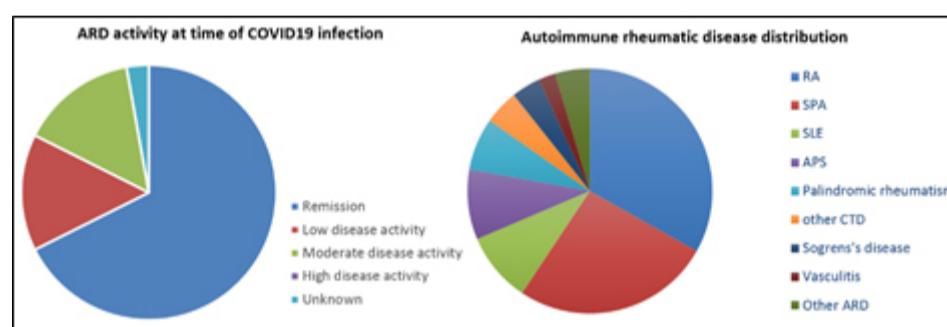
Table 1: cohort baseline demographic and comorbidities characteristics.

Autoimmune rheumatic disease characteristics:

There was a wide variation in the ARD in our cohort. Among the inflammatory arthritis diseases, rheumatoid arthritis was the most common underlying ARD (43 patients, 39.8%), followed by spondyloarthropathy (SPA) group 15.7% (axial SPA 7.4%, peripheral SPA 2.1%, and psoriatic arthritis 6.5%).

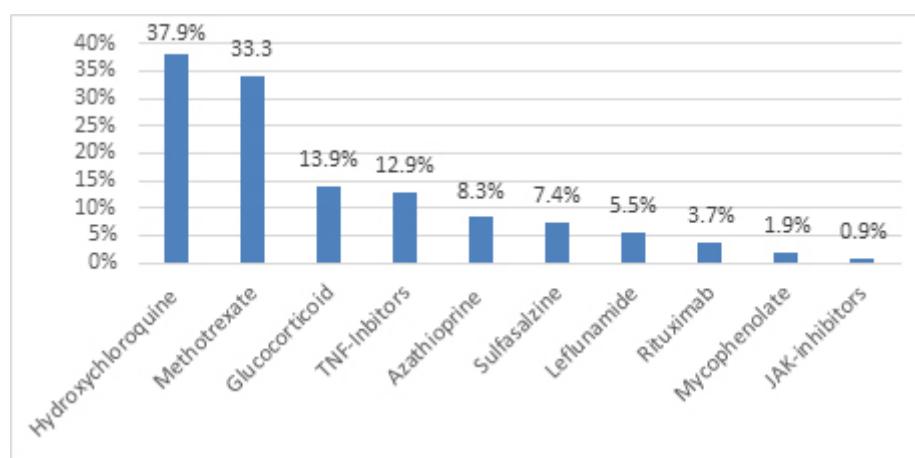
The systemic lupus erythematosus (12 patients, 11.1%) was the most common condition in the connective tissue disease group, followed by Sjogren's syndrome (5 patients, 4.6%).

Twelve patients (11.1%) had antiphospholipid syndrome (APS). 67.6% of the patients were in remission at the time of COVID-19 infection, and the remaining were having low to moderate rheumatic disease activity.



Immunosuppressing/immunomodulating medication use:

The majority of the patients (80.5%) were on at least one immunosuppressive or immunomodulating agent, and 28% were receiving dual immunosuppressive drugs at the time of SARS-CoV-2 infection. Hydroxychloroquine and methotrexate were the most commonly used DMARDs, 37.9% and 34.2%, respectively. 19 (17.6) patients were receiving biologic treatment; 12 on TNF-alpha inhibitors, 4 on rituximab, and 1 on JAK-inhibitor. Immunosuppressive medications were stopped in 38.9% of the cohort. 78.9% of them were symptomatic, and 16.7% required oxygen support. Graph 2 is demonstrating immunosuppressive/immunomodulating medications distribution.



Graph 2: distribution of immunosuppressive/immunomodulating use at the time of SARS-CoV-2 infection.

SARS-CoV-2 infections characteristics:

One-third of the patients did not report any symptoms during their SARS-CoV-2 infections. The chief complaints in the symptomatic group were fever (61.1%) followed by cough (48.1%) and myalgia (40.6%). Gastrointestinal symptoms were reported in one-fifth of the patients. 31.1% of the patients required hospitalization, and oxygen supplements supported 18.5%.

An intensive care unit with invasive and non-invasive ventilation support was needed in 11 (10.2%) patients.

There was one death in this cohort.

	n (%)
Symptomatic COVID-19 infection	76 (70)
Fever	66 (61.1)
Headache	40 (37)
Sore throat	37 (34.3)
Cough	52 (48.1)
Shortness of breathing	26 (24.1)
Arthralgia	16 (14.8)
Myalgia	33 (40.6)
Management:	
No treatment/ supportive care	69 (63.9)
Lopinavir	6 (5.6)
Oseltamivir	11 (10.2)
Favipiravir	2
Azithromycin	30 (27.8)
Ceftriaxone	8 (7.4)
Augmentin	3 (2.8)
Hydroxychloroquine	32 (29.7)
IL-1 inhibitor	1 (0.9)
IL-6 inhibitor	1 (0.9)
Glucocorticoids	7 (6.5)
IVIG	1 (0.9)

Table 2: COVID-19 infection characteristics.

	Did not require oxygen support	Required oxygen support	p-value	OR (95%CI)
Not on immunosuppression Any immunosuppression Hydroxychloroquine Methotrexate Glucocorticoid Leflunomide Sulfasalazine TNF alfa inhibitors Rituximab Azathioprine	11 (88.6) 78 (88.6) 35(85.4) 32 (88.9) 11 (73.3) 5 (83.3) 6 (75.0) 13 (92.9) 2 (50.0) 8 (88.9)	2 (10.0) 10 (11.4) 6(14.6) 12 (11.1) 4 (26.7) 1 (16.7) 2 (25.0) 1 (7.1) 2 (50.0) 1 (11.1)	0.861 0.861 0.362 1.000 0.062 0.656 0.194 0.613 0.060 1.000	0.867 (0.175-4.303) 1.154 (0.232-5.729) 1.743 (0.522-5.818) 1.000 (0.280-3.572) 0.259 (0.067-1.003) 1.655 (0.177-15.48) 3.000 (0.533-16.89) 0.580 (0.069-4.879) 9.400 (1.191-74.16) 1.000 (0.114-8.770)
	Monotherapy Dual therapy Triple therapy	50 (94.3) 22 (88.0) 6 (60.0)	3 (5.7) 3 (12.0) 4 (40.0)	0.077 0.872 0.013
	Low disease activity Moderate/high disease activity	80 (89.9) 13 (81.3)	9 (10.1) 3 (18.8)	0.475 0.381
	Rheumatoid arthritis SLE Spondyloarthropathy	37 (86) 11 (91.7) 17 (100)	6 (14) 1 (8.3) 0 (0)	0.445 1.000 0.112
	DM Morbid obesity Hypertension	19 (76.0) 3 (3.1) 13 (65.0)	6 (24.0) 0 (0) 7 (35.0)	0.019 0.535 0.000
	Cardiovascular disease Chronic kidney disease Interstitial lung disease Cancers	0 (0) 1 (25) 2 (66.7) 3 (100)	4 (100) 3 (75) 1(33.3) 0 (0)	0.000 0.004 0.214 0.535
				0.886 (0.827-0.949) 8.938 (2.466-32.4.5) 0.077 (0.040-0.150) 31.66 (2.97-336.77) 4.273 (0.358-51.04) 0.886 (0.827-0.949)

The risk of COVID-19 infection in patients with Autoimmune Rheumatic diseases during the peak of infection in Qatar: A cross-section study of 700 patients

This was a cross-section study conducted through phone interviews on patients with ARDs residing in Qatar from January 2020 to July 30th, 2020.

The study gathered information on the demographic, medical history, COVID-19 exposure risk, symptoms suggestive of COVID-19, and confirmation of a COVID-19 infection.

Eligible patients were identified from the list of patients with ARDs following Hamad General Hospital's rheumatology clinic. We recruited 700 patients (mean age 43.2 + 12.3 years; Female 73%) (Table 1).

Rheumatoid arthritis and SLE were the most common autoimmune diseases (37% and 21%, respectively) among the recruited patients. About a quarter of patients (26%) had active disease at the interview time.

Hydroxychloroquine was the most commonly used treatment (44%), followed by methotrexate (25%) and TNF-inhibitors (18%).

Only 16% of patients were on glucocorticoids, defined as a regular treatment for more than 3months regardless of dose.

We identified 75 patients (11%) who tested positive for SARS-CoV-2 RT-PCR during the study period, representing the peak of the COVID-19 pandemic in Qatar.

Factors associated with COVID-19 in patients with ARDs:

The sociodemographic and clinical variables were compared between patients with ARDs who contracted SARS-CoV-2 and those who did not and are shown in Table 1. Infected patients were mostly male [33 (44%) vs 155 (25%), P < 0.01] but were similar to patients with no COVID-19 with regards to age and ethnicity.

The prevalence of diabetes mellitus was higher in COVID-19 patients compared to non-COVID-19 patients [18 (24%) vs 87 (14%), P=0.02], whereas obesity and SLE were more common in non-COVID-19 patients (P=0.04 and P=0.02 respectively).

Long-term treatment with hydroxychloroquine was numerically (but not statistically significantly) more prevalent in non-COVID-19 patients [26 (35%) vs 288 (46%), P=0.06], and no differences in ARD medications, steroids, NSAIDs, and ACE-I/ARB were otherwise observed.

History of close contact with COVID-19 patients was significantly higher in patients who contracted COVID-19 compared to those who did not [45 (60%) vs 41 (7%), P < 0.01].

Variables	All Patients with ARDs (n=700)	COVID-19 (n=75)	Non-COVID-19 (n=625)	P-value
Age (years)	43.2 (12.3)	42.8 (12.6)	43.2 (12.3)	0.77
Sex (male)	188 (27%)	33 (44%)	155 (25%)	< 0.01
Ethnicity:				0.07
Asian	266 (38%)	39 (52%)	227 (36%)	
Levant	73 (10%)	7 (9%)	66 (11%)	
Gulf	191 (27%)	16 (21%)	175 (28%)	
African	147 (21%)	13 (17%)	134 (21%)	
Others	23 (3%)	0 (0%)	23 (4%)	
Co-morbid conditions:				
Hypertension	148 (21%)	19 (25%)	129 (21%)	0.35
Diabetes	105 (15%)	18 (24%)	87 (14%)	0.02
Obesity	79 (11%)	3 (4%)	76 (12%)	0.04
Chronic kidney disease	33 (5%)			
Chronic heart disease	18 (3%)			
Interstitial lung disease	8 (1%)			
Type of ARD:				
RA	260 (37%)	34 (45%)	226 (36%)	0.12
SLE	151 (22%)	8 (11%)	143 (23%)	0.02
Sjogren's syndrome	59 (8%)			
APLS	39 (6%)			
Other CTDs**	25 (4%)			
Ankylosing spondylitis	75 (11%)			
Psoriatic arthritis	41 (6%)			
Other SpA	15 (2%)			
Behcet's disease	10 (1%)			
ARD medications:				
Glucocorticoids	114 (16%)	14 (19%)	100 (16%)	0.56
NSAIDs	22 (3%)	5 (7%)	27 (4%)	0.26

NSAIDs	32 (5%)	5 (1%)	27 (4%)	0.36
Hydroxychloroquine	314 (45%)	26 (35%)	228 (46%)	0.06
Mycophenolate mofetil	67 (10%)	1 (1%)	66 (11%)	0.01
Methotrexate	173 (25%)	25 (33%)	148 (24%)	0.07
Azathioprine	48 (7%)	8 (11%)	40 (6%)	0.17
Sulfasalazine	60 (9%)	5 (7%)	55 (9%)	0.53
Leflunomide	26 (4%)	3 (4%)	23 (4%)	0.89
Anti-TNF	124 (18%)	13 (17%)	111 (18%)	0.93
JAKi	26 (4%)	1 (1%)	25 (4%)	0.25
Rituximab	33 (5%)	5 (7%)	28 (5%)	0.40
Cyclophosphamide	1 (0.1%)	0 (0%)	1 (0.2%)	0.73
Tocilizumab	11 (2%)	0 (0%)	11 (2%)	0.25
ACEi/ARB	37 (5%)	5 (7%)	32 (5%)	0.57
Disease activity:				0.24
Remission	516 (74%)	51 (68%)	465 (74%)	
Active	184 (26%)	24 (32%)	160 (26%)	
Flu vaccination	299 (43%)	30 (40%)	269 (43%)	0.62
Close contact with COVID-19 patient	86 (12%)	45 (60%)	41 (7%)	< 0.01

Table 1: Characteristics of patients with ARD and differences in demographics and clinical variables between patients with COVID-19 and patients without*

* Values are presented as number (%) for categorical variables and mean (SD) for continuous variables.

** Other CTDs includes systemic sclerosis, mixed connective tissue disease, undifferentiated connective tissue disease, and idiopathic inflammatory myositis

ACEi/ARB = Angiotensin-converting enzyme inhibitors / Angiotensin II receptor blockers, Anti-TNF = Anti-tumor necrosis factor, APLS = Antiphospholipid syndrome, ARD = Autoimmune rheumatic disease, COVID-19 = Coronavirus 2019 disease, CTD = Connective tissue disease, JAKi = Janus kinase inhibitor, NSAIDs = Non-steroidal anti-inflammatory drugs, RA = Rheumatoid arthritis, SLE = Systemic lupus erythematosus, SpA = Spondyloarthritis.

Statistically significant and clinically relevant variables on the univariate analysis were considered for multivariate logistic regression stratified by the binary outcome of COVID-19 patients vs non-COVID 19 patients to identify factors independently associated with COVID-19. The final model is presented in Table 2.

Male gender was associated with a 2.5-fold increase in the risk of COVID-19 (adjusted odds ratio [aOR] 2.56, 95% confidence interval [CI] 1.35 – 4.88, P < 0.01).

Of the medical and ARD-specific variables, diabetes was found to increase the risk of COVID-19 by 2-fold with a tendency towards statistical significance (aOR 2.14, 95% CI 1.0 – 4.6, P = 0.051). However, a history of close contact with a COVID-19 confirmed case carried a 28-fold increase in the risk of COVID-19 (aOR 27.89, 95% CI 14.85 – 52.38, P < 0.01).

Variable	Adjusted Odds Ratio	95% Confidence Interval	P-Value
Age (years)	0.99	0.96 – 1.01	0.28
Sex (Male)	2.56	1.35 – 4.88	< 0.01
Diabetes	2.14	1.00 – 4.60	0.051
SLE	0.57	0.22 -1.50	0.25
Hydroxychloroquine	0.60	0.30 – 1.24	0.17
Close contact with COVID-19 patient	27.89	14.85 – 52.38	< 0.01

Table 2. Factors independently associated with COVID-19 in patients with ARDs

COVID-19 = Coronavirus 2019 disease, SLE = Systemic lupus erythematosus.

Although long-term hydroxychloroquine use was numerically higher in patients without COVID-19 infection, it was not independently associated with the disease. In the stratified analysis of the subgroup of patients with close contact with COVID-19 positive case (n = 86), however, a significant difference was found in hydroxychloroquine use between patients who contracted COVID-19 and those who did not [16 (35%) vs 30 (65%), P < 0.01].

Discussion

We will continue to follow the international guidelines on managing ARD during the COVID-19 pandemic.

We will tailor the guidelines according to local needs and resources.

Rheumatology consultation should be appropriately placed for any patient with ARD admitted or quarantined for SARS-CoV-2 infection.

This involvement will help manage the underlying diseases during the infection to reduce morbidity/ or mortality chances.

All patients with ARD are recommended to receive COVID-19 vaccines, particularly mRNA-based vaccines. Vaccination for pregnant and breast-feeding patients will be deferred until further data is available.

The experience gained in effectively using telemedicine to manage ARD helped us develop methods to recognize patients at risk of flare or uncontrolled disease. We are evaluating the need to blend this service into our long-term patient care.

Reference:

- Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis.* 2014;73(7):1316-22.
- Senolt L. Emerging therapies in rheumatoid arthritis: focus on monoclonal antibodies. *F1000Res.* 2019;8.
- Schmid AS, Neri D. Advances in antibody engineering for rheumatic diseases. *Nat Rev Rheumatol.* 2019;15(4):197-207.
- Furer V, Rondaan C, Heijstek M, van Assen S, Bijl M, Agmon-Levin N, et al. Incidence and prevalence of vaccine preventable infections in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD): a systemic literature review informing the 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD. *RMD Open.* 2019;5(2):e001041.
- Soy M, Keser G, Atagunduz P, Tabak F, Atagunduz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol.* 2020;39(7):2085-94.
- Perricone C, Triggiani P, Bartoloni E, Cafaro G, Bonifacio AF, Bursi R, et al. The anti-viral facet of anti-rheumatic drugs: Lessons from COVID-19. *J Autoimmun.* 2020;111:102468.
- Yazdany J. COVID-19 in Rheumatic Diseases: A Research Agenda. *Arthritis Rheumatol.* 2020;72(10):1596-9.
- Favalli EG, Monti S, Ingegnoli F, Balduzzi S, Caporali R, Montecucco C. Incidence of COVID-19 in Patients With Rheumatic Diseases Treated With Targeted Immunosuppressive Drugs: What Can We Learn From Observational Data? *Arthritis Rheumatol.* 2020;72(10):1600-6.
- Quartuccio L, Valent F, Pasut E, Tascini C, De Vita S. Prevalence of COVID-19 among patients with chronic inflammatory rheumatic diseases treated with biologic agents or small molecules: A population-based study in the first two months of COVID-19 outbreak in Italy. *Joint Bone Spine.* 2020;87(5):439-43.
- Zhong J, Shen G, Yang H, Huang A, Chen X, Dong L, et al. COVID-19 in patients with rheumatic disease in Hubei province, China: a multicentre retrospective observational study. *Lancet Rheumatol.* 2020;2(9):e557-e64.
- Emmi G, Bettoli A, Mattioli I, Silvestri E, Di Scala G, Urban ML, et al. SARS-CoV-2 infection among patients with systemic autoimmune diseases. *Autoimmun Rev.* 2020;19(7):102575.
- Zen M, Fuzzi E, Astorri D, Saccon F, Padoan R, Ienna L, et al. SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: A cross-sectional study on 916 patients. *J Autoimmun.* 2020;112:102502.
- Rocha APD, Atallah AN, Pinto A, Rocha-Filho CR, Milby KM, Civile VT, et al. COVID-19 and patients with immune-mediated inflammatory diseases undergoing pharmacological treatments: a rapid living systematic review. *Sao Paulo Med J.* 2020;138(6):515-20.
- D'Silva KM, Serling-Boyd N, Wallwork R, Hsu T, Fu X, Gravalles EM, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. *Ann Rheum Dis.* 2020;79(9):1156-62.
- Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis.* 2020;79(7):859-66.
- Scire CA, Carrara G, Zanetti A, Landolfi G, Chighizola C, Alunno A, et al. COVID-19 in rheumatic diseases in Italy: first results from the Italian registry of the Italian Society for Rheumatology (CONTROL-19). *Clin Exp Rheumatol.* 2020;38(4):748-53.

17. Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, et al. American College of Rheumatology Guidance for the Management of Rheumatic Disease in Adult Patients During the COVID-19 Pandemic: Version 2. *Arthritis Rheumatol.* 2020;72(9):e1-e12.
18. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med.* 2020;383(2):120-8.
19. Furur V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis.* 2020;79(1):39-52.
20. Flemming A. mRNA vaccine shows promise in autoimmunity. *Nat Rev Immunol.* 2021;21(2):72.

[Home](#)[Forward message](#)[Introduction](#)[Chapters](#)[Editors team](#)[Contact us](#)

Copyright © 2022 Ministry of Public Health. All rights reserved.



Search this site



Rehabilitation Medicine

COVID 19 HMC e-Resource: Rehab Chapter

Authors

- Dr. Rafat Mohmamed Abdullah Saad
- Dr. Fatma Jassim S.J. AL-Kuwari
- Dr. Ginny Varghese
- Dr. Krishnaprasad Ittilavalappil Narayananakutty
- Mr. Amjad Annethattil
- Mr. Salah T. Kh. Adarbeh
- Ms. Noor Al Huda Amer Ali Al Jabri
- Mr. Subburaj Senthuran
- Mr. Mohammed Sajid Hussain
- Mr. Ibin Kariyathankavil

Keywords: COVID-19, Rehabilitation, long COVID, Physiotherapy, Occupational Therapy, Pulmonary rehabilitation.

Table of Contents:

1. Introduction
2. Rehabilitation requirements and interventions of patients with COVID-19
3. Respiratory sequelae
4. Neurological sequelae
5. Musculoskeletal sequelae
6. Psychiatric sequelae
7. Post-intensive care syndrome (PICS) and post-COVID-19 syndrome (long COVID)
8. Organization of rehabilitation services
9. Rehabilitation Experience in Qatar during the COVID-19 pandemic
10. Recommendations and Challenges

Introduction:

COVID-19 pandemic has significantly increased the burden of disease and disability globally, created new healthcare challenges, and has affected the delivery of conventional health care services¹. At the time of writing, the pandemic shows no signs of abating. The vaccines against COVID-19 and their efficacy on populations are yet to be determined. While remaining focused on reducing the spread and mortality of the disease, prevention of disability and optimization of function is paramount to address the complications of COVID-19. Patients who require prolonged intensive care are likely to develop persistent physical, cognitive, and psychological impairments upon discharge, necessitating rehabilitation to help them return to normal function or adapt to living with disability².

WHO defines rehabilitation as "a set of interventions designed to optimize functioning and reduce disability in health conditions in interaction with their environment".

This translates into aiming to make a person achieve as much independence in their daily life as possible after a physical and or cognitive impairments. It involves both adults and children, at any stage of their condition whether acute or chronic. Rehabilitation is always patient-centered; therefore, its interventions are tailored to meet an individual's abilities and goals. There are multiple aspects to be considered in the rehabilitation patient, including mobility, cognitive, self-care independence, psychological and social components. Rehabilitation interventions include mobility, strengthening, speech, swallowing therapy, self-care activity training, pain management, spasticity management with botulinum toxin injections,

medications and therapy; bowel and bladder management, sexual rehabilitation, providing walking aids, orthotic and prosthetic devices, home visits, a study of accessibility and recommendations for adaptations needed for family, social and job reintegration.

The process involves a multi-disciplinary team comprising a rehabilitation physician, nurse, physiotherapist, occupational therapist, speech therapist, respiratory therapist, orthotist, dietician, social worker, case manager, and psychologist. The staff composition can vary between regions depending on availability and requirements.

Rehabilitation is an integral part of the health care pathway by relieving pressure on acute services in the wake of the pandemic and aiding patients to re integrate into society.

Globally around 2.4 billion people are estimated to need rehabilitation services.

Rehabilitation also minimizes patients functional decline and promotes patient discharge from the hospital as well as in reducing readmissions, which is crucial during hospital bed shortages. Since the current pandemic scale is unprecedented in recent history, the rehabilitation response scale is likewise expected to be extraordinary compared to the pre-pandemic services.

The evidence of benefit from rehabilitation interventions in different phases of illness is emerging, and many international professional associations have come with specialty-specific guidelines^{3,4}. Table 1 depicts typical rehabilitation interventions in the acute, subacute and chronic phase.

In addition to the increased workload created by COVID-19 associated cardiopulmonary, musculoskeletal, neurological, and psychological/psychiatric complications of the disease, COVID-19 has created another set of challenges in the field of rehabilitation. These challenges include diminished workforce due to sickness, quarantine, and redeployment to frontline services, restrictions on hands-on interventions and group therapy, isolation of patients from families, and its socio-economic and psychosocial effects. Patients with other conditions (spinal injury, stroke, acquired brain injury, significant fractures, etc.) require ongoing rehabilitation interventions for their functional optimization.

Withdrawal of rehab services for these groups can be risky, and hence their care should be uninterrupted.

The feasibility of telemedicine interventions for individual high-risk category patients like the elderly, especially for some interventions based on education and advice, also needs further exploration⁵.

Rehabilitation requirements and interventions of patients with COVID-19

COVID-19 can be classified according to disease severity. The Chinese Centre for Disease Control and Prevention data that had approximately 44,500 patients showed that 81 per cent had mild disease with no pneumonia or mild pneumonia, 14 % had severe disease (those with hypoxia, dyspnea, or > 50 % lung involvement), and 5 % with critical disease complicated by multiorgan failure, shock, and respiratory failure.

Severe COVID-19 illness requires invasive mechanical ventilation in the critical care unit.

Mechanical ventilation, extracorporeal membrane oxygenation (ECMO), and prolonged immobilisation can impair muscle strength, neuropathy, physical function, respiratory function, cognitive status, swallowing, and communication.

The potential for delirium is also increased. In the long-term, they are also at risk for post-intensive care syndrome.

Persistent symptoms of fatigue and breathlessness in 60 per cent of cases among those with the milder disease are of concern as it affects the quality of life and function and requires monitoring to evaluate the long-term implications of this disease on the population⁶.

Respiratory sequelae

Pulmonary complications of COVID-19 range from acute; like pneumonia, acute respiratory distress syndrome (ARDS), pulmonary embolism to chronic such as interstitial lung disease, pulmonary hypertension, or respiratory failure requiring oxygen support. Several studies also show that patients with a milder disease also reported symptoms of fatigue, breathlessness, and cough lasting weeks to months after initial presentation^{7,8},

In patients with critical COVID-19 illness, some patients (younger, less severe lung involvement, and short ICU stay) have a good progression, with full-near functional and respiratory recovery. Other patients show persistent dyspnea, which can be present at rest, on passive mobilization, or during active effort⁹. Persistent oxygen desaturation has also been reported, likely due to developing pulmonary fibrosis.

Reduced exercise capacity is also seen with deconditioning which is most commonly associated with prolonged immobilization in critically ill patients. Deconditioning can be seen in elderly subjects or those with some pre-existing disability or even in moderate COVID-19¹⁰. It can also lead to other factors, such as myopathy, cardiac and autonomic dysfunction. Severe deconditioning can significantly impede the patient's safe discharge to the community¹¹. Such groups will need intensive, multi-disciplinary, in-patient rehabilitation at the earliest, with extended pulmonary rehabilitation in some.

Neurological sequelae

The most common neurological symptoms reported in patients with prolonged mechanical ventilation were dizziness and headache¹². Patients with encephalitis display confusion and behavioral changes while executive dysfunction, memory are affected in some cases post Covid. As coronaviruses are neurotropic, a direct CNS lesion mechanism of SARS-CoV-2 has been suggested.

The most frequently reported neurological disturbances of COVID-19 are anosmia and ageusia (80% of symptomatic patients)¹³.

The most frequent mechanism of neurological involvement is probably indirect. Several reports of cerebrovascular events have been considered related to COVID-19 without clear evidence of direct causality. SARS-CoV-2 can produce hypercoagulability, endothelitis, and vascular endothelial dysfunction, precipitating a stroke¹⁴.

Other groups of immune-mediated diseases are also reported, e.g., Guillain-Barré Syndrome (GBS)¹⁵ and its variants and inflammatory meningoencephalitis.

Brain and spinal cord demyelination have also been reported¹⁶.

Another neurological complication frequently reported after COVID-19 critical illness is critical-illness-related myopathy and neuropathy (CRIMYNE).

Most cases reported are myopathic forms, with severe proximal muscle wasting.

The lower and upper limbs peripheral nerve deficits are reported, albeit less frequently¹⁷. Recovery after CRIMYNE is challenging, with persisting weakness, loss of function, and endurance for two years or longer.

Post-extubation dysphagia (PED) has been reported in a significant number of patients requiring mechanical ventilation for ARDS.

It is most likely to be mechanical, but diminished proprioception and laryngeal injury can be possible factors¹⁸.

Dysphagia screening to protect the airway from aspiration is a critical intervention in patients with severe COVID-19.

Musculoskeletal sequelae

Patients with ARDS from COVID-19 can require mechanical ventilation in the prone position. The difficulties with mobilisation in such circumstances increase the risk of joint trauma or dislocations.

Many patients develop joint stiffness and chronic joint pain.

Some develop bony complications and muscle weakness due to high-dose steroid use in the acute phase. As little as 2 weeks in the critical care unit can lead to joint contractures and are associated with mobility impairments years after discharge, necessitating prolonged rehabilitation¹⁹.

Psychiatric sequelae

The COVID-19 pandemic has resulted in psychological distress in varied populations ranging from clinical workers, patients, and the general population. With its life-threatening and life-altering implications coupled with social isolation, the pandemic's novel nature has led to a mental health pandemic.

Encephalopathy, cerebrovascular effects, medications, critical illness are postulated to cause neuropsychiatric manifestations²⁰. 20-40 % of those who suffer severe COVID-19, have depression, Post Traumatic Stress Disorder, or anxiety after recovery^{21,22}.

Patients, their relatives, and treating clinicians reported psychiatric issues. The most common reported issues are anxiety, depression, fear, anger, and post-traumatic stress disorder²³. In critical and severe COVID-19, especially in the elderly population, it is often difficult to differentiate a psychiatric manifestation from delirium. Patients with mild illness or asymptomatic persons, isolated or in quarantine, may experience boredom, loneliness, and anger and can even be at risk for substance abuse and deliberate self-harm²⁴.

Awareness by organizations and clinicians about the psychiatric manifestations and interventions can mitigate some of its impacts.

Surveillance for mental health decline or domestic abuse with appropriate reporting and referral systems and learning coping strategies are some of the advocated approaches²⁵.

Post-intensive care syndrome (PICS) and post-COVID-19 syndrome (long COVID)

It is estimated that approximately 50 % of all the patients requiring mechanical ventilation develop PICS.

Post intensive care syndrome is a spectrum of physical deficits (weakness, balance, and endurance problems) and or neurocognitive problems like anxiety and depression that affect survivors of critical illness and persists after the patient has been discharged from the intensive care unit. Appropriate rehabilitation, family education, support, and close follow-up are essential to managing this disabling condition²⁶.

Post-COVID-19 syndrome is defined as signs and symptoms that develop during or following an infection consistent with SARS-CoV-2 that continue for more than 12 weeks and are not explained by an alternative diagnosis.

Long COVID symptoms usually appear in clusters, sometimes overlap with PICS, can fluctuate over time, and affect any of the body's systems. Common symptoms include persistent cough, low-grade fever, breathlessness, and fatigue.

Chest pain, palpitations, myalgia, arthralgia, headaches, vision changes, hearing loss, loss of taste or smell, impaired mobility, numbness in extremities, tremors, memory loss, mood changes, rashes, gastrointestinal symptoms, neurocognitive difficulties, and mental health issues can also occur. Consequently, there is a significant impact on survivors' quality of life that could impede their ability to return to a productive environment. Nearly 90% of hospitalized patients who recovered from COVID-19 reported persistence of at least one symptom 2 months post-discharge. Many patients recover spontaneously with supportive care, rest, symptomatic therapy, and a gradual increase in activity²⁷.

The organisation of rehabilitation services

Rehabilitation should begin as early as possible, ideally, while the patient is still in intensive care, once the medical condition permits. The National Institute for Health and Care Excellence (NICE) recommends progressive rehabilitation programs are best initiated within the first 30 days (post-acute phase) to have the most significant impact on recovery²⁸.

After extubation, if the complexity is low (cardiovascular and pulmonary stability, without cognitive impairment, no CRIMYNE or signs of post-intensive care syndrome), the patient can be transferred to step down or acute care unit for a short period and then discharged home under the active surveillance of family physician.

Most patients have good recovery and can be managed by specialized outpatient therapy or community rehabilitation resources as needed.

If the complexity is high, the patient should be transferred to the acute care unit and arranged for an acute rehab service assessment for early intervention followed by triage into post-acute pathways.

A small number of patients have more complex rehabilitation needs that require prolonged specialist rehabilitation services. In-patient rehabilitation admission criteria from acute care require patient to be afebrile, with stable oxygen saturation and respiratory rate for three days, and no radiologic progression of disease²⁹.

When the patients are fit to leave the hospital, they need access to support at home, followed by community reintegration programs. Patients with a life-long, complex disability may be transferred to specialist nursing home care with periodic rehabilitation surveillance. The flow of patients during their rehabilitation process is illustrated in figure 1.

Infection control is paramount to protect other vulnerable patients and staff. The infection control measures should include using separate service streams and access to the necessary personal protective equipment (PPE).

Optimally, two streams of care should be organised for COVID-19 positive and negative patients to minimise the risk of internal contamination and improve the appropriate use of PPE and staff safety.

All staff working with COVID-19 patients should be screened before and after each shift for symptoms and fever. Some procedures are considered as high risk for infection like in the treatment of dysphagia which involves close contact and cough inducing procedures. The treating clinicians should be aware and take recommended precautions. When the patient in a COVID-19 unit becomes clinically unstable, there should be a proper pathway for swift transfer of the patient to acute care. The rapid response team should be aware of the patient's COVID-19 status to take adequate precautions, and the patient should be treated in a room, separate from other patients.

Another scenario is the development of COVID-19 infections in patients already hospitalised in rehabilitation settings for other conditions. If it is a minor illness, the patient can be treated in rehabilitation settings because of the difficulty and risk of transferring a patient with a significant disability to an acute care unit.

However, these patients need strict surveillance to identify any rapid deterioration in their clinical condition.

In the wake of an infectious disease outbreak, utilizing teleconsultation and telehealth services 30 wherever feasible can significantly reduce healthcare personnel exposure and save PPEs for acute usage. The creative use of communication technologies aids patients and families to reduce the barriers imposed by isolation and helps to cope with stress³¹.

Rehabilitation Experience in Qatar during the COVID-19 pandemic

The COVID-19 pandemic posed a significant challenge to all health professionals, including rehabilitation care providers, resulting in a rethink and reorganization of healthcare delivery.

Qatar's Ministry of Health took an early action on Mar 13, 2020, in response to the COVID-19 pandemic by bringing out "Qatar national preparedness and response plan for communicable diseases," which is a comprehensive action plan of the country to manage the pandemic³².

Qatar Rehabilitation Institute (QRI), which is under the Hamad Medical Corporation, is a tertiary care centre delivering the highest quality rehab services through in-patient, outpatient, day rehabilitation, and community-based rehabilitation services.

In-patient services are extended to stroke, traumatic brain injury, spinal cord injury, polytrauma, and other complex disabling conditions requiring multi-disciplinary rehabilitation interventions.

Patients aged 14 and above are admitted to the adult rehabilitation service, and below 14 years are accepted under pediatric rehabilitation service.

The rehab adult multi-disciplinary team (MDT) comprises of the physician, physiotherapist, occupational therapist, speech therapist, dietician, nurse, clinical pharmacist, psychologist, prosthetic and orthotic service, social service, and community-based rehabilitation (CBR) team members. Rehabilitation is delivered through an inter-disciplinary approach with patient and family centered care.

Tough times call for tough measures - our journey through the pandemic.

In-patient services continued to operate during the pandemic. The admitted patients needed care, but extra precautions were taken to prevent them from contracting COVID-19. Facility-wide infection control measures were put in place to prevent the virus's spread.

Mask-wearing for all persons in the facility became compulsory. Visitors had temperature checks and screened for their clinical status through the mobile "Ehteraz" app (the contact Covid -tracing mobile app for the State of Qatar).

Daily screening of all medical personnel catering to patients and strict hygiene measures, especially hand hygiene, was emphasized.

Wall-mounted disinfectants were made available at all locations. In the therapy gyms, social distancing and scheduling patients at adequate time intervals were initiated to adhere to social distancing norms. Activity rooms were converted to gym areas to incorporate more patients due to the gym's space restriction.

Common areas and equipment were sanitized after each patient use. PPEs were made available for therapists treating the patients with measures and instructions for the appropriate disposal of PPEs. Shift duties were put in place to ensure adequate spacing and social distancing for therapists.

MDT rounds and case conferences were initially stopped and gradually reintroduced when the country showed a decline in active cases. Only one attendant was allowed to stay with the patient after testing negative for COVID-19.

Visitor timings were restricted to 15 minutes, and a maximum of two visitors was allowed, with appropriate PPEs. All temporary home visit passes and outdoor group trips were suspended. Any patient or staff showing symptoms were tested, and if found positive, contact tracing and isolation were implemented immediately in coordination with a dedicated infection control team.

Considering the vulnerable population, including geriatric, immunocompromised, and multiple comorbid conditions, only COVID-19 negative patients were initially accepted.

There was a delay in patient acceptance due to requirements of a negative PCR result. As information evolved about COVID-19, clinically stable patients with positive COVID-19 tests were accepted based on the non-infectious cut-off of the cyclical threshold value of the PCR test.

In May 2020 – QRI admitted the first post-COVID-19 patient. COVID-19 survivors were assessed on admission, using standard outcome measures to assess their disabilities and impact on their daily life.

The commonly used assessment tools used for patients were post-COVID-19 functional scale (PCFS)³³ modified Borg dyspnea and fatigue scale³⁴, 6 Minute walk Test, modified Medical Research Council for dyspnea scale (mMRC)³⁴, and Functional Ambulation Category (FAC) . After prolonged ICU stay, most patients had post-intensive care syndrome (PICS) and the most pronounced was ICU-acquired weakness.

There was a marked reduction in these patients exercise capacity with a reduced participation in ADL (activities of daily living) due to functional or cognitive limitations. Reassessment was carried out every two weeks with standard measures to monitor improvements by the MDT.

Based on the possible influence of COVID-19 on lung and heart function, it was recommended to use a pulse oximeter to monitor oxygen saturation and heart rate³⁵ continuously.

Due to the limitation in the feasibility of pre-rehab assessment of lung function and exercise testing, exercise training is started with low intensity and a subsequent gradual progression to moderate intensity functional and strengthening exercises. Clinical practice recommendation (CPR) was developed for the physiotherapy management of post-COVID-19 patients in outpatient department, a multisystem screening tool for determining a requirement for Physiotherapy (Appendix 1).

Aquatic physiotherapy services were also closed due to the health care authorities' restrictions at the peak of the pandemic. A corporate guideline was formulated with all areas covered and infection control measures to resume services in due course. The patients were limited to one per pool and a 15 – 20-minute time difference was maintained between two patients to disinfect the common area.

Early pulmonary rehabilitation assumes a vital role in COVID-19 as it is primarily a respiratory illness with a long term respiratory sequela^{e34}. Respiratory therapists initiate pulmonary rehabilitation after a thorough examination of the patient's lung function and endurance. After acute management, some post-COVID-19 patients require non-invasive ventilation (NIV), while others require oxygen support with a nasal canula to improve the Functional Residual Capacity (FRC), avoid atelectasis and improve oxygenation.

Dyspnea with routine activity was a common complaint. Self-proning was recommended to our patients to improve oxygenation, enhance alveolar ventilation, and decrease ventilation-perfusion matching. Most of the patients on oxygen were gradually weaned off, and few were discharged on supplemental oxygen. Patients with a neurological deficit or severe muscle weakness are very susceptible to secretion pooling in their lungs, which impedes recovery.

Recurrent chest infections, increased work of breathing and desaturations are an endless cycle if not managed well from the beginning. Cough assist, positive expiratory pressure devices were aggressively used with those patients to clear the chest. Breathing exercises to increase respiratory muscle strength are crucial to improve patients functional outcomes. On discharge, patients are referred to continue with pulmonary rehabilitation programs. Due to the sheer volume of patients requiring pulmonary rehabilitation and to relieve pressure on the services, a home program is taught to follow through until they get a formal appointment.

Occupational therapists assess impairments in physical and cognitive functioning, do ADL evaluation and the management to encourage early mobilization and self-care. In addition, they recommend seating, environmental modifications and assistive devices. Daily routines and rituals, which contribute to one's sense of self and well-being, can be adversely affected by the pandemic, leading to depression. Occupational therapists may help them adapt to the 'new normal' and establish meaningful routines that support the quality of life.

Speech-language pathologists (SLP) provide rehabilitation services for damage caused by mechanical ventilation, including injury to vocal cords from breathing tubes and deconditioning of the muscles needed for swallowing or neurogenic communication. Speech therapists are at higher risk of infection exposure due to several assessments, like oral care and exams, bedside swallowing test, cough reflex tests, flexible endoscopy evaluation of swallow (FEES test), and video fluoroscopic examination of swallowing (VFS). Hence such evaluations were restricted and were done with strict infection control practices³⁶.

All COVID-19 patients admitted are routinely screened for the presence of anxiety, depression, and impairment in different aspects of cognition. The mood disorders are expected³⁷, and if detected, are managed by arranging for appropriate counselling sessions, education, psychologist support, and pharmacotherapy when indicated. The caregiver burden is also acknowledged and provided appropriate support. Cognitive impairment is managed through appropriate cognitive rehabilitation interventions to improve memory, attention span, orientation, language, and executive functions.

COVID 19 illness produces a catabolic state and pushes the patient into malnourishment.

Dietary management plays a crucial role in reversing the catabolic state and helps in recovery ³⁸. Many COVID-19 survivors have dysphagia, necessitating the diet's consistency to be modified or use a nasogastric tube for feeding. A good nutritional status allows for better resilience, and a worse nutritional status represents an adverse prognostic factor for recovery.

The risk of malnutrition in COVID-19 patients is related to chronic conditions like diabetes, chronic obstructive pulmonary disease, renal insufficiency, cardiovascular diseases, and the reduction of food intake caused by nausea and the loss of appetite.

QRI dietetics department provided evidence-based integrated management of the nutritional impairments in COVID-19.

COVID-19 patients require close monitoring of their therapy and activity tolerance and the use of supplemental oxygen to maintain an appropriate level of therapy and activities.

The treatment is coordinated and monitored by the rehab physician which could last for a period of 4 to 8 weeks or up to 3 months in some advanced cases. At the time of writing, QRI has admitted more than 100 severe COVID-19 survivors and discharged with significant improvements in outcome measures.

After recovery, some patients were repatriated to their home country, while some continued rehabilitation for their residual deficits through outpatient services.

Outpatient services, including clinics and therapy services, were suspended at the pandemic's onset upon the directives from health authorities. The services remained dynamic to adapt as per the evolving situation. Within a short period, all the outpatient services – clinics and therapy were moved to a virtual platform called VSee clinic, with audio and video integrated to interact more effectively.

Referrals directed to the outpatient department of QRI were screened, and patients were called to offer them either a telephone or video consultation based on their preferences.

All video calls were made after receiving patient consent. During the first consultation, a subjective assessment was performed, including discussing the patients' needs and motivation to undertake virtual rehabilitation. Safety of performing the exercises at home was of utmost priority.

Online exercises were advised only to patients who were able to do them or patients who had caretakers to assist them.

A simple sit-to-stand (STS) test was performed to assess the suitability for exercise and exercise plan was developed and demonstrated. Follow-up appointments continued at a given schedule as per the care plan. All chronic patients were given videos of exercises demonstrated by therapists to be carried out at home.

Three times weekly telephonic support was provided for patients on a home exercise program. Virtual classes were also arranged.

Gradually, when the country's COVID-19 caseload decreased, the facility was permitted to accept patients for face-to-face consultations and treatment.

The outpatient team had to cater to its conventional patient population and post-COVID-19 cases in various recovery phases referred from various facilities.

A dedicated clinic was allocated to delivering physiotherapy care to post-COVID-19 patients. Before the outpatient services opened, the facility was reorganized to maintain social distance while delivering exercises.

It provided a route map for patients to ingress and egress the facility; aides were directed to sanitize the therapy equipment after each use and restricted the number of patients to a minimum in the gyms.

One of the most critical aspects in managing post-COVID-19 patients was to educate the patient and caregivers regarding the disease process and take precautions to stop further transmission of the virus, whether in person, maintaining social distancing standards, or via telehealth services³⁹.

Additional information and education regarding functional activities and strategies to overcome fatigability and improve endurance tolerance while performing ADL or any other functional tasks, based on the rehabilitation needs and goals set, were also provided through videos and telehealth services.

In line with this, the adult occupational therapy services developed a "QR code" to enable patients and caregivers to scan and download patient and family education materials onto their mobile devices or tabs, minimising the need for in-person education in a safe, environment-friendly, and time-efficient manner.⁴⁰

Day Rehabilitation service provides daily rehabilitation programs on an outpatient basis, reducing the burden on in-patient and regular outpatient services.

At the beginning of the pandemic in Qatar, no patients were accepted from home. Extra sessions were given for the inpatients, decreasing their length of stay and improving outcomes.

With the virtual platform's introduction, selected patients undertook day rehab therapy.

By July 2020, with the gradual reintroduction of outpatients, all patients were on site and no virtual patients remained. The service-maintained vitals and Ehteraaz check on all its patients, adhering to social distancing and the infection control measures followed in QRI.

Community rehabilitation services provide home assessment followed by recommendations and a follow-up of discharged patients at their homes.

The virtual platform was maintained till the easing of social distancing restrictions. CRS resumed on-site duties with the lifting of restrictions.

Recommendations and Challenges

COVID-19 has brought out many challenges and opportunities for change and improvement.

Traditionally rehabilitation involves hands-on and face-to-face interactions and interventions. Therapy in groups, multi-disciplinary team rounds, and case conferences with family members constitutes a typical rehabilitation day.

COVID-19 has made "social distancing" the norm and has led the rehabilitation team to seek new strategies to adapt to the changing situation. While the restrictions imposed by the pandemic have been stressful for the patient and staff, new ways of practice have evolved with technology being a crucial part of the process.

Rehabilitation measures for COVID-19 survivors can be delivered in hospitals, rehabilitation institutions, and communities. According to their intervention purposes, these measures include preventive, therapeutic, health-promoting, and palliative care.

Rehabilitation professionals develop individualized rehabilitation programs according to the health condition and functional state, the expected outcomes, the expectations of patients and their families, and the type of rehabilitation setting.

Recommendations

A systematic and comprehensive functional assessment and evaluations are recommended before rehabilitation. It involves subjective assessments, clinical examination, and evaluation of activity and participation.

Tools to evaluate the dyspnea, fatigue, pain, mood, musculoskeletal system, motor function, and cardiopulmonary function should be used before rehabilitation and reevaluated to assess the patient progress.

ADL assessments and quality of life assessments are also essential components of assessing global health and activity participation in COVID-19 survivors⁴¹.

Exercise, repeated functional movements, psychosocial support, and self-management are core rehabilitation interventions⁴².

Measures for mitigating the spread of infection

- Wearing the mask, compliance with hand hygiene, staff and visitor monitoring is mandatory.
- Patients and staff's distancing should be maintained with the recommended 2-meter distance between persons.
- A separate unit for rehabilitating COVID-19 patients is recommended with dedicated staff. Patients can be brought early to the facility and discharged according to the facility's requirement for beds and the patient's condition.
- Patients should remain in their rooms to avoid exposure and spread of the disease. Adequate access to communication devices, either through a patient's device or through the unit's dedicated device should be available to communicate with the patient's family.
- Procedures or therapy which can risk an infectious spread, should be identified and the recommended precautions should be taken.
- Proper doffing and donning techniques should be maintained.
- After each patient's use, gym equipment should be disinfected as per the manufacturer's guidelines. Single-use equipment is preferred, like TheraBand instead of weights, disposable electrodes, pads, gels, etc.
- Telemedicine, with virtual clinics and therapy, is valuable in reducing the infectious spread

Pulmonary rehabilitation

The main clinical manifestations of COVID-19 are respiratory, which includes pneumonia, increased airway secretions, and obstructive atelectasis. For hospitalised COVID-19 patients, respiratory rehabilitation alleviates dyspnea symptoms, anxiety, depression and eventually improves physical functions, quality of life, recovery, and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their families caregivers⁴³.

The optimal rehabilitation time is uncertain, but it should balance the patient's benefits and risks. Rehabilitation should be carried out when vital signs are stable, and the changes in vitals should be monitored throughout.

The therapist can use body position drainage, vibration and clapping, active cycle of breathing techniques, and other techniques or equipment to clear the airways. An upright sitting or standing position can increase diaphragm activity, improve the ventilation/perfusion in the lung, increase tidal volume, improve the peak flow rate of cough, and reduce the sense of breathing difficulty. It should be initiated as early as the patient's clinical condition permits.

Early mobilization reduces the risk of complications, promotes cardiopulmonary function, and shortens recovery time. Inspiratory muscle training, respiratory control training, biofeedback, etc., can also be used as part of pulmonary rehabilitation interventions in later stages.

Exercise therapy

During the acute phase of illness, aerobic exercise or respiratory rehabilitation is not recommended⁴⁴.

However, to prevent complications of pressure sores, deconditioning, joint contractures, "phase 1" mobilisation is done with sitting balance exercises, use of a tilt table, and muscle strengthening exercises. Patients with an independent sitting balance and a Medical Research Council power score of 3 or higher can perform "phase 2" mobilisation with supported/active weight-bearing with exercises, sit-to-stand, marching on the spot to mobilize from the bed⁴⁵. Early rehabilitation can significantly reduce mechanical ventilation duration, risk of delirium and eventually improve the patient's functional status⁴⁶.

Exercise therapies improve the functional level of the cardiac muscles, reverse the disuse atrophy of skeletal muscles, and increase the compensatory ability of the non-involved organs providing an increase in functional reserve. It primarily includes aerobic training, strength training, balance training, and coordination training.

Aerobic exercises are customized to the patient's disease and residual dysfunction. Aerobic exercises include slow walking, brisk walking, slow jogging, cycling, arm ergometry, and swimming.

They begin at a low intensity of fewer than 3 METS and progressively increase intensity and duration. A total of 3 to 5 sessions of 20-30 min are carried out per week. Patients who are prone to fatigue should perform intermittent exercises. Neuromuscular electrical stimulation can be used to assist with strengthening⁴⁷.

Strength training: Progressive resistance training is recommended. Each target muscle group should be loaded at 8 to 12 repetitions, 1 to 3 sets/time, with 2-min rest intervals between sets. The sessions' frequency should be 2 to 3 sessions/week for 6 weeks with a 5% to 10% weekly increase in intensity⁴⁸.

Balance training: Using postural stability training, training in different surfaces, and balance trainers.

Joint active and passive motion: Long-term bed rest can lead to joint stiffness, contracture, and other changes. Patients should be guided to carry out active and passive motions of the spine and limb joints at least 1-2 times per day to maintain

their normal range of motion.

Exercise termination criteria are as follows (any one):

1. Respiratory system: blood oxygen saturation $\leq 90\%$ or more than 4% lower than the baseline value; respiratory frequency >40 times/min; dyspnea or shortness of breath, aggravation, fatigue, and intolerable fatigue.
2. Cardiovascular system: systolic pressure <90 mm Hg or >180 mm Hg; mean arterial pressure <65 mm Hg or >110 mm Hg, or more than 20% change from baseline; heart rate <40 times/min or >120 times/min; new arrhythmia and myocardial ischemia.
3. Nervous system: decreased level of consciousness.

Psychological intervention

COVID-19 patients often demonstrate negative emotional stress responses like panic attacks, anxiety, and somatisation symptoms, affecting physical function, sleep, and overall mental health. For patients in the hospital, eliminating stressors, establishing a positive and optimistic mood through family and staff support, early psychological and behavioral interventions can help. These behavioral interventions can be complemented by appropriate pharmacotherapy.

For patients in the community and their families, mental health services play a role in avoiding panic and stress and establish a positive lifestyle and behavior. Provision of special psychological services for those who suffer from critical psychological events during the pandemic, such as family members' death, is also essential.

The mental well-being of staff should be periodically evaluated as the pandemic's stress can lead to depression, anxiety, lack of motivation and decreased performance. Teaching coping measures through education, knowledge about helplines, etc., helps staff manage their stress.

Other interventions

Occupational therapy (OT) focuses on ADL and strategies for independence and providing assistive technology and aids as needed. OT also addresses cognitive and psychological issues. Vocational rehab is crucial for improving the quality of life in COVID-19 survivors.

Speech-language pathologists assess and treat dysphagia and voice impairments resulting from prolonged intubation and may also address communication issues.

Education of patients and families about the disease, patients' condition, managing expectations of recovery, and self-management is vital for successful rehabilitation.

Discharge planning should also be done to facilitate the patient's movement and final disposition from the rehab unit.

Virtual Rehabilitation

Tele-consultation and services have made a massive impact in the medical services worldwide during the COVID-19 pandemic. It provided professional information, education, and practical solutions regarding COVID-19 and its management. It also enabled rehabilitation professionals to provide adequate psychosocial support and counselling services to patients and families⁴⁹.

Virtual care may be preferable to face-to-face interactions during the pandemic, considering easy community spread by the symptomatic or asymptomatic person. Virtual care allows personalized consultation and treatment via telephone or internet-based calling service. Pre-recorded sessions provide generic materials. Secure virtual purpose-built care platforms are preferred, but other means like Zoom, Skype, Facetime may be used. Limitations of VR include non-availability of seamless connectivity, technical malfunctions, the possibility of a personal data security breach, physical examination assessment difficulties (e.g., assessing tone), limitations of cognition, and the safety of mobility-impaired participants⁵⁰. The initial assessment should assess all these aspects before continuing with the tele-rehab.

Tele rehab services are now considered for cases that require milder interventions or for those who are well underway in their rehab process to ease the burden and avoid the spread of infections in outpatient services.

One emerging concept is pre-rehabilitation, which advocates rehabilitative interventions like smoking cessation, regular exercise, good nutrition, and stress reduction⁵¹.

Healthcare services must prepare for the rehabilitation pandemic, which is expected to follow the COVID-19 pandemic globally.

Increasing disabilities should lead to the planning of a more disability-inclusive society mindful of creating employment opportunities.

With telework becoming common, disabled persons can have better employment opportunities with support from companies and the government⁵².

Most of the information we have about the current pandemic is from early case reports and few controlled trials. As we look at the long-term disability associated with COVID-19, there is a need for further research and guidance regarding rehabilitation specific to COVID-19.

Challenges

1. New illness- SARS-CoV-2 is a new virus. The pathophysiology and clinical manifestations were mostly unknown, and hence the preventive and treatment protocol is updated continuously. Illness and infectivity duration was

- unknown initially, creating extended hospital stays and rehab admissions delays. The long-term effects were uncertain, and many patients developed permanent lung damage.
2. The magnitude of the pandemic- The scale of the pandemic was massive, and numbers kept on progressively increasing. The surge of cases was unforeseen. The acute medical services needed to ramp up its facilities by creating more ICU and hospital beds and redeploying more staff from non-acute services like rehab. This has strained rehab services, which were already strained by the rapid influx of patients from the acute side. This was overwhelming and pushed many rehab professionals to a stage of burnout.
 3. Wide case-mix: COVID-19 is a multisystem disease and has resulted in multisystem disabilities. Patients admitted with COVID-19 associated deconditioning, pulmonary dysfunction, critical illness neuropathy, stroke, etc., stayed for a longer duration than their counterparts without COVID-19.
 4. Lack of protocol- At the start of the pandemic, there was no definite protocol to deal with COVID-19 patients, their isolation, infection precautions, rehab program, etc., which contributed to a delay in their discharge. Initially, protocols for other illnesses were modified and used, which created uncertainty among rehab professionals. There were no specific functional measures or interventions to address this group of patients.
 5. Business continuity- continuity of the essential rehab services were affected by the pandemic. Many outpatient services were suspended, and people who routinely used those services could not access them. As social distancing mandated a limited number of patients in exercise areas, the rehab environment changed. There was a disruption in group therapy and recreational therapy, which affected rehabilitation outcomes in non-COVID-19 patients.
 6. Lack of services- The pandemic created an urgent need for a large number of pulmonary and cardiac rehabilitation services, which were not available, and the professionals who were specialised in those services were also sparse. Also, there was a lack of comprehensive guidelines on when to initiate pulmonary rehabilitation in COVID-19 patients due to the fear of disease spread.
 7. Infection risk- One of the main challenges in organising rehabilitation services is protecting against the spread of infections, from patient to health care provider or vice versa and between patients.
 8. Long-term health issues- While most COVID-19 patients recover without complications, around 20 per cent of those who suffered severe COVID-19 illness requiring hospitalisation need rehabilitation support for the physical, cognitive, and psychological consequences⁵⁰. Post intensive care syndromes and long COVID are increasingly recognised in COVID-19 survivors. Awareness about this possible long-term functional consequence is vital for primary care physicians for possible rehabilitation interventions. A dedicated COVID-19 clinic to evaluate and support these patients will help us understand this novel disease's long-term effects.
 9. Financial strain- COVID-19 pandemic has created tremendous financial strain, not only at the personal level but also for businesses, industries, and countries. People lost their livelihood and could not bear the medical expenses. Many of them left for their home country without undergoing rehabilitation.
 10. Psychological issues- The panic of the pandemic, isolation from the family due to travel restrictions, and quarantine have created psychological stress in many in the form of anxiety and depression. The long-term effects of such psychological stress are currently unknown.

As the COVID-19 evolves, so has our understanding of this novel disease. However, we are not in the clear, and its consequences are still being understood. Health care systems and professionals should be aware of and be prepared for long-term physical, cognitive, and psychological disabilities that impact function and life quality.

The rehabilitation professionals aid in achieving independence and help in integrating the individual into the community and society

References

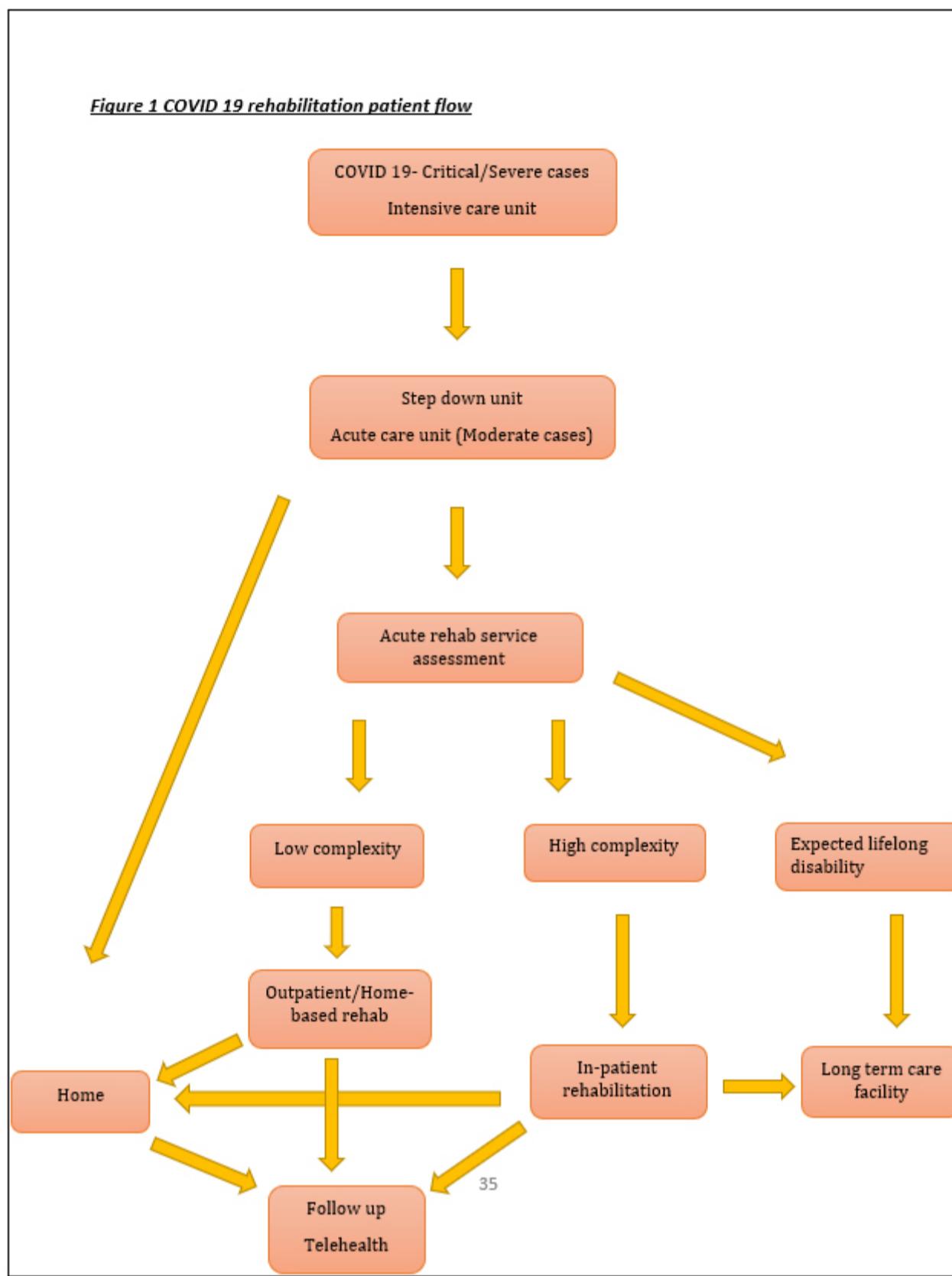
1. De Biase S, Cook L, Skelton DA, Witham M, Ten Hove R. The COVID-19 rehabilitation pandemic. *Age Ageing*. 2020;49(5):696-700. doi:10.1093/ageing/afaa118
2. Maya Sabatello, Scott D. Landes & Katherine E. McDonald (2020) People with Disabilities in COVID-19: Fixing Our Priorities, *The American Journal of Bioethics*, 20:7, 187-190, DOI: 10.1080/15265161.2020.1779396
3. <https://www.paho.org/en/documents/rehabilitation-considerations-during-covid-19-outbreak>
4. <https://www.bsrm.org.uk/downloads/covid-19bsrmissue2-11-5-2020-forweb11-5-20.pdf>
5. McGee, J. S., Meraz, R., Myers, D. R., & Davie, M. R. (2020). Telehealth services for persons with chronic lower respiratory disease and their informal caregivers in the context of the COVID-19 pandemic. *Practice Innovations*, 5(2), 165-177. <http://dx.doi.org/10.1037/pri0000122>
6. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, Walshaw C, Kemp S, Corrado J, Singh R, Collins T, O'Connor RJ, Sivan M. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol*. 2021 Feb;93(2):1013-1022. doi: 10.1002/jmv.26368. Epub 2020 Aug 17. PMID: 32729939.
7. Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, Dong W. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin Microbiol Infect*. 2021 Jan;27(1):89-95. doi: 10.1016/j.cmi.2020.09.023. Epub 2020 Sep 23. PMID: 32979574; PMCID: PMC7510771.
8. Goërtz YMJ, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FVC, Houben-Wilke S, Burtin C, Posthuma R, Franssen FME, van Loon N, Hajian B, Spies Y, Vijlbrief H, van 't Hul AJ, Janssen DJA, Spruit MA. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ Open Res*. 2020 Oct 26;6(4):00542-2020. doi: 10.1183/23120541.00542-2020. PMID: 33257910; PMCID: PMC7491255.
9. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, Lei C, Chen R, Zhong N, Li S. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J*. 2020 Jun 18;55(6):2001217. doi: 10.1183/13993003.01217-2020. PMID: 32381497; PMCID: PMC7236826
10. George PM, Barratt SL, Condliffe R, Desai SR, Devaraj A, Forrest I, Gibbons MA, Hart N, Jenkins RG, McAuley DF, Patel BV, Thwaite E, Spencer LG. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*. 2020 Nov;75(11):1009-1016. doi: 10.1136/thoraxjnl-2020-215314. Epub 2020 Aug 24. PMID: 32839287; PMCID: PMC7447111.
11. Carda S, Invernizzi M, Bavikatte G, Bensmail D, Bianchi F, Deltombe T, Draulans N, Esquenazi A, Francisco GE, Gross R, Jacinto LJ, Moraleda Pérez S, O'Dell MW, Reebye R, Verduzco-Gutierrez M, Wissel J, Molteni F. The role of physical and rehabilitation medicine in the COVID-19 pandemic: The clinician's

- view. *Ann Phys Rehabil Med.* 2020 Nov;63(6):554-556. doi: 10.1016/j.rehab.2020.04.001. Epub 2020 Apr 18. PMID: 32315802; PMCID: PMC7166018.
12. Beghi E, Feigin V, Caso V, Santalucia P, Logroscino G. COVID-19 Infection and Neurological Complications: Present Findings and Future Predictions. *Neuroepidemiology.* 2020;54(5):364-369. doi: 10.1159/000508991. Epub 2020 Jul 1. PMID: 32610334; PMCID: PMC7445369.
 13. Lechien JR, Chiesa-Estomba CM, De Sati DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S, El Afia F, Distinguin L, Chekkouri-Idrissi Y, Hans S, Delgado IL, Calvo-Henriquez C, Lavigne P, Falanga C, Barillari MR, Cammaroto G, Khalife M, Leich P, Souchay C, Rossi C, Journe F, Hsieh J, Edjlali M, Carlier R, Ris L, Lovato A, De Filippis C, Coppee F, Fakhry N, Ayad T, Saussez S. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol.* 2020 Aug;277(8):2251-2261. doi: 10.1007/s00405-020-05965-1. Epub 2020 Apr 6. PMID: 32253535; PMCID: PMC7134551.
 14. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* 2020 May 2;395(10234):1417-1418. doi: 10.1016/S0140-6736(20)30937-5. Epub 2020 Apr 21. PMID: 32325026; PMCID: PMC7172722.
 15. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, Franciotta D, Baldanti F, Daturi R, Postorino P, Cavallini A, Micieli G. Guillain-Barré Syndrome Associated with SARS-CoV-2. *N Engl J Med.* 2020 Jun 25;382(26):2574-2576. doi: 10.1056/NEJMc2009191. Epub 2020 Apr 17. PMID: 32302082; PMCID: PMC7182017.
 16. Zanin L, Saraceno G, Panciani PP, Renisi G, Signorini L, Migliorati K, Fontanella MM. SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neurochir (Wien).* 2020 Jul;162(7):1491-1494. doi: 10.1007/s00701-020-04374-x. Epub 2020 May 4. PMID: 32367205; PMCID: PMC7197630.
 17. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T. Neurological associations of COVID-19. *Lancet Neurol.* 2020 Sep;19(9):767-783. doi: 10.1016/S1474-4422(20)30221-0. Epub 2020 Jul 2. PMID: 32622375; PMCID: PMC7332267.
 18. Brodsky MB, Pandian V, Needham DM. Post-extubation dysphagia: a problem needing multi-disciplinary efforts. *Intensive Care Med.* 2020 Jan;46(1):93-96. doi: 10.1007/s00134-019-05865-x. Epub 2019 Nov 25. PMID: 31768568; PMCID: PMC7219527.
 19. Clavet H, Doucette S, Trudel G. Joint contractures in the intensive care unit: quality of life and function 3.3 years after hospital discharge. *Disabil Rehabil.* 2015;37(3):207-13. doi: 10.3109/09638288.2014.913707. Epub 2014 May 2. PMID: 24787236.
 20. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, González E, Redondo-Peñas I, Perona-Moratalla AB, Del Valle-Pérez JA, Gracia-Gil J, Rojas-Bartolomé L, Feria-Vilar I, Monteagudo M, Palao M, Palazón-García E, Alcahut-Rodríguez C, Sopelana-Garay D, Moreno Y, Ahmad J, Segura T. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology.* 2020 Aug 25;95(8):e1060-e1070. doi: 10.1212/WNL.0000000000009937. Epub 2020 Jun 1. PMID: 32482845; PMCID: PMC7668545.
 21. Rabiee A, Nikayin S, Hashem MD, Huang M, Dinglas VD, Bienvenu OJ, Turnbull AE, Needham DM. Depressive Symptoms After Critical Illness: A Systematic Review and Meta-Analysis. *Crit Care Med.* 2016 Sep;44(9):1744-53. doi: 10.1097/CCM.0000000000001811. PMID: 27153046; PMCID: PMC7418220.
 22. Nikayin S, Rabiee A, Hashem MD, Huang M, Bienvenu OJ, Turnbull AE, Needham DM. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. *Gen Hosp Psychiatry.* 2016 Nov-Dec; 43:23-29. doi: 10.1016/j.genhosppsych.2016.08.005. Epub 2016 Aug 28. PMID: 27796253; PMCID: PMC5289740.
 23. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, Wu J, Du H, Chen T, Li R, Tan H, Kang L, Yao L, Huang M, Wang H, Wang G, Liu Z, Hu S. Factors Associated with Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019. *JAMA Netw Open.* 2020 Mar 2;3(3): e203976. doi: 10.1001/jamanetworkopen.2020.3976. PMID: 32202646; PMCID: PMC7090843.
 24. Xiang YT, Yang Y, Li W, Zhang L, Zhang Q, Cheung T, Ng CH. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. *Lancet Psychiatry.* 2020 Mar;7(3):228-229. doi: 10.1016/S2215-0366(20)30046-8. Epub 2020 Feb 4. PMID: 32032543; PMCID: PMC7128153.
 25. Holmes EA, O'Connor RC, Perry VH, Tracey I, Wessely S, Arseneault L, Ballard C, Christensen H, Cohen Silver R, Everall I, Ford T, John A, Kabir T, King K, Madan I, Michie S, Przybylski AK, Shafran R, Sweeney A, Worthman CM, Yardley L, Cowan K, Cope C, Hotopf M, Bullmore E. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. *Lancet Psychiatry.* 2020 Jun;7(6):547-560. doi: 10.1016/S2215-0366(20)30168-1. Epub 2020 Apr 15. PMID: 32304649; PMCID: PMC7159850.
 26. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ.* 2020 Aug 11;370:m3026. doi: 10.1136/bmj.m3026. PMID: 32784198.
 27. Halpin S, O'Connor R, Sivan M. Long COVID and chronic COVID syndromes. *J Med Virol.* 2020 Oct 9:10.1002/jmv.26587. doi: 10.1002/jmv.26587. Epub ahead of print. PMID: 33034893; PMCID: PMC7675759.
 28. <https://bestpractice.bmjjournals.com/topics/en-us/3000168/guidelines>
 29. Wade DT. Rehabilitation after COVID-19: an evidence-based approach. *Clin Med (Lond).* 2020 Jul;20(4):359-365. doi: 10.7861/clinmed.2020-0353. Epub 2020 Jun 9. PMID: 32518105; PMCID: PMC7385804.
 30. Monaghesh E, Hajizadeh A. The role of telehealth during COVID-19 outbreak: a systematic review based on current evidence. *BMC Public Health.* 2020;20(1):1193. Published 2020 Aug 1. doi:10.1186/s12889-020-09301-4
 31. Sacco G, Lléonart S, Simon R, Noublanche F, Annweiler C; TOVID Study Group. Communication Technology Preferences of Hospitalized and Institutionalized Frail Older Adults During COVID-19 Confinement: Cross-Sectional Survey Study. *JMIR Mhealth Uhealth.* 2020 Sep 18;8(9):e21845. doi: 10.2196/21845. PMID: 32896832; PMCID: PMC7518882.
 32. <https://www.moph.gov.qa/Style%20Library/MOPH/Videos/COVID-19%20REPORT%20WEB.pdf>
 33. Klok FA, Boon GJAM, Barco S, Endres M, Geelhoed JJM, Knauss S, Rezek SA, Spruit MA, Vehreschild J, Siegerink B. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. *Eur Respir J.* 2020 Jul 2;56(1):2001494. doi: 10.1183/13993003.01494-2020. PMID: 32398306; PMCID: PMC7236834.
 34. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, Make B, Rochester CL, Zuwallack R, Herreras C. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest.* 2007 May;131(5 Suppl):4S-42S. doi: 10.1378/chest.06-2418. PMID: 17494825.
 35. <http://www.unify-cr.cz/obrazky-soubory/covid-recommendations-kgnf-8deed.pdf>
 36. Bolton L, Mills C, Wallace S, Brady MC; Royal College of Speech and Language Therapists (RCSLT) COVID-19 Advisory Group. Aerosol generating procedures, dysphagia assessment and COVID-19: A rapid review. *Int J Lang Commun Disord.* 2020 Jul;55(4):629-636. doi: 10.1111/1460-6984.12544. Epub 2020 Jun 1. PMID: 32478950; PMCID: PMC7300802.
 37. Ustun G. Determining depression and related factors in a society affected by COVID-19 pandemic. *The International Journal of Social Psychiatry.* 2020 Jun;20764020938807. DOI: 10.1177/0020764020938807.
 38. Brugliera L, Spina A, Castellazzi P, Cimino P, Arcuri P, Negro A, Houdayer E, Alemano F, Giordani A, Mortini P, Iannaccone S. Nutritional management of COVID-19 patients in a rehabilitation unit. *Eur J Clin Nutr.* 2020 Jun;74(6):860-863. doi: 10.1038/s41430-020-0664-x. Epub 2020 May 20. PMID: 32433599; PMCID: PMC7237874.
 39. McGee, J. S., Meraz, R., Myers, D. R., & Davie, M. R. (2020). Telehealth services for persons with chronic lower respiratory disease and their informal caregivers in the context of the COVID-19 pandemic. *Practice Innovations,* 5(2), 165-177. <http://dx.doi.org/10.1037/pri0000122>
 40. NahmNahtam Newsletter (Issue 6, July, 2020). Publication of HMC. <http://itawasol>

41. Zeng B, Chen D, Qiu Z, Zhang M, Wang G; Rehabilitation Group of Geriatric Medicine branch of Chinese Medical Association, division of Management of Medical Rehabilitation Institution of Chinese Hospital Association, Rehabilitation Institution Management division of Chinese Rehabilitation Medical Association, division of Rehabilitation Psychology, Chinese Psychological Association, division of Disability Classification Research, Chinese Association of Rehabilitation of Disabled Persons, Wang J, Yu P, Wu X, An B, Bai D, Chen Z, Deng J, Guo Q, He C, Hu X, Huang C, Huang Q, Huang X, Huang Z, Li X, Liang Z, Liu G, Liu P, Ma C, Ma H, Mi Z, Pan C, Shi X, Sun H, Xi J, Xiao X, Xu T, Xu W, Yang J, Yang S, Yang W, Ye X, Yun X, Zhang A, Zhang C, Zhang P, Zhang Q, Zhao M, Zhao J. Expert consensus on protocol of rehabilitation for COVID-19 patients using framework and approaches of WHO International Family Classifications. *Aging Med (Milton)*. 2020 Jul 6;3(2):82-94. doi: 10.1002/agm2.12120. PMID: 32666026; PMCID: PMC7338700.
42. Turner-Stokes L, Bill A, Dredge R. A cost analysis of specialist in-patient neurorehabilitation services in the UK. *Clin Rehabil*. 2012 Mar;26(3):256-63. doi: 10.1177/0269215511417469. Epub 2011 Oct 5. PMID: 21975469.
43. Herridge MS, Moss M, Hough CL, Hopkins RO, Rice TW, Bienvenu OJ, Azoulay E. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. *Intensive Care Med*. 2016 May;42(5):725-738. doi: 10.1007/s00134-016-4321-8. Epub 2016 Mar 30. PMID: 27025938.
44. Chinese Association of Rehabilitation Medicine; Respiratory Rehabilitation Committee of Chinese Association of Rehabilitation Medicine; Cardiopulmonary Rehabilitation Group of Chinese Society of Physical Medicine and Rehabilitation. [Recommendations for respiratory rehabilitation of coronavirus disease 2019 in adult]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2020 Apr 12;43(4):308-314. Chinese. doi: 10.3760/cma.j.cn112147-20200228-00206. PMID: 32294814.
45. Green M, Marzano V, Leditschke IA, Mitchell I, Bissett B. Mobilization of intensive care patients: a multi-disciplinary practical guide for clinicians. *J Multidiscip Healthc*. 2016 May 25;9:247-56. doi: 10.2147/JMDH.S99811. PMID: 27307746; PMCID: PMC4889100.
46. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009 May 30;373(9678):1874-82. doi: 10.1016/S0140-6736(09)60658-9. Epub 2009 May 14. PMID: 19446324.
47. Vitacca M, Carone M, Clini EM, Paneroni M, Lazzeri M, Lanza A, Privitera E, Pasqua F, Gigliotti F, Castellana G, Banfi P, Guffanti E, Santus P, Ambrosino N; ITS - AIPO, the ARIR and the SIP/IRS. Joint Statement on the Role of Respiratory Rehabilitation in the COVID-19 Crisis: The Italian Position Paper. *Respiration*. 2020;99(6):493-499. doi: 10.1159/000508399. Epub 2020 May 19. PMID: 32428909; PMCID: PMC7316664.
48. Lau HM, Ng GY, Jones AY, Lee EW, Siu EH, Hui DS. A randomised controlled trial of an exercise training program's effectiveness in patients recovering from severe acute respiratory syndrome. *Aust J Physiother*. 2005;51(4):213-9. doi: 10.1016/s0004-9514(05)70002-7. PMID: 16321128; PMCID: PMC7130114.
49. Evans YN, Golub S, Sequeira GM, Eisenstein E, North S. Using Telemedicine to Reach Adolescents During the COVID-19 Pandemic. *J Adolesc Health*. 2020 Oct;67(4):469-471. doi: 10.1016/j.jadohealth.2020.07.015. Epub 2020 Aug 5. PMID: 32768330; PMCID: PMC7403159.
50. Simpson R, Robinson L. Rehabilitation After Critical Illness in People With COVID-19 Infection. *Am J Phys Med Rehabil*. 2020 Jun;99(6):470-474. doi: 10.1097/PHM.0000000000001443. PMID: 32282359; PMCID: PMC7253039.
51. Silver JK. Prehabilitation could save lives in a pandemic. *BMJ*. 2020 Apr 6;369:m1386. doi: 10.1136/bmj.m1386. PMID: 32253187.
52. Moon NW, Linden MA, Bricout JC, Baker PM. Telework rationale and implementation for people with disabilities: considerations for employer policymaking. *Work*. 2014;48(1):105-15. doi: 10.3233/WOR-131819. PMID: 24346279.

Phase of care	Rehabilitation interventions	Provider
Acute phase (ICU/Ventilatory support)	Interventions to improve oxygenation, airway secretion clearance, ventilation weaning, tracheostomy care, aspiration prevention	Respiratory therapist Physiotherapist
	Nutrition optimization	Dietician
Subacute phase (Step down/Hospital ward)	Addressing ongoing impairments in mobility, respiratory function, cognition, swallow, nutrition, and communication Promote independence with activities of daily living Provide psychosocial support	Multi-disciplinary team
Long term phase (Rehabilitation centers, outpatient programs, mobile and home health service, telemedicine service)	Graded exercise programs, education on energy conservation and behavior modification, home modification, and assistive aids, rehabilitation for any specific individual impairments	Multi-disciplinary team
	Pulmonary rehabilitation interventions	The specialized pulmonary rehabilitation team

Table 1 Rehabilitation interventions in different phases of care

**Figure 1 COVID 19 rehabilitation patient flow**

Appendix-1**Appendix-1**