UPDATE ARTICLE

The 2019 Novel Coronavirus Outbreak – A Global Threat

Wasim Yunus Khot[1], Milind Y Nadkar[2]

Abstract

The 2019 Novel Corona virus infection (COVID 19) is an ongoing public health emergency of international significance. There are significant knowledge gaps in the epidemiology, transmission dynamics, investigation tools and management. In this article, we review the available evidence about this disease. Every decade has witnessed the evolution of a new coronavirus epidemic since the last three decades. The varying transmission patterns, namely, nosocomial transmission and spread through mildly symptomatic cases is an area of concern. There is a spectrum of clinical features from mild to severe life threatening disease with major complications like severe pneumonia, ARDS, acute cardiac injury and septic shock. Presence of bilateral ground glass opacity and consolidation on imaging in appropriate clinical background should raise a suspicion about COVID 19. Poor prognostic factors include **Mu**ltilobular infiltration on chest imaging, **L**ymphopenia, **B**acterial co-infection, **S**moking history, Chronic medical conditions like Hyper**t**ension and **a**ge >60 years (MuLBSTA score). Diagnosis is confirmed with PCR based testing of appropriate respiratory samples. Management is primarily supportive, with newer antivirals (lopinavir ritonavir and Remdesivir) under investigation. Role of steroids is still inconclusive. Standard infection control and prevention techniques should be followed. Vigilant screening of suspected cases and their contacts is important. Isolation of symptomatic cases and home quarantine of asymptomatic contacts is recommended. To conclude, controlling this highly transmissible disease requires international co-ordination.

The novel corona virus outbreak that we are facing reflects the times we live in. The tremendous development in transport and communication means that a contagion and the panic associated with its spread travels faster than ever, making it difficult to contain both. The world is at risk of devastating epidemics which lead to loss of life, economic losses and social unrest. The current outbreak will be a test of how prepared we are for such a fast-moving, virulent respiratory pathogen pandemic.[1]

In the late December 2019, multiple health facilities in Wuhan reported clustering of patients who presented with pneumonia of unknown cause. These cases were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China. Zhu et al identified the source of the pneumonia clusters, and described a novel coronavirus detected from lower respiratory tract samples of these patients.[2] On 29th Jan WHO declared 2019 nCoV as public health emergency of international concern. First confirmed case of nCoV in India was diagnosed on 30th January 2020. The disease caused by this has been christened as COVID-19 (**Co**rona **vi**rus **d**isease 20**19**) by WHO on 11th Feb 2020.[3]

The Agent

2019-nCoV belong to subgenus Sarbecovirus of the genus Betacoronavirus of the family coronaviridae.[2] Viruses of the family Coronaviridae possess a single-strand, positive-sense RNA genome ranging from 26 to 32 kb in length. Next-generation sequencing and phylogenetic analysis of the genome revealed 2019-nCoV was closely related (88% identical) to two bat-derived SARS-like coronaviruses and more distant from SARS-CoV (79%) and MERS-CoV (50%).[4] Structural analysis suggested that 2019-nCoV might be able to bind to the angiotensin-converting enzyme 2 receptor in humans similar to SARS CoV which was confirmed by Zhou et al.[5]

Coronaviruses before 2019 nCoV

Up till now 6 human coronavirus species were known. HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1 cause only mild upper respiratory disease, and in rare cases cause severe infection at extremes of age.[6] In 2002-2003, an unusual atypical pneumonia emerged in mainland China called severe acute respiratory syndrome (SARS) caused by new SARS CoV. It was transmitted in health care and hospital settings, generally five or more days after the onset of disease and from patients who were severely ill. Infected persons presented with fever, myalgia, malaise, and chills or rigor, cough. Shortness of breath, tachypnea, or pleurisy developed later in the course of the illness. 20 to 30 percent of patients required admission to an intensive care unit requiring mechanical ventilation.[7] The next decade saw emergence of another corona virus (MERS CoV) first isolated from a Saudi man with pneumonia and renal failure.[8] Human-to-human transmission occurred but limited to families and close contacts, or nosocomial infection.[9] The outbreak occurred mostly in the Middle East but imported cases have also been observed in Europe, Asia and North America. An outbreak of 186 confirmed cases occurred in South Korea.[10] Presentation with fever, chills, cough, shortness of breath (most likely with severe hypoxemic respiratory failure), and myalgia along with gastrointestinal symptoms, acute kidney damage has been reported.[11] The comparative features of these epidemic causing coronaviridae are tabulated in Table 1.

[1]Assistant Professor, [2]Professor and Head, Department of Medicine, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra

Received: 05.02.2020; Accepted: 11.02.2020

Table 1: Comparison between SARS, MERS, COVID-19

	SARS	MERS CoV	COVID-19
Year	2002-2003	2012-2013	2019-2020
Country of origin	China	Middle East	Wuhan, China
Animal Host	Himalayan palm civets and raccoon dog	Dromedary camels	Bat; Intermediate host ??
Receptor	ACE 2	DPP4	ACE 2
Incubation Period	2 – 10 days	2 – 14 days	2-7 days
Mortality	10%	35 %	2-3%

ACE: Angiotensin converting enzyme, DDP4: Dipeptidyl peptidase-4[7,9]

Table 2: Clinical features 2019 nCoV[15,19,26]

Clinical feature	Huang et al (n-41) %	Chen et al (n-99)%	Wang et al (n-138) %
Fever	98	83	98
Cough	76	82	59
Myalgia and fatigue	44	11	70
Dyspnoea	55	31	31
Sore throat	0	5	17
Diarrheoa	3	2	10

2019 novel CoV: Epidemiology and transmission dynamics

The mean incubation period was 5.2 days with the 95th percentile of the distribution at 12.5 days. In its early stages, the epidemic doubled in size every 7.4 days. .R0 i.e. the basic reproductive number was estimated to be approximately 2.2, meaning that on average each patient has been spreading infection to 2.2 other people.[12] A modelling study by Wu et al estimated basic reproductive number for 2019-nCoV to be 2·68 and epidemic doubling time as 6·4 days.[13] As new data will emerge these numbers are likely to change.

The majority of the cases reported early on were related to exposure at the Huanan Seafood Wholesale Market where a large variety of vertebrate and invertebrate animals, wild caught and farm raised, were sold.[14] It has been postulated that bats are the primary source and spread to humans occurred possibly via transmission from wild animals illegally sold in the market.[15] There was an exponential increase in non-linked cases by late December.[12,15] Spread from person-to-person happens among close contacts (about 6 feet) mainly via respiratory droplets through contact with mucous membrane of mouth, nose and possibly eyes.[16] A familial cluster of cases from Shenzen and Vietnam provided the first evidence suggesting such human to human transmission.[17,18] There is also evidence of presumed hospital based transmission and infection. In a study by Wang et al 57 cases (41.3%) were likely infected in the hospital. These included 17 (12.3%) patients and 40 (29%) health care workers. Patient-to-patient transmission also occurred.[19] The human to human transmission is mostly from symptomatic infected patients. But a report of transmission of 2019-nCoV infection from an asymptomatic contact in Germany had created widespread panic questioning our understanding of current transmission dynamics of this virus. Infection appeared to have been transmitted during the incubation period of the index patient.[20] But this has been disputed in other reports suggesting that patient had nonspecific complaint like myalgia and fatigue during transmission and was not totally asymptomatic.[21]

Presence of asymptomatic or mildly symptomatic patients may have a potential impact on the spread of pandemic. Efficient human-to-human transmission is a required for rapid and large scale spread of a respiratory pathogen.[22] The severity of disease is an important factor for virus's ability to spread.[23] There is an inverse co-relation between number of mild or asymptomatic cases and our ability to control an outbreak. A mildly symptomatic or asymptomatic infected person will not seek health care and thus remain undiagnosed, continue working and travelling in crowded places. Thus potentially spreading the virus to their contacts both locally and internationally.[22,23] Nosocomial transmission is also a serious risk for rapid spread.[19] Another important factor determining whether or not the virus can cause a sustained outbreak is the basic reproduction number, *R*0. When *R* is greater than 1, sustained transmission can occur. To break the chain of transmission *R* needs to be less than 1.[24] For the current outbreak R0 is estimated to be 2.2 to 2.68.[13,12] We need to prevent little more than half of infections, so that the *R0* can be brought down to below 1.[24]

Table 3: Complications associated with 2019 nCoV[15,19,26]

Complication	Huang et al (n-41) %	Chen et al (n-99) %	Wang et al (n-138) %
ARDS	55	31	31.2
Oxygen requirement	66	76	76
Non invasive ventilation	24	13	10.9
Invasive mechanical ventilation	5	4	12.3
ECMO	5	3	2.9
Shock	7	4	8.7
Acute cardiac injury	12	13	7.2
Acute kidney injury	7	3	3.6
Renal replacement therapy	-	9	1.45
Death	15	11	4.3

2019 novel CoV: Clinical spectrum of infection

Novel Coronavirus may present with mild, moderate, or severe illness. The severe form includes severe pneumonia, ARDS, sepsis and septic shock.[25] The 2019 novel Corona virus associated disease (COVID 19) is predominantly seen in older population with chronic medical conditions. There is male preponderance. Median age was 55-59 years.[12,26,19] More than 75% admitted cases in one series were older than 50 years of age.[26]

The clinical features are summarized in Table 2. Fever was the most common presenting symptom (83-98%), followed by cough (59-82%) associated with expectoration (27-28%). Myalgia and fatigue (11- 69 %) were another significant presenting feature.[15,19,26] As compared to SARS and MERS CoV, upper respiratory symptoms (0-5%) and intestinal symptoms nausea, vomiting(1%) and diarrhea (2%) were less common in earlier series.[15,26] But Wang et al reported sore throat(17%), anorexia (39.9%) and diarrhea(10%) more frequently.[19] Other less common complaints were headache, confusion, chest pain, hemoptysis.[27]

Complications

Major complications (Table 3) during hospitalization included ARDS (31-55%), acute cardiac injury (7-12%), arrhythmias(16%), acute kidney injury(3-7%) and shock (4-9%).[15,19,26] As compared to SARS and MERS CoV, complication and mortality rates are lower. Less than one third cases required admission to intensive care unit. Many severe cases required non-invasive (11-24%) and invasive (4-12%) mechanical ventilation. Few with persistent hypoxemia required ECMO (3%).[15,19,26] Eleven patients died

Table 4: Case definition[35]

2019 novel CoV: Case Definitions	
Suspect case	A. Patient with severe acute respiratory infection (fever, cough, and requiring admission to hospital), AND with no other etiology that fully explains the clinical presentation AND history of travel to or residence in China during the 14 days prior to symptom onset, OR B. Patient with any acute respiratory illness AND at least one of the following during the 14 days prior to symptom onset: a. Close contact with a confirmed or probable case of 2019- nCoV infection, or b. Worked in or attended a health care facility where patients with confirmed or probable 2019-nCoV acute respiratory disease patients were being treated.
Probable case	A suspect case for whom testing for 2019- nCoV is inconclusive or is tested positive using a pan-coronavirus assay and without laboratory evidence of other respiratory pathogens
Confirmed case	A person with laboratory confirmation of 2019-nCoV infection, irrespective of clinical signs and symptoms.
Close contact	1. Health care associated exposure, including providing direct care for nCoV patients, working with health care workers infected with nCoV, visiting patients or staying in the same close environment of an nCoV patient 2. Working together in close proximity or sharing the same classroom environment with a with nCoV patient 3. Traveling together with nCoV patient in any kind of conveyance 4. Living in the same household as a nCoV patient

out of 99 in the study by Chen et al.[26] The mortality in later series by Wang et al was less(4.3%).[19]

The median time from onset of symptoms and development of breathlessness was 5-8 days, of ARDS was 8-9 days[15,19] and for requirement of mechanical ventilation was 10.5 days.[15] Thus most of clinical worsening and complications develop later i.e. from second week onward. This is similar to that seen in SARS as the peak replication of coronavirus is observed in the second week of illness. These findings are important as we must monitor cases with 2019 nCoV for a longer period as these patients may worsen later.[27]

Laboratory features

WBC count was normal in most of the patients. Leucopenia (9%) and leucocytosis (24%) were seen along with neutrophilia (38%) and thrombocytopenia (12%). Lymphopenia (Absolute lymphocyte count <1.1x10^9) was a common finding.[19,26] Decreased haemoglobin, elevated creatinine, BUN, creatine kinase, lactate dehydrogenase, hypoalbuminemia, prolonged prothrombin time and abnormal hepatic transaminase levels were seen in some patients. Acute phase reactants, namely C reactive protein and ferritin were elevated.[26] The presence of these laboratory abnormalities indicate associated cellular immune deficiency, coagulation activation, myocardial, hepatic and renal injury which may lead to fatal outcomes.[19]

Radiological features

Bilateral pneumonia (75-100%) on Chest radiograph and CT scan was the most common finding in admitted patients.[15,19,26] Typical CT findings included bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities, with a predominantly rounded morphology or linear abnormality or a crazy-paving pattern distributed in peripheral lung fields.[28] In a study by Wang et al, all the patients had bilateral distribution of patchy shadows and ground glass opacities.[26] One patient had pneumothorax. The typical findings in ICU patients were bilateral multiple lobular and sub-segmental areas of consolidation while those of non-ICU patients were bilateral ground-glass opacity and subsegmental areas of consolidation. Follow up scans showed resolution of consolidation but the ground glass opacities remained.[15] In one of the case reports, the sequential chest radiograph showed progression from normal to unilateral lower lobe pneumonia to basilar streaky opacities in both lungs, a finding consistent with atypical pneumonia. The radiological worsening correlated with clinical deterioration.[29] In a study of CT scans of 21 patients with 2019-nCoV infection, the involvement was also bilateral (76%) and multilobular i.e. more than 2 lobes (71%). Interestingly, three patients (14%) had normal scans at diagnosis.[28] A normal chest CT scan does not exclude the diagnosis.[30]

Prognostic factors

Old age and underlying chronic medical conditions were associated with adverse outcomes. Lymphopenia, leucocytosis, neutrophilia were associated with need for ICU and mortality.[19,26] In the nonsurvivors, the neutrophil count, D-dimer, blood urea, and creatinine levels continued to increase, and the lymphocyte counts continued to decrease until death occurred.[21] The characteristics of patients who died were in line with MuLBSTA score an early warning model for predicting mortality in viral pneumonia.[26,31] MuLBSTA score > 12 is a predictor of mortality - Multilobular infiltration : 5 points;Lymphopenia (lymphocytes<0.8x10^9): 4 points, Bacterial co-infection: 4 points; Smoking history: Acute smoker 3 point, quit smoker 2 point; Hypertension : 2 point; Age > 60 years: 2 point.[31] Further validation of this score is needed for 2019 nCoV pneumonia. These prognostic markers can be used to prioritise patients requiring intensive care and aggressive management.

Differential Diagnosis

During an outbreak settings other prevalent infections are often overlooked. Coinfections are also possible. Seasonal influenza can present with similar clinical picture with bilateral pneumonia and ARDS. Tropical infections like Dengue, Malaria, Leptospirosis and Rickettsial fever are still common cause of ARDS in tropical country like India.[32] Bacterial pneumonia by both typical and atypical organisms should be ruled out.

2019 novel CoV: Laboratory diagnosis

All suspected cases as per case definition (Table 4) should undergo necessary laboratory diagnosis for confirmation of infection as per WHO and MOHFW guidelines.[33,34]

1. Respiratory material (nasopharyngeal and oropharyngeal swab in ambulatory patients and sputum (if produced) and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease) should be sent in viral transport media with cold chain maintained.
2. Serum for serological testing, acute sample and convalescent sample (this is additional to respiratory materials)

Safety procedures should be followed during sample collection and transport. Nucleic acid amplification tests/RTPCR are currently used for 2019-nCoV.[33]

Management

A. **Supportive care:** Management is mainly supportive in early cases and organ support in intensive care in form non-invasive and invasive mechanical ventilation, ECMO, renal replacement therapy in critically ill patients. The WHO and MOHFW has come up with management guidance documents for 2019 nCoV which are updated regularly based on available evidence.[35,36]

B. **Role of Corticosteroids**: WHO advises against routine use of corticosteroids for nCoV associated pneumonia outside of clinical trial except when needed for other indications.[37] Corticosteroids use during SARS CoV and MERS CoV outbreak were associated with adverse outcome like delayed clearance of viral RNA from blood.[38-40] In SARS CoV patients steroids use was associated with adverse events like psychosis, diabetes, increase risk avascular necrosis.[38,39,41] Some benefit of corticosteroid therapy was shown in carefully selected critically ill SARS patients.[42] Corticosteroids have been used in many patients during the current outbreak of 2019 nCoV by the Chinese experts. At present insufficient evidence exists to recommend routine use of corticosteroids and its use should be judicious in critically ill patients at lowest dose for shortest time.[43,44] The outcome of ongoing studies will provide further evidence for or against steroids.

C. **Potential therapeutic agents**

At present no specific antiviral treatment is available for coronaviruses. Existing therapies are being repurposed for use in this outbreak based on animal studies and experience with SARS and MERS CoV. The most promising of these being protease inhibitor lopinavir ritonavir which has been used in many patients in China and other countries. Some patients with SARS and MERS CoV had shown favourable response to lopinavir/ritonavir.[45] Remdesivir is another potential drug with an ongoing trial in China. It was used in a case of nCoV in US with favourable outcome.[29] Baricitinib is another potential drug candidate.[46] No vaccine is currently available.

Preventive and public health measures

Early recognition of patients with SARI associated with nCoV infection is important. Infection prevention and control guidelines by WHO and MOHFW are to be followed.[35,36] Standard precautions namely hand hygiene, use of PPE, safe waste management etc. should be followed at all time. Droplet precautions and contact precautions should be followed if working within 6 feet of a patient. Apply airborne precautions when performing an aerosol generating procedure. Passengers coming from China and nearby countries are being screened for signs and symptoms at all the major airports. Symptomatic contacts should be isolated for infection control, and undergo diagnostic evaluation and management. Asymptomatic patients should remain at home (home quarantine) for at least 28 days after the last exposure with daily monitoring for symptoms. A positive case is to be managed at designated healthcare facility. Patient should be discharged after chest radiograph has cleared and two specimens turn negative within 24 hours.[47]

Current Status of the outbreak

At the time of going to print, more than 71000 cases have been reported globally out of which above 52000 are laboratory confirmed. More than 70000 are from China alone with more than 1700 deaths. Outside of China 25 countries have reported a total of 683 confirmed cases with three deaths. The numbers are increasing exponentially and yet to reach a plateau.[48,49] India has reported three confirmed cases till now all from Kerala with none of them having severe disease.[50]

Conclusion

The COVID-19 is still an ongoing outbreak. New insights into the pathophysiology, transmission dynamics, clinical features and management of this virus are developing. It is highly transmissible infection but mortality is less compared to SARS and MERS. National and International health care agencies have shown appropriate co-ordination in handling of this outbreak up till now and further international cooperation is the need of the hour. Only time will tell how this story of COVID-19 unfolds further.

References

1. Annual report on global preparedness for health emergencies Global Preparedness Monitoring Board [Internet]. [cited 2020 Feb 7]. Available from: https://apps.who.int/gpmb/assets/annual_report/GPMB_annualreport_2019.pdf
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; 0:null.
3. WHO Coronavirus press conference 11 February, 2020 [Internet]. [cited 2020 Feb 12]. Available from: https://www.who.int/docs/default-source/coronaviruse/transcripts/who-audio-emergencies-coronavirus-full-press-conference-11feb2020-final.pdf?sfvrsn=e2019136_2
4. 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. The Lancet [Internet]. 2020 Jan 30 [cited 2020 Feb 8];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30251-8/abstract
5. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; 1–4.
6. Chan JFW, Li KSM, To KKW, Cheng VCC, Chen H, Yuen K-Y. Is the discovery of the novel human betacoronavirus 2c EMC/2012 (HCoV-EMC) the beginning of another SARS-like pandemic? *J Infect* 2012; 65:477–89.
7. Peiris JSM, Yuen KY, Osterhaus ADME, Stöhr K. The severe acute respiratory syndrome. *N Engl J Med* 2003; 349:2431–41.
8. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia. *N Engl J Med* 2012; 367:1814–20.
9. Ramadan N, Shaib H. Middle East respiratory syndrome coronavirus (MERS-CoV): A review. *Germs* 2019; 9:35–42.
10. Middle East Respiratory Syndrome Coronavirus Outbreak in the Republic of Korea, 2015. *Osong Public Health Res Perspect* 2015; 6:269–78.
11. Middle East respiratory syndrome coronavirus (MERS-CoV) [Internet]. [cited 2020 Feb 8]. Available from: https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov)
12. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N Engl J Med* 2020; 0:null.
13. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. The Lancet [Internet]. 2020 Jan 31 [cited 2020 Feb 9];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30260-9/abstract
14. Li J, Li J, Xie X, Cai X, Huang J, Tian X, et al. Game consumption and the 2019 novel coronavirus. Lancet Infect Dis [Internet]. 2020 Feb 7 [cited 2020 Feb 9];0(0). Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30063-3/abstract
15. 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. The Lancet [Internet]. 2020 Jan 24 [cited 2020 Feb 9];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30183-5/abstract
16. Transmission of Novel Coronavirus (2019-nCoV) | CDC [Internet]. 2020 [cited 2020 Feb 10]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/about/transmission.html
17. Chan JF-W, Yuan S, Kok K-H, To KK-W, 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. The Lancet [Internet]. 2020 Jan 24 [cited 2020 Feb 9];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30154-9/abstract
18. Phan LT, Nguyen TV, Luong QC, Nguyen TV, Nguyen HT, Le

HQ, et al. Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam. N Engl J Med [Internet]. 2020 Jan 28 [cited 2020 Feb 8]; Available from: https://doi.org/10.1056/NEJMc2001272

19. 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 [Internet]. 2020 Feb 7 [cited 2020 Feb 9]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2761044
20. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany [Internet]. 2020 [cited 2020 Feb 9]. Available from: https://www.nejm.org/doi/10.1056/NEJMc2001468
21. KupferschmidtFeb. 3 K, 2020, Pm 5:30. Study claiming new coronavirus can be transmitted by people without symptoms was flawed [Internet]. Science | AAAS. 2020 [cited 2020 Feb 9]. Available from: https://www.sciencemag.org/news/2020/02/paper-non-symptomatic-patient-transmitting-coronavirus-wrong
22. Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A Novel Coronavirus Emerging in China - Key Questions for Impact Assessment. *N Engl J Med* 2020.
23. Gibbons CL, Mangen M-JJ, Plass D, Havelaar AH, Brooke RJ, Kramarz P, et al. Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods. *BMC Public Health* 2014; 14:147.
24. Thompson R. Pandemic potential of 2019-nCoV. Lancet Infect Dis [Internet]. 2020 Feb 7 [cited 2020 Feb 9];0(0). Available from: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30068-2/abstract
25. Novel Corona Virus | Ministry of Health and Family Welfare | GOI [Internet]. [cited 2020 Feb 9]. Available from: https://mohfw.gov.in/diseasealerts/novel-corona-virus
26. 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. The Lancet [Internet]. 2020 Jan 30 [cited 2020 Feb 9];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30211-7/abstract
27. Chan KH, Poon LLLM, Cheng VCC, Guan Y, Hung IFN, Kong J, et al. Detection of SARS Coronavirus in Patients with Suspected SARS. *Emerg Infect Dis* 2004; 10:294–9.
28. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology* 2020; 200230.
29. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med [Internet]. 2020 Jan 31 [cited 2020 Feb 9]; Available from: https://www.nejm.org/doi/10.1056/NEJMoa2001191
30. Kanne JP. Chest CT Findings in 2019 Novel Coronavirus (2019-nCoV) Infections from Wuhan, China: Key Points for the Radiologist. *Radiology* 2020; 200241.
31. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, et al. Clinical Features Predicting Mortality Risk in Patients With Viral Pneumonia: The MuLBSTA Score. Front Microbiol [Internet]. 2019 Dec 3;10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6901688/
32. Magazine R, Rao S, Chogtu B, Venkateswaran R, Shahul HA, Goneppanavar U. Epidemiological profile of acute respiratory distress syndrome patients: A tertiary care experience. *Lung India Off Organ Indian Chest Soc* 2017; 34:38–42.
33. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases [Internet]. [cited 2020 Feb 9]. Available from: https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117.
34. Specimen Collection, Packaging and Transport Guidelines for 2019 novel Coronavirus (2019-nCoV) [Internet]. [cited 2020 Feb 12]. Available from: https://mohfw.gov.in/sites/default/files/5Sample%20collection_packaging%20%202019-nCoV.pdf.
35. MOHFW Clinical Management Guidelines [Internet]. [cited 2020 Feb 8]. Available from: https://mohfw.gov.in/sites/default/files/Guidelines%20on%20Clinical%20management%20of%20severe%20acute%20respiratory%20illness.pdf.
36. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected [Internet]. [cited 2020 Feb 11]. Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.
37. WHO situation report [Internet]. [cited 2020 Feb 8]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf?sfvrsn=20a99c10_4.
38. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med* 2006; 3:e343.
39. Lee N, Allen Chan KC, Hui DS, Ng EKO, Wu A, Chiu RWK, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J Clin Virol Off Publ Pan Am Soc Clin Virol 2004; 31:304–9.
40. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med* 2018; 197:757–67.
41. Li Y, Wang S, Gao H, Wang J, Wei C, Chen L, et al. [Factors of avascular necrosis of femoral head and osteoporosis in SARS patients' convalescence]. *Zhonghua Yi Xue Za Zhi* 2004; 84:1348–53.
42. Chen R, Tang X, Tan S, Liang B, Wan Z, Fang J, et al. Treatment of Severe Acute Respiratory Syndrome With Glucosteroids: The Guangzhou Experience. *Chest* 2006; 129:1441–52.
43. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. The Lancet [Internet]. 2020 Feb 7 [cited 2020 Feb 10];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30317-2/abstract.
44. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. The Lancet [Internet]. 2020 Feb 11 [cited 2020 Feb 13];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30361-5/abstract.
45. Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; 59:252.
46. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. The Lancet [Internet]. 2020 Feb 4 [cited 2020 Feb 10];0(0). Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30304-4/abstract.
47. MOHFW guidelines for coronavirus [Internet]. [cited 2020 Feb 11]. Available from: https://mohfw.gov.in/sites/default/files/Corona%20Discharge-Policy.pdf.
48. WHO situation report COVID-19 [Internet]. [cited 2020 Feb 17]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200216-sitrep-27-covid-19.pdf?sfvrsn=78c0eb78_2.
49. Coronavirus COVID-19 (2019-nCoV) JHU updated tracking map [Internet]. [cited 2020 Feb 17]. Available from: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6.
50. MOHFW GOI press release 11 feb 2020 [Internet]. [cited 2020 Feb 12]. Available from: https://pib.gov.in/newsite/erelcontent.aspx?relid=199266.