The Daily COVID-19 Literature Surveillance Summary

August 31, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Epidemiology

- Smoking Is Associated With COVID-19 Progression: A Meta-analysis: Authors affiliated with University of California, San Francisco and Mahidol University conducted a meta-analysis (n= 19 studies between January 1 and April 28, 2020 from China, U.S., and Korea) of 11,590 total patients with COVID-19 and found that 731 of these patients reported a history of smoking. Of these 731 patients, 29.8% (n=218) were found to have progression of their COVID-19, while only 17.6% of non-smokers were noted to have disease progression. Additionally, a significant relationship between smoking and COVID-19 progression was observed (OR: 1.91, 95% Cl: 1.42-2.59, p = 0.001; Figure 1). The authors support smoking cessation as a reasonable practice during this time, although further investigation is needed on COVID-19 progression in current versus former smokers to support the claim that smoking cessation can stunt the pandemic.

- Household Composition May Explain COVID-19 Racial/Ethnic Disparities: A summary of a study by the Agency for Healthcare Research and Quality (U.S.), written by JAMA scientific news writer Rita Rubin, MA, explains that the higher observed death rates from COVID-19 in Black and Hispanic patients compared to White patients may be due to differences in exposure to the virus from work. A simple analysis of risk factors (e.g. age and preexisting conditions) does not explain the ethnic/racial disparities in COVID-19 death rates, but it may be explained by the fact that Black and Hispanic individuals are more frequently employed in a job where in-person essential work is required compared to White individuals. This suggests that amount of viral exposure may be linked to differential death rates among ethnic/racial groups.

Management

- Marked factor V activity elevation in severe COVID-19 is associated with venous thromboembolism: Pathologists from the Massachusetts General Hospital conducted a prospective cohort study of 102 patients with severe COVID-19 in March through April 2020, showing elevated Factor V activity at unprecedented levels in the hospital's history (median 150 IU/dL with 16% of values above 200 IU/dL), which was associated with thromboembolitic complications (Figure 1). The authors suggest Factor V levels may serve as an important diagnostic and prognostic marker for COVID-19, and recommend further investigation of increased anticoagulation doses for prophylaxis in patients with severe COVID-19 and markedly elevated Factor V activity.

- Heart Failure In Covid-19 Patients: Prevalence, Incidence And Prognostic Implications: Researchers within the departments of cardiology, clinical analytics, and pharmacy at the Hospital Universitario La Paz, Spain performed a single-center, retrospective study on 3,080 COVID-19-positive patients (with a 30-day or more follow-up) and heart failure. Based on this study's findings (illustrated below), the authors suggest maintaining heart failure guideline directed medical therapy (GDMT) when possible or re-instituting these regimens at discharge.

Adjusting Practice During COVID-19

- A Novel Non-contact Self-Injection-Locked Radar for Vital Sign Sensing and Body Movement Monitoring in COVID-19 Isolation Ward: A case series of two patients with COVID-19 in hospital isolation, conducted at Kaohsiung Medical University Hospital in Taiwan, investigated the accuracy of patient vitals collected by a novel contactless device, a non-contact self-injection-locked radar (Figure 1), compared to a nurse's vital sign testing. Over the course of patient isolation (13 days and 5 days), the patients' temperatures and heart rates were insignificantly different between the device's and nurse's measurements. This novel device needs to be tested on a larger sample size to prove its effectiveness and may need to record other vitals to be useful, but the use of a contactless way of recording vitals will be of high utility in the future due to ability to monitor infectious patients from a distance.

R&D: Diagnosis & Treatments

- Hydroxychloroquine for treatment of non-severe COVID-19 patients; systematic review and meta-analysis of controlled clinical trials: Researchers in Biostatistics, Human Data Science, and Neuropsychiatry located in Egypt performed a meta-analysis of clinical trials of hydroxychloroquine for patients with COVID-19 between June up to July-18, 2020. Their findings were (Figure 4):

    - Progression of disease (within 28 days) between the two groups (those treated with hydroxychloroquine and those not treated) was not statistically significant, with risk difference (RD) -0.00 (-0.04 to 0.04)
    - Mortality at five days was not statistically significant, with RD 0.01 (-0.01 to 0.03).
    - Mortality at 28 days was not statistically significant, with RD 0.00 (-0.01 to 0.01).
    - Radiological progression gauged by CT scan was statistically significant with RD of -0.2 (-0.36 to -0.03).
    - Viral clearance as measured via pharyngeal swab showed no statistically significant differences between the groups

with RD of 0.04 (-0.1 to 0.18).

These findings show that the use of hydroxychloroquine has no additional clinical benefit that would outweigh the risk profile of this drug and has little viral clearance.

- Large Simple Double-Blind Randomized Trials for the Rapid Assessment of the Effectiveness of COVID-19 Vaccines: An ethicist affiliated with the Institute for Medical Information Processing, Biometry, and Epidemiology at the University of Munich in Germany responds to the human challenge study by Eyal et al (2020) to accelerate coronavirus vaccine licensure. The author raises concerns about inherent sampling bias and ethical issues of the proposed challenge trials for COVID-19, citing the study design's need for young, healthy participants without definitive knowledge of risk factors for severe or fatal complications of COVID-19 and the lack of an effective and safe treatment to avoid any adverse consequence. The author instead proposes the large, simple, randomized trial (LSRT) as an alternative to the challenge trial because the LSRT allows for a wide eligibility criteria with large sample sizes and short-term treatment with minimal follow-up, suggesting LSRTs may yield more representative data than the exclusive challenge trials.

TABLE OF CONTENTS

EPIDEMIOLOGY

SMOKING IS ASSOCIATED WITH COVID-19 PROGRESSION: A META-ANALYSIS

Patanavanich R, Glantz SA.. Nicotine Tob Res. 2020 Aug 24;22(9):1653-1656. doi: 10.1093/ntr/ntaa082.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

Authors affiliated with University of California, San Francisco and Mahidol University conducted a meta-analysis (n= 19 studies between January 1 and April 28, 2020 from China, U.S., and Korea) of 11,590 total patients with COVID-19 and found that 731 of these patients reported a history of smoking. Of these 731 patients, 29.8% (n=218) were found to have progression of their COVID-19, while only 17.6% of non-smokers were noted to have disease progression. Additionally, a significant relationship between smoking and COVID-19 progression was observed (OR: 1.91, 95% Cl: 1.42-2.59, p = 0.001; Figure 1). The authors support smoking cessation as a reasonable practice during this time, although further investigation is needed on COVID-19 progression in current versus former smokers to support the claim that smoking cessation can stunt the pandemic.

FIGURES

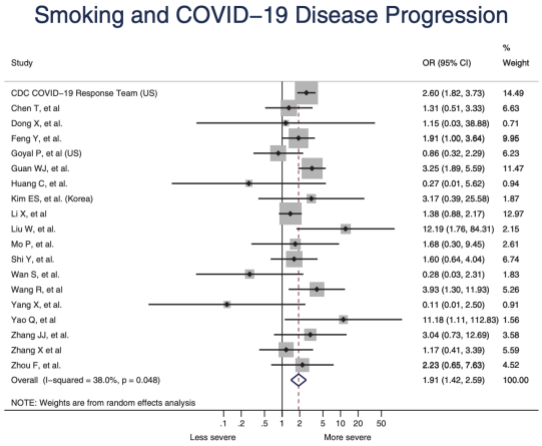

Figure 1. Smoking is associated with COVID-19 progression. All papers from China unless otherwise indicated. CI = confidence interval; OR = odds ratio.

HOUSEHOLD COMPOSITION MAY EXPLAIN COVID-19 RACIAL/ETHNIC DISPARITIES

Rubin R.. JAMA. 2020 Aug 25;324(8):732. doi: 10.1001/jama.2020.14375.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

A summary of a study by the Agency for Healthcare Research and Quality (U.S.), written by JAMA scientific news writer Rita Rubin, MA, explains that the higher observed death rates from COVID-19 in Black and Hispanic patients compared to White patients may be due to differences in exposure to the virus from work. A simple analysis of risk factors (e.g. age and preexisting conditions) does not explain the ethnic/racial disparities in COVID-19 death rates, but it may be explained by the fact that Black and Hispanic individuals are more frequently employed in a job where in-person essential work is required compared to White individuals. This suggests that amount of viral exposure may be linked to differential death rates among ethnic/racial groups.

MODELING

STRATEGIES AT POINTS OF ENTRY TO REDUCE IMPORTATION RISK OF COVID-19 CASES AND RE-OPEN TRAVEL

Dickens BL, Koo JR, Lim JT, Sun H, Clapham HE, Wilder-Smith A, Cook AR.. J Travel Med. 2020 Aug 25:taaa141. doi: 10.1093/jtm/taaa141. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

In this epidemiological modeling study, public and global health experts collected incidence and mortality data from 153 countries between January 22 and August 6, 2020 and report importation risk reduction strategies including testing all arriving travelers from countries with ongoing COVID-19 transmission and isolating COVID-19 positive travelers for 14 days with release to community only after a negative test would be most effective in minimizing case importation. Authors suggest that these policies be implemented (assuming adequate testing practices are in place) to reduce COVID-19 transmission on a global scale.

SUMMARY

Summary of six COVID-19 importation reduction strategies explored by authors (Figures 2,3):
1. No screening; all other models were compared against this strategy to determine how effectively they reduced case importation.
2. Screening all incoming travelers and 7-day isolation for test-positive travelers with release into the community only after a negative test is identified. This strategy reduced case importation by 90.2%.
3. Screening all incoming travelers and 14-day isolation for test-positive travelers with release into the community only after a negative test is identified. This was the most effective strategy and reduced case importation by 91.7%.
4. No screening with 7-day mandatory quarantine for all travelers. This strategy reduced case importation by 55.4%.
5. No screening with 14-day mandatory quarantine for all travelers. This strategy reduced case importation by 91.2% and could prove to be highly effective in countries where testing is not feasible.
6. Screening all passengers and entry prohibited for those testing positive. The strategy reduced case importation by 77.2%.
The authors also report an average of 79.6% of infected travelers are expected to be infectious upon arrival to the destination country (Figure 4).

ABSTRACT

BACKGROUND: With more countries exiting lockdown, public health safety requires screening measures at international travel entry points which can prevent the reintroduction or importation of the SARS-CoV-2 virus. Here, we estimate the number of cases captured, quarantining days averted and secondary cases expected to occur with screening interventions. METHODS: To estimate active case exportation risk from 153 countries with recorded COVID-19 cases and deaths, we created a simple data-driven framework to calculate the number of infectious and upcoming infectious individuals out of 100 000 000 potential travellers from each country, and assessed six importation risk reduction strategies; Strategy 1 (S1) has no screening on entry, S2 tests all travellers and isolates test positives where those who test negative at 7 days are permitted entry, S3 the equivalent but for a 14 day period, S4 quarantines all travellers for 7 days where all are subsequently permitted entry, S5 the equivalent for 14 days and S6 the testing of all travellers and prevention of entry for those who test positive. RESULTS: The average reduction in case importation across countries relative to S1 is 90.2% for S2, 91.7% for S3, 55.4% for S4, 91.2% for S5 and 77.2% for S6. An average of 79.6% of infected travellers are infectious upon arrival. For the top 100 exporting countries, an 88.2% average reduction in secondary cases is expected through S2 with the 7-day isolation of test positives, increasing to 92.1% for S3 for 14-day isolation. A substantially smaller reduction of 30.0% is expected for 7-day all traveller quarantining, increasing to 84.3% for 14-day all traveller quarantining. CONCLUSIONS: The testing and isolation of test positives should be implemented provided good testing practices are in place. If testing is not feasible, quarantining for a minimum of 14 days is recommended with strict adherence measures in place.

FIGURES

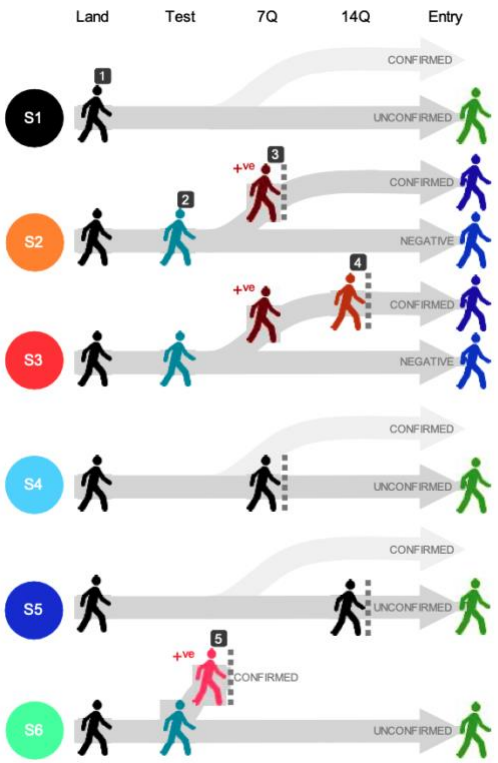

Figure 2. Depiction of scenarios (S1–S6) and outcomes, which are labelled and colour coded. Individuals who land or receive no testing measures in Strategy 1, 4 and 5 are displayed as (1) in dark grey. Individuals who land and are tested in Strategy 2, 3 and 6 are presented as (2) in blue and those who are tested positive and quarantined for at least 7 days are shown as (3) in red. For Strategy 3, individuals who are tested and remain quarantined until 14 days are represented as (4) in orange. For Strategy 6, individuals who are denied entry when tested upon landing are presented as (5) in pink. Dark grey routes represent active pathways on arrival and light grey signify inactive routes where no testing is conducted. A dotted line signifies the denial of entry up to that timepoint or complete denial of entry for Strategy 6. For Strategy 4 and 5, quarantine measures are in place at 7 days and 14 days, respectively, and for Strategy 2 and 3, isolation measures are in place for those who test positive. At the end time point, individuals who tested positive and have been cleared (purple), tested negative (dark blue) and are unconfirmed (green) are presented.

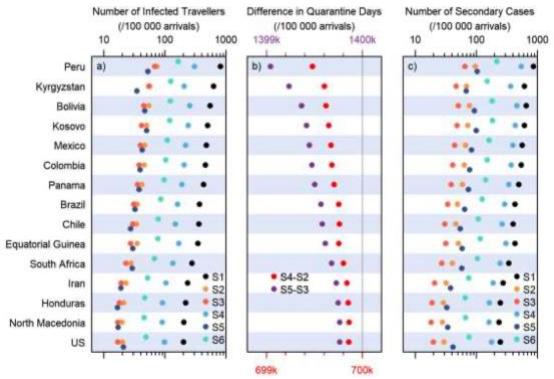

Figure 3. Panel a) shows the estimated number of infected travellers per 100 000 arrivals from countries of origin on a logarithmic scale, panel b) the differences in quarantine days between Strategy 2 (7 day isolation) and Strategy 4 (7 day quarantine), and Strategy 3 (14 day isolation) and Strategy 5 (14 day quarantine) and panel c) the number of secondary cases estimated to occur as individuals are permitted entry according to the travellers' infectious time remaining.

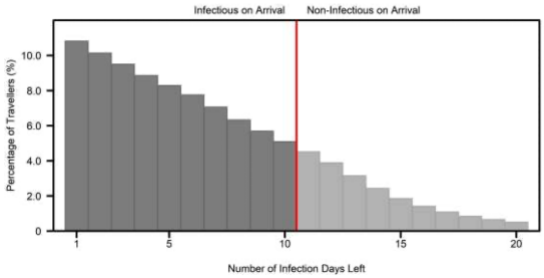

Figure 4. The number of infection days left shown as a proportion among travelers arriving. Those who are infectious on arrival are in dark grey, and those who are not infectious yet are in light grey.

IMMUNE ALTERATIONS IN A PATIENT WITH SARS-COV-2-RELATED ACUTE RESPIRATORY DISTRESS SYNDROME

Bouadma L, Wiedemann A, Patrier J, Surénaud M, Wicky PH, Foucat E, Diehl JL, Hejblum BP, Sinnah F, de Montmollin E, Lacabaratz C, Thiébaut R, Timsit JF, Lévy Y.. J Clin Immunol. 2020 Aug 22. doi: 10.1007/s10875-020-00839-x. Online ahead of print.
Level of Evidence: Other - Case Report

BLUF

A longitudinal analysis of the immune response in a fatal case report of an 80-year-old male COVID-19 patient admitted at Bichat Claude Bernard ICU with repeatedly positive RT-PCR tests via nasopharyngeal, blood, and pleural samples despite receiving remdesivir and interferon β-1a (Figure 1). They found an increase in differentiated effector memory CD4+, CD8+T cells expressing PD1/CD57 (exhaustion/senescent) markers, γδ T-cells (15-fold rise), expansion of antibody secreting cells (ASC) and Th1/Th2 pro-inflammatory cytokine storm. These observed immune alterations indicate the need for further studies aimed at the following: controlling viral replication to minimize hyper-inflammation, and using immunomodulators targeting cytokine storm (Figures 2, 3).

SUMMARY

A longitudinal analysis of an 80-year-old male patient who repeatedly tested positive for COVID-19 by RT-PCR via nasopharyngeal, blood, and pleural samples:

The patient visited the emergency department after 3 days of fever and diarrhea and presented with dyspnea with purulent sputum. On examination, O2sat: 88% on ambient air, pulse: 65/min, BP: 132/82 mmHg, RR: 17 breaths/min. Since he did not meet the SARS-CoV-2 criteria by ECDC, he was diagnosed with community-acquired pneumonia and treated with amoxicillin-clavulanate. On day 5, he was transferred to ICU due to acute respiratory failure and subsequently developed multi-organ failure with ARDS. On day 7, he was diagnosed with COVID-19 and treated with remdesivir. CT scan on day 10 showed bilateral pleuro-pneumopathy with pleural effusions and ground-glass opacities. Interferon β-1a was administered on day 23 and the patient died the next day (Figure 1).

They quantified 72 serum analytes of this patient compared to 5 healthy donors (HD) and 5 septic shock (SS) patients, and found alterations in immune responses as follows (Figures 2 ,3):

- Increase in effector memory CD4+, CD8+ T cells, and low naive CD4+, CD8+T cells (IQR 42.9% [35.3–49.8] and 29.5% [13.4–45], respectively) relative to that of 5 HDs.
- Higher frequency of T cells expressing senescent (CD57) and exhausted (PD1) markers.
- 15-fold rise of γδ T cells expressing CD16 and not NKG2A.
- Increase in activated memory B cells, antibody-secreting cells (24.1 and 34.3%, respectively) than that in HD (2.6% [2.1–3.8] and 0.32% [0.25–0.75], respectively).
- Higher frequency of pro-inflammatory cytokines, activation of Th1/Th2 immunomodulators than that in HD/SS patients.
- Proliferation of NK cells, subsequent disappearance, low to undetectable monocytes suggesting lung trafficking.
- Higher levels of biomarkers of cytotoxicity, apoptosis, and endothelial activation (MIG, VEGF, IL-7, Granzyme B, GRO-a, PDGF-BB, RANTES, etc).

ABSTRACT

We report a longitudinal analysis of the immune response associated with a fatal case of COVID-19 in Europe. This patient exhibited a rapid evolution towards multiorgan failure. SARS-CoV-2 was detected in multiple nasopharyngeal, blood, and pleural samples, despite antiviral and immunomodulator treatment. Clinical evolution in the blood was marked by an increase (2-3-fold) in differentiated effector T cells expressing exhaustion (PD-1) and senescence (CD57) markers, an expansion of antibody-secreting cells, a 15-fold increase in gammadelta T cell and proliferating NK-cell populations, and the total disappearance of monocytes, suggesting lung trafficking. In the serum, waves of a pro-inflammatory cytokine storm, Th1 and Th2 activation, and markers of T cell exhaustion, apoptosis, cell cytotoxicity, and endothelial activation were observed until the fatal outcome. This case underscores the need for well-designed studies to investigate complementary approaches to control viral replication, the source of the hyperinflammatory status, and immunomodulation to target the pathophysiological

response. The investigation was conducted as part of an overall French clinical cohort assessing patients with COVID-19 and registered in clinicaltrials.gov under the following number: NCT04262921.

FIGURES

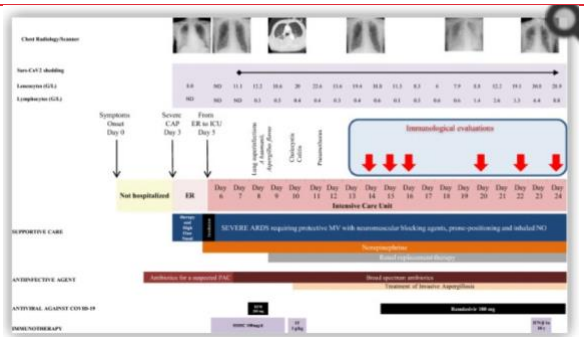

Figure 1: Timeline from arrival in Europe to death in the ICU. Upper panels summarize the clinical, biological (leucocyte and lymphocyte counts), and radiological data of the patient. Lower panels indicate the support, anti-infectious, and immunomodulatory treatments received by the patient throughout his hospitalization. The timing of immunological evaluations is indicated by the red arrows. TA, tracheal aspirate; SOFA, sepsis-related organ failure assessment; CAP, community acquired-pneumonia; MV, mechanical ventilation; NO, nitric oxide; REM, remdesivir; HSCH, hydrocortisone hemisuccinate; IT, immunoglobulin therapy; IFN β1a, interferon β1a.

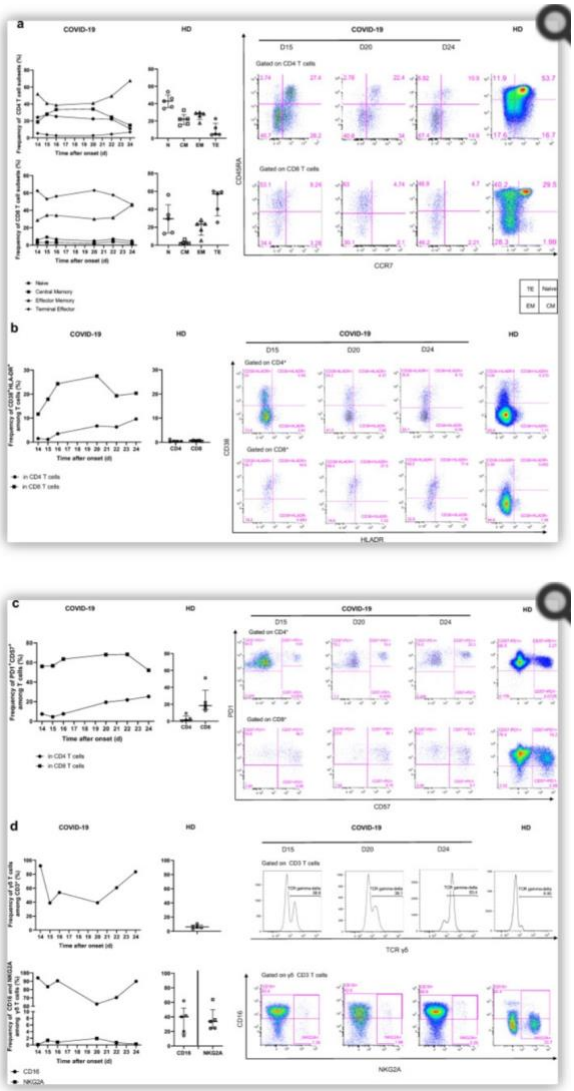

Figure 2: Kinetics and activation status of immune-cell subsets throughout the infection. a–c Frequency (left set of plots) of CD4 and CD8 T cell subsets (CD45RA+CCR7+: naïve (N), CD45RA+CCR7−: central memory (CM), CD45RA−CCR7−: effector

memory (EM), CD45RA+CCR7−: terminal effector (TE)) (a), activated CD38+HLADR+ (b), and exhausted PD1+CD57+ CD4 and CD8 T cells (c). d Frequency of γδ T cells (gated on CD3+ T cells) and CD16 and NKG2A expression (gated on γδ CD3 T cells).

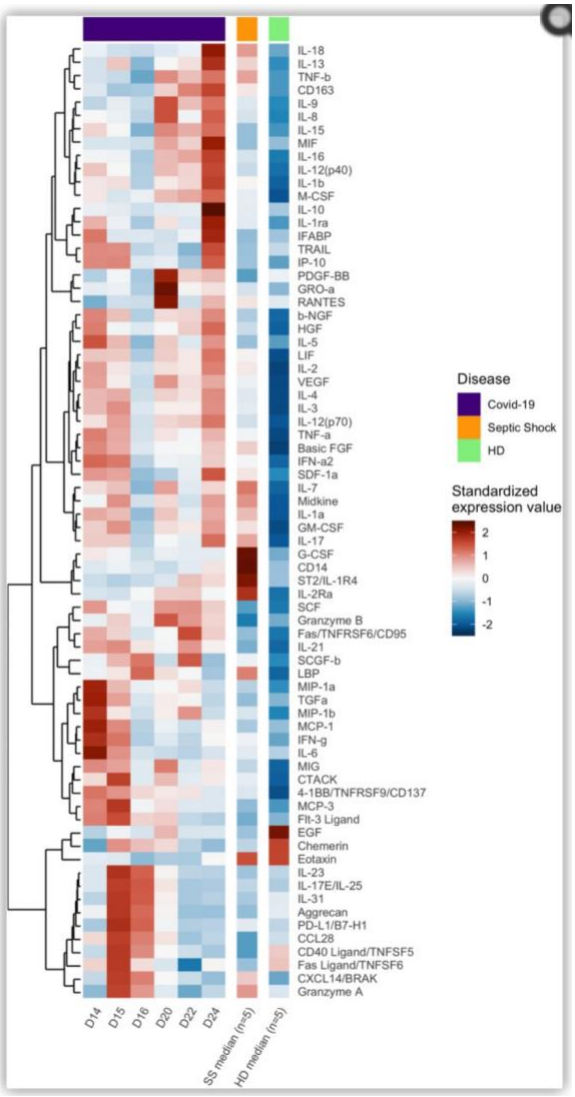

Figure 3: Heatmap of standardized biomarker expression in serum throughout the infection. The colors represent standardized expression values centered around the mean, with variance equal to 1. Biomarker hierarchical clustering was computed using the Euclidean distance and Ward's method [11]. HD, healthy donors (n = 5); SS, septic shock (n = 5).

COVID-19 OUTBREAK AND HOSPITAL AIR QUALITY: A SYSTEMATIC REVIEW OF EVIDENCE ON AIR FILTRATION AND RECIRCULATION

Mousavi E, Kananizadeh N, Martinello R, Sherman J.. Environ Sci Technol. 2020 Aug 26. doi: 10.1021/acs.est.0c03247. Online ahead of print.

Level of Evidence: 1 - Systematic review of randomized trials

BLUF

An interdisciplinary group of researchers performed a systematic literature review of 109 publications (Figure 4) about the safety implications of air filtration and circulation in healthcare facilities. The authors determined that:

- HEPA filtration is valuable in the filtration of submicron particles, such as SARS-CoV-2
- Combination HEPA/air recirculation is especially effective in mitigating growth of bacterial colonies and surrogate particulate matters (Table 4)
- Portable HEPA filtration has shown to help decrease viral load (Table 4)
- Novel combination of portable HEPA placement, with air discharge into a portable anteroom can both achieve reduction in viral load of a virus while simultaneously achieving the benefit of containment of the virus.

These findings suggest that enhanced air quality can be achieved within healthcare facilities using HEPA filtration methods to enhance patient and worker safety during times of normal functioning and health pandemics.

ABSTRACT

The outbreak of SARS-CoV-2 has made us all think critically about hospital indoor air quality and the approaches to remove, dilute, and disinfect pathogenic organisms from the hospital environment. While specific aspects of the coronavirus infectivity, spread, and its routes of transmission are still under rigorous investigation, it seems that a recollection of knowledge from the literature can provide useful lessons to cope with this new situation. As a result, a systematic literature review was conducted on the safety of air filtration and air recirculation in healthcare premises. This review targeted a wide range of evidence from codes and regulations, to peer-reviewed publications, and best practice standards. The literature search resulted in 394 publications, of which 109 documents were included in the final review. Overall, even though solid evidence to support current practice is very scarce, proper filtration remains one important approach to maintain the cleanliness of indoor air in hospitals. Given the rather large physical footprint of the filtration system, a range of short-term, and long term solutions from the literature are collected. Nonetheless, there is a need for a rigorous and feasible line of research in the area of air filtration and recirculation in healthcare facilities. Such efforts can enhance the performance of healthcare facilities under normal conditions or during a pandemic. Past innovations can be adopted for the new outbreak at low-to-minimal cost.

FIGURES

TODO: ERROR EMBEDDING IMAGE: https://covid19lst.qualtrics.com/jfe/file/F_2AEigrPxJWF3hGl

Table 4 Summary of Select Publications on Filtration in Healthcare Settings. Data are Presented in Chronological Order

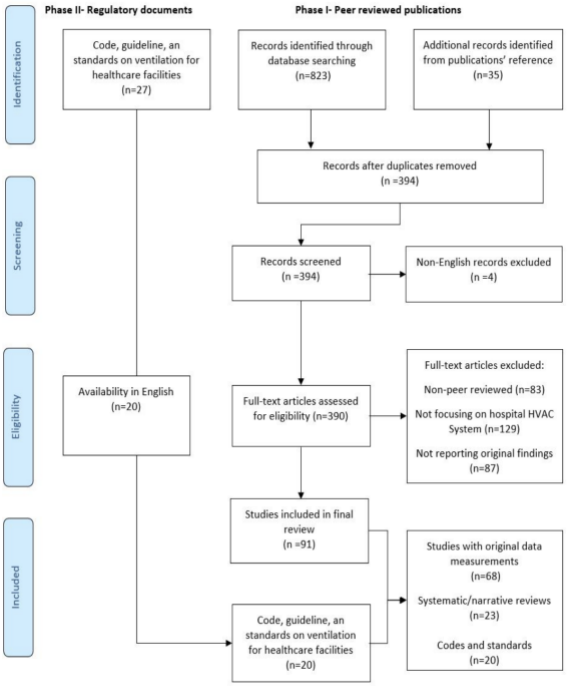

Figure 4 Flow Diagram of Record Identification, Eligibility, and Inclusion-Chart style courtesy to PRISMA [31]

CRITICAL CARE

MARKED FACTOR V ACTIVITY ELEVATION IN SEVERE COVID-19 IS ASSOCIATED WITH VENOUS THROMBOEMBOLISM

Stefely JA, Christensen BB, Gogakos T, Cone Sullivan JK, Montgomery GG, Barranco JP, Van Cott EM.. Am J Hematol. 2020 Aug 24. doi: 10.1002/ajh.25979. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

Pathologists from the Massachusetts General Hospital conducted a prospective cohort study of 102 patients with severe COVID-19 in March through April 2020, showing elevated Factor V activity at unprecedented levels in the hospital's history (median 150 IU/dL with 16% of values above 200 IU/dL), which was associated with thromboembolitic complications (Figure 1). The authors suggest Factor V levels may serve as an important diagnostic and prognostic marker for COVID-19, and recommend further investigation of increased anticoagulation doses for prophylaxis in patients with severe COVID-19 and markedly elevated Factor V activity.

SUMMARY

The study included 102 patients with severe COVID-19 (92% on ventilators, 7% on ECMO). Of the cohort, 47% had line clots, 23% developed DVT/PE, and 22% died before the study's conclusion. In comparison to the historical control cohort, the COVID-19 cohort had significantly elevated D-dimer (median: 2849 ng/mL, n=101) and elevated fibrinogen levels (median: 763 mg/dL, n=91) (Figure 1). Median Factor V activity level was 150 IU/dL with 16% of values above 200 IU/dL). Factor V Leiden did not account for such findings evident by normal activated protein C resistance assays. Initially elevated Factor V levels followed by normal-low values was associated with decompensation and DIC.

ABSTRACT

Coagulopathy causes morbidity and mortality in patients with Coronavirus Disease 2019 (COVID-19) due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Yet, the mechanisms are unclear and biomarkers are limited. Early in the pandemic, we observed markedly elevated factor V activity in a patient with COVID-19, which led us to measure factor V, VIII, and X activity in a cohort of 102 consecutive inpatients with COVID-19. Contemporaneous SARS-CoV-2-negative controls (n = 17) and historical pre-pandemic controls (n = 260-478) were also analyzed. This cohort represents severe COVID-19 with high rates of ventilator use (92%), line clots (47%), deep vein thrombosis or pulmonary embolism (DVT/PE) (23%), and mortality (22%). Factor V activity was significantly elevated in COVID-19 (median 150 IU/dL, range 34-248 IU/dL) compared to contemporaneous controls (median 105 IU/dL, range 22-161 IU/dL) ($P < 0.00001$)-the strongest association with COVID-19 of any parameter studied, including factor VIII, fibrinogen, and D-dimer. Patients with COVID-19 and factor V activity >150 IU/dL exhibited significantly higher rates of DVT/PE (16/49, 33%) compared to those with factor V activity <=150 IU/dL (7/53, 13%) ($P = 0.03$). Within this severe COVID-19 cohort, factor V activity associated with SARS-CoV-2 viral load in a sex-dependent manner. Subsequent decreases in factor V were linked to progression toward DIC and mortality. Together, these data reveal marked perturbations of factor V activity in severe COVID-19, provide links to SARS-CoV-2 disease biology and clinical outcomes, and nominate a candidate biomarker to investigate for guiding anticoagulation therapy in COVID-19.

FIGURES

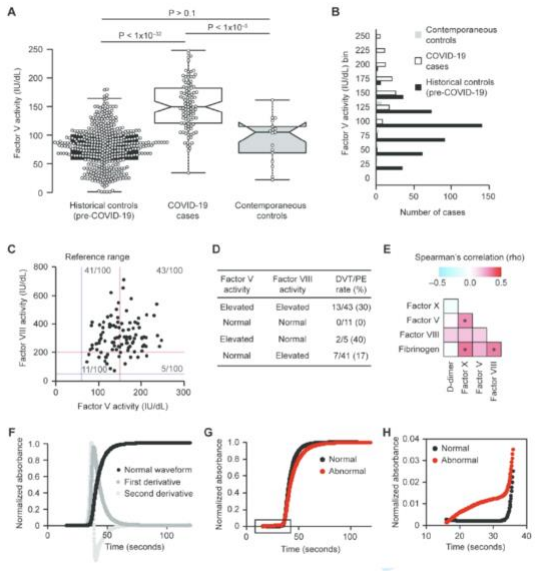

Figure 1: Factor V activity is markedly elevated in patients with severe COVID-19.
(A) Box plot indicating factor V activity in a cohort of severe COVID-19 cases compared to contemporaneous SARS-CoV-2 negative controls and historical controls prior to the COVID-19 pandemic. Center lines show the medians; box limits indicate the 25th and 75th percentiles as determined by R software; whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles; notches represent the 95% confidence interval for each median; data points are plotted as open circles. n = 446, 102, 17 sample points. P-values, two-sided, heteroscedastic Student's t-test.
(B) Histogram of factor V activity values in the COVID-19 cohort (n = 102), contemporaneous controls (n = 17), and historical controls (n = 446).
(C) Scatter plot of the activities of factor V and factor VIII in a cohort of patients with severe COVID-19. The reference ranges are indicated by blue (lower limit) and red (upper limit) lines.
(D) Table of cases with elevations of factor V or factor VIII activity and the rate of DVT/PE in these groups.
(E) Matrix of correlations (Spearman's rho) for the indicated coagulation parameters. Asterisks indicate significant correlations with a Bonferroni-corrected P-value < 0.05.
(F) Example of a normal aPTT waveform and the first and second derivatives of this waveform. The solid black line tracks light absorbance over time during the aPTT. Initially, the line is flat. The abrupt rise in the black line is when clot formation occurs, and the time at which it occurs is the aPTT result in seconds. When the clot occurs, the sample changes from a liquid (plasma) to a solid (clot), which absorbs more light. After clot formation, the sample undergoes no further changes, therefore the light absorbance remains unchanged and the line is flat again. The waveform and its first and second derivatives are automatically calculated by the analyzer.
(G) Comparison of a normal aPTT waveform and an abnormal aPTT waveform in COVID-19 patients from the current study. The portion within the rectangle is expanded in panel H.
(H) Expanded view of the initial portion of the aPTT waveforms in panel G, showing the abnormal slope. When the initial slope of the line rises upward instead of remaining flat before clot formation, this indicates an abnormal waveform that is suggestive of DIC.

MEDICAL SUBSPECIALTIES

CARDIOLOGY

HEART FAILURE IN COVID-19 PATIENTS: PREVALENCE, INCIDENCE AND PROGNOSTIC IMPLICATIONS

Rey JR, Caro-Codón J, Rosillo SO, Iniesta ÁM, Castrejón-Castrejón S, Marco-Clement I, Martín-Polo L, Merino-Argos C, Rodríguez-Sotelo L, García-Veas JM, Martínez-Marín LA, Martínez-Cossiani M, Buño A, Gonzalez-Valle L, Herrero A, López-Sendón JL, Merino JL.. Eur J Heart Fail. 2020 Aug 24. doi: 10.1002/ejhf.1990. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers within the departments of cardiology, clinical analytics, and pharmacy at the Hospital Universitario La Paz, Spain performed a single-center, retrospective study on 3,080 COVID-19-positive patients (with a 30-day or more follow-up) and heart failure. Based on this study's findings (illustrated below), the authors suggest maintaining heart failure guideline directed medical therapy (GDMT) when possible or re-instituting these regimens at discharge.

SUMMARY

The findings of this study include, but are not limited to, the following:

-As compared to patients without congestive heart failure (CHF), patients with a history of CHF (n=152) were more likely to:
•develop acute heart failure (AHF; 11.2% vs 2.1%, p less than 0.001)
•have greater levels of N-terminal pro b-type natriuretic peptide (NT-proBNP)
•receive more hydroxycloroquine (85.5% versus 77.0%; p=0.014) and anticoagulant therapy (57.7% versus 7.7%, p less than 0.001)
•have less ICU admissions (2.1% versus 8.0%; p=0.037)
•utilize less mechanical ventilation (2.1% versus 7.6%; p=0.046)
•have higher mortality during follow-up (48.7% versus 19.0%; p less than 0.001; Figure 2)

-A history of CHF, COPD, bleeding and receipt of blood products, older age, and atrial arrhythmias were independent predictors of AHF, with arrhythmias being the strongest predictor (Table 3).

-The removal of heart failure guideline directed medical therapy (GDMT; specifically ACE/ARB inhibitors, beta blockers and mineralocorticoid receptor antagonists) were not associated with AHF, but were associated with greater mortality (Figure 3).

ABSTRACT

AIMS: Data regarding impact of COVID-19 in chronic heart failure (CHF) patients and its potential to trigger acute heart failure (AHF) is lacking. The aim of this work was to study characteristics, cardiovascular outcomes and mortality in patients with confirmed COVID-19 infection and prior diagnosis of HF. Also, to identify predictors and prognostic implications for AHF decompensations during hospital admission and to determine whether there was a correlation between withdrawal of HF guideline-directed medical therapy (GDMT) and worse outcomes during hospitalization. METHODS AND RESULTS: A total of 3080 consecutive patients with confirmed COVID-19 infection and at least 30-day follow-up were analyzed. Patients with previous history of CHF (152, 4.9%), were more prone to develop AHF (11.2% vs 2.1%; p<0.001) and had higher levels of NT-proBNP. Also, previous CHF group had higher mortality rates (48.7% vs 19.0%; p<0.001). In contrast, 77 patients (2.5%) were diagnosed of AHF and the vast majority (77.9%) developed in patients without history of HF. Arrhythmias during hospital admission and CHF were main predictors of AHF. Patients developing AHF had significantly higher mortality (46.8% vs 19.7%; p<0.001). Finally, withdrawal of beta-blockers, mineralocorticoid antagonists and ACE/ARB inhibitors was associated with a significant increase of in-hospital mortality. CONCLUSIONS: Patients with COVID-19 have a significant incidence of AHF, entity that carries within a very high mortality. Moreover, patients with history of CHF are prone to develop acute decompensation after COVID-19 diagnosis. Withdrawal of GDMT was associated with higher mortality.

FIGURES

	Non-adjusted			Adjusted		
Variable	OR (95% CI)	Standard error	P value	OR (95% CI)	Standard error	P value
Age (per 5-year increase)	1.33 (1.23-1.45)	0.06	<0.001	1.28 (1.16-1.41)	0.06	<0.001
Atrial arrhythmias during admission	6.42 (3.26-12.64)	2.22	<0.001	4.64 (2.19-9.83)	1.78	<0.001
Chronic heart failure	6.02 (3.42-10.60)	1.74	<0.001	2.51 (1.33-4.76)	0.82	0.005
Bleeding during admission	1.77 (1.11-2.80)	0.42	0.016	1.60 (0.98-2.62)	0.40	0.061
COPD	4.21 (2.46-7.19)	1.15	<0.001	2.51 (1.40-4.49)	0.75	0.002

Table 3. Univariate and Multivariate logistic regression model for the predication of AHF during follow-up

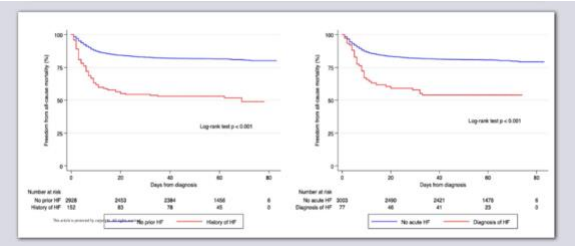

Figure 2. Left panel: Survival analysis showed significant differences (p less than 0.001) between patients with and without CHF. Right panel: Kaplan-Meier survival curves stratified by clinical diagnosis of AHF showing significant differences (p less than 0.001) in mortality.

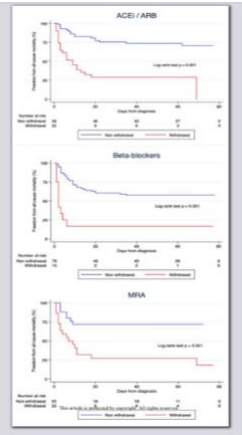

Figure 3: Kaplan-Meier survival analysis in patients receiving chronic treatment with ACEi/ARB (upper panel), BB (middle panel) and MRA (lower panel) showed that patients discontinuing these drugs at the time of admission had worse survival during follow-up

ADJUSTING PRACTICE DURING COVID-19

A NOVEL NON-CONTACT SELF-INJECTION-LOCKED RADAR FOR VITAL SIGN SENSING AND BODY MOVEMENT MONITORING IN COVID-19 ISOLATION WARD

Tsai CY, Chang NC, Fang HC, Chen YC, Lee SS.. J Med Syst. 2020 Aug 26;44(10):177. doi: 10.1007/s10916-020-01637-z.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

A case series of two patients with COVID-19 in hospital isolation, conducted at Kaohsiung Medical University Hospital in Taiwan, investigated the accuracy of patient vitals collected by a novel contactless device, a non-contact self-injection-locked radar (Figure 1), compared to a nurse's vital sign testing. Over the course of patient isolation (13 days and 5 days), the patients' temperatures and heart rates were insignificantly different between the device's and nurse's measurements. This novel device needs to be tested on a larger sample size to prove its effectiveness and may need to record other vitals to be useful, but the use of a contactless way of recording vitals will be of high utility in the future due to ability to monitor infectious patients from a distance.

ABSTRACT

BACKGROUND: The outbreak of Coronavirus disease (COVID-19) pandemic has become the most serious global health issue. Isolation policy in hospitals is one of the most crucial protocols to prevent nosocomial infection of COVID-19. It is important to monitor and assess the physical conditions of the patients in isolation. METHODS: Our institution has installed the novel non-contact wireless sensor for vital sign sensing and body movement monitoring for patients in COVID-19 isolation ward. RESULTS: We have collected and compared data between the radar record with the nurse's handover record of two patients, one recorded for 13 days and the other recorded for 5 days. The P value by Fisher's exact test were 0.139 (temperature, $P > 0.05$) and 0.292 (heart beat rate, $P > 0.05$) respectively. CONCLUSIONS: This is the first report about the application experience of this equipment. Therefore we attempted to share the experience and try to apply this equipment in COVID-19 patients in future to offer the more reliable and safe policy.

FIGURES

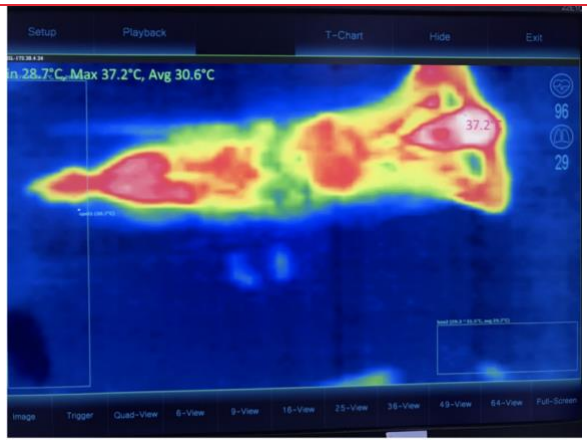

Figure 1. The thermography without high resolution image of patient can protect the privacy of the patient. The heart rate and respiratory rate are listed on the right side.

ACUTE CARE

CRITICAL CARE

TRAUMA CARE IN THE TIMES OF COVID

Kaur S, Kumar V, Ghoshal S, Banerjee N, Sagar S.. Br J Surg. 2020 Aug 25. doi: 10.1002/bjs.11967. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

A letter to the editor by authors affiliated with the Division of Trauma Surgery & Critical Care at All India Institute of Medical Sciences in New Delhi, India discuss trauma care in a low middle-income country during the COVID-19 pandemic highlighting increased requirement for PPE, holding procedures until COVID-19 status is known (unless patient is unstable), negative pressure COVID-19 operating room designations, 7-day post-operative isolation, and telemedicine use for follow-up. They present this information to contribute to ongoing advancements in best practice trauma care.

MEDICAL SUBSPECIALTIES

PHYSICAL EXERCISE AS A TOOL TO MINIMIZE THE CONSEQUENCES OF THE COVID-19 QUARANTINE: AN OVERVIEW FOR CYSTIC FIBROSIS

Fernandez-Del-Valle M, Donadio MVF, Pérez-Ruiz M.. Pediatr Pulmonol. 2020 Aug 25. doi: 10.1002/ppul.25041. Online ahead of print.

Level of Evidence: Other - Guidelines and Recommendations

BLUF

A commentary by experts in exercise science from USA, Brazil, and Spain outlined the benefits of an exercise prescription (in addition to physiotherapy) for cystic fibrosis (CF) patients including modifications to account for reduced social mobility and confinement during the COVID-19 pandemic (Figure 2), while emphasizing exercise as beneficial for CF patients by increasing airway clearance and decreasing inflammation (Figure 1). Authors suggest CF patient adherence to modified exercise prescriptions under a multidisciplinary team may be a beneficial compliment to physiotherapy.

ABSTRACT

Coronavirus (SARS-CoV-2) outbreak leading to the coronavirus disease (Covid-19) has become a global pandemic. Patients with Cystic Fibrosis (CF) are considered of major risk, as respiratory tract infections are more severe than in the general population, with a higher risk of complications and a negative impact on lung function. The performance of physical exercise is considered as key for its well-known general benefits and also as a complementary method to help airway clearance. Therefore, physical exercise is also considered as key in the therapeutic strategy during the quarantine period. However, the impossibility to perform exercise with appropriate prescription and monitoring is of considerable worry to health care professionals. Thus, alternative strategies, such as online measures to monitor this therapy and, consequently, to achieve a safe and effective dose is highly needed. Exercise regimens should include strength and endurance, as well as balance and flexibility exercises. Patients are highly encouraged to participate in exercise programs to maintain fitness and exercise should be continued during the quarantine period. This commentary provides a summary of the main effects and benefits of physical exercise, as well as the main recommendations for its adequate execution, including exercise modality, frequency, intensity and volume.

FIGURES

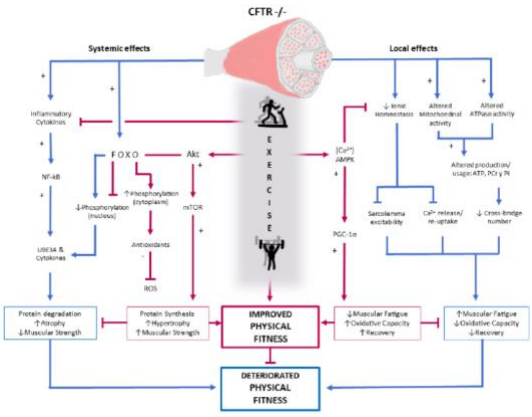

Figure 1. Schematic of the systemic and local effects of CFTR-/- with and without exercise.

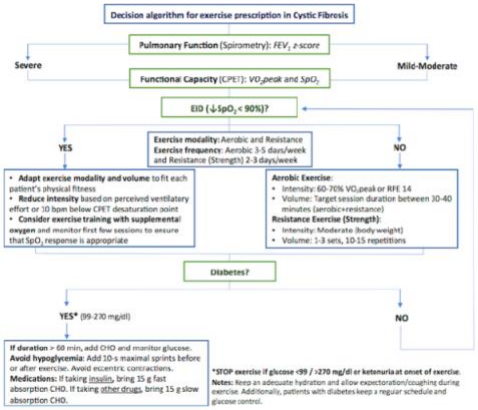

Figure 2. Decision algorithm for exercise prescription in patients with Cystic Fibrosis.

CARDIOLOGY

MANAGING SEVERE AORTIC STENOSIS IN THE COVID-19 ERA

Tanguturi VK, Lindman BR, Pibarot P, Passeri JJ, Kapadia S, Mack MJ, Inglessis I, Langer NB, Sundt TM, Hung J, Elmariah S..
JACC Cardiovasc Interv. 2020 Aug 24;13(16):1937-1944. doi: 10.1016/j.jcin.2020.05.045. Epub 2020 Jun 1.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

Cardiologists in the United States and Canada presented guidelines for severe aortic stenosis (AS) management and treatment during the COVID-19 pandemic (Tables 1,2), suggesting the guidelines could assist in delivering timely care while minimizing SARS-CoV-2 exposure and infection in this high-risk population (Figure 1).

SUMMARY

Specific author recommendations include:
- Use of telemedicine to discuss and monitor symptoms indicative of progression and severity of disease
- Reconsider routine inpatient and outpatient tests for AS patients unless results are needed for clinical decision making
- Implement changes to procedural and recovery protocols for invasive procedures including transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR)

ABSTRACT

The novel coronavirus-19 (COVID-19) pandemic has created uncertainty in the management of patients with severe aortic stenosis (AS). This population experiences high mortality from delays in treatment of valve disease but is largely overlapping with the population of highest mortality from COVID-19. We present strategies for managing patients with severe AS in the COVID-era. We suggest transitions to virtual assessments and consultation, careful pruning and planning of necessary testing, as well as fewer and shorter hospital admissions. These strategies center on minimizing patient exposure to COVID-19 and expenditure of human and health-care resources without significant sacrifice to patient outcomes during this public health emergency. Areas of innovation to improve our care during this time include increased use of wearable and remote devices to assess patient performance and vital signs, devices for facile cardiac assessment, and widespread use of clinical protocols for expedient discharge with virtual physical therapy and cardiac rehabilitation options.

FIGURES

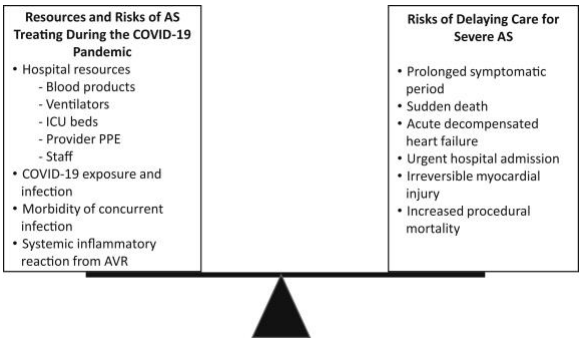

Figure 1. Risks of Treating Severe AS Balanced With Risks of Delayed Treatments.

Typical Care	COVID-19-Era Care
Patient assessment by primary cardiologist	
• In-person detailed assessment and physical examination • Routine outpatient echocardiography	• Virtual or telephone assessment to screen for symptoms. • Outpatient TTE only if uncertain about AS severity or other cardiac concerns
Patient assessment by consulting providers	
• In-person consultation with cardiac surgery, interventional cardiology, and/or other heart team providers • Heart team discussion	• Virtual or telephone assessment by cardiac surgery, interventional cardiology, and/or other heart team providers • Virtual heart team discussion
Testing	
• Dental panorex radiography and clearance • Pulmonary function test • Carotid Doppler ultrasound • Invasive coronary angiography • TAVR-protocol CTA of chest, abdomen, and pelvis (if TAVR candidate)	• Dental panorex radiography only for known dental pathology/caries • Defer pulmonary function test unless required for decision making • Defer carotid Doppler ultrasound • Coronary angiography performed in the same admission pre-SAVR or during TAVR • TAVR-protocol CTA extended to include neck, chest, abdomen, and pelvis and coronary screen (if TAVR candidate)
Post-procedurally	
• Rapid mobilization • Patient observed for 24-72 h post-TAVR • Patient observed inpatient for 5 to 7 days post-SAVR • Home PT and/or inpatient rehabilitation • Outpatient cardiac rehabilitation	• Rapid mobilization • Emphasis on discharge within 24-48 h post-TAVR • Expedited discharge post-SAVR if feasible • Avoid home PT and inpatient rehabilitation • Virtual outpatient physical therapy and cardiac rehabilitation.

AS = aortic stenosis; COVID-19 = coronavirus disease 2019; CTA = computed tomographic angiography; PT = physical therapy; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; TTE = transthoracic echocardiography.

Table 1. Typical Versus COVID-19-Era Care of a Patient With Symptomatic Severe AS.

Urgent AVR
• Severe or unstable symptoms ○ Progressive or severe heart failure symptoms (NYHA functional class III or IV), including weight gain, rapidly decreasing exertional capacity, or dyspnea with minimal exertion ○ Progressive or severe angina ○ Syncope or new-onset pre-syncope ○ New decline in left ventricular ejection fraction
Consider AVR on the basis of local resources
• Moderate, stable symptoms ○ Heart failure symptoms (NYHA functional class II or III), including weight gain, reduced exertional capacity, or exertional dyspnea, that have remained stable and allow routine daily activities ○ Stable, mild angina ○ Chronic, stable left ventricular systolic dysfunction
Defer AVR during COVID-19 pandemic
• Mild, stable symptoms ○ Generalized fatigue ○ NYHA functional class II heart failure symptoms, including stable exertional dyspnea (allowing at least 1 flight of stairs)

AVR = aortic valve replacement; COVID-19 = coronavirus disease 2019; NYHA = New York Heart Association.

Table 2. Severe Aortic Stenosis Treatment Priorities During the COVID-19 Era.

HYDROXYCHLOROQUINE FOR TREATMENT OF NON-SEVERE COVID-19 PATIENTS; SYSTEMATIC REVIEW AND META-ANALYSIS OF CONTROLLED CLINICAL TRIALS

Elsawah HK, Elsokary MA, Elrazzaz MG, ElShafey AH.. J Med Virol. 2020 Aug 18. doi: 10.1002/jmv.26442. Online ahead of print.
Level of Evidence: 1 - Systematic review of randomized trials or n-of-1 trials

BLUF

Researchers in Biostatistics, Human Data Science, and Neuropsychiatry located in Egypt performed a meta-analysis of clinical trials of hydroxychloroquine for patients with COVID-19 between June up to July-18, 2020. Their findings were (Figure 4):

- Progression of disease (within 28 days) between the two groups (those treated with hydroxychloroquine and those not treated) was not statistically significant, with risk difference (RD) -0.00 (-0.04 to 0.04)
- Mortality at five days was not statistically significant, with RD 0.01 (-0.01 to 0.03).
- Mortality at 28 days was not statistically significant, with RD 0.00 (-0.01 to 0.01).
- Radiological progression gauged by CT scan was statistically significant with RD of -0.2 (-0.36 to -0.03).
- Viral clearance as measured via pharyngeal swab showed no statistically significant differences between the groups with RD of 0.04 (-0.1 to 0.18).

These findings show that the use of hydroxychloroquine has no additional clinical benefit that would outweigh the risk profile of this drug and has little viral clearance.

ABSTRACT

BACKGROUND: Being a pandemic and having a high global case fatality rate directed us to assess the evidence strength of hydroxychloroquine efficacy in treating COVID-19 arising from clinical trials and to update the practice with the most reliable clinical evidence. METHODS: A comprehensive search was started in June up to July-18, 2020 in many databases, including PubMed, Embase and others. Of 432 studies found, only six studies fulfilled the inclusion criteria which includes: clinical trials, age>12 years with non-severe COVID-19, PCR-confirmed COVID-19, hydroxychloroquine is the intervention beyond the usual care. Data extraction and bias risk assessment were done by two independent authors. Both fixed-effect and random-effect models were utilized for pooling data using risk difference as a summary measure. The primary outcomes are clinical and radiological COVID-19 progression, SARS-CoV-2 clearance in the pharyngeal swab, and mortality. The secondary outcomes are the adverse effects of hydroxychloroquine. RESULTS: Among 609 COVID-19 confirmed patients obtained from pooling 6 studies, 294 patients received Hydroxychloroquine and 315 patients served as a control. Hydroxychloroquine significantly prevent early radiological progression relative to control with risk difference and 95% confidence interval of -0.2 (-0.36 to -0.03). On the other hand, hydroxychloroquine did not prevent clinical COVID-19 progression, reduce 5-days mortality, or enhance viral clearance on days 5, 6, 7. Moreover, many adverse effects were reported with hydroxychloroquine therapy. CONCLUSIONS: Failure of hydroxychloroquine to show viral clearance or clinical benefits with additional adverse effects outweigh its protective effect from radiological progression in non-severe COVID-19 patients. Benefit-risk balance should guide hydroxychloroquine use in COVID-19.

FIGURES

Figure 4. Forest plot of radiological and clinical progression and mortality using the fixed-effect model and risk difference with 95% confidence interval.

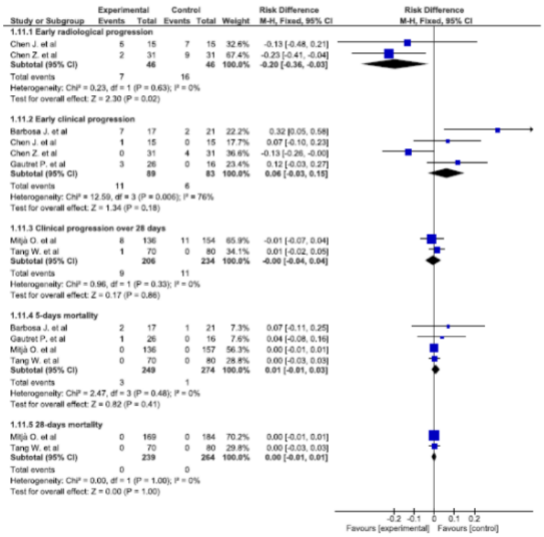

Figure 4: Forest plot of radiological and clinical progression and mortality using the fixed-effect model and risk difference with 95% confidence interval.

LARGE SIMPLE DOUBLE-BLIND RANDOMIZED TRIALS FOR THE RAPID ASSESSMENT OF THE EFFECTIVENESS OF COVID-19 VACCINES

Hasford J.. J Infect Dis. 2020 Aug 26:jiaa456. doi: 10.1093/infdis/jiaa456. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

An ethicist affiliated with the Institute for Medical Information Processing, Biometry, and Epidemiology at the University of Munich in Germany responds to the human challenge study by Eyal et al (2020) to accelerate coronavirus vaccine licensure. The author raises concerns about inherent sampling bias and ethical issues of the proposed challenge trials for COVID-19, citing the study design's need for young, healthy participants without definitive knowledge of risk factors for severe or fatal complications of COVID-19 and the lack of an effective and safe treatment to avoid any adverse consequence. The author instead proposes the large, simple, randomized trial (LSRT) as an alternative to the challenge trial because the LSRT allows for a wide eligibility criteria with large sample sizes and short-term treatment with minimal follow-up, suggesting LSRTs may yield more representative data than the exclusive challenge trials.

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