Various Causes of Mortality in Covid-19 Patients

Rohit Dabas*, Nandita Sharma

Jawaharlal Nehru Medical, Sawangi Meghe, Wardha, India

ABSTRACT

Covid-19 disease or the coronavirus disease is the presently ongoing pandemic of the world. Both the developed and developing nations have been experiencing a wave of the virus. Many case numbers and death counts have been reported from it and this has put a massive burden load on the medical health care facilities. The whole of the world has till now experienced one fatal wave of the viral infection and many nations are suffering with the second wave presently. And it is still an alarming situation as the virus continues to mutate and spread. The epidemiology and the managing strategies of the contagious infection varies vastly across the world due to differences in population size, available medical healthcare infrastructure, governing strategies & policies. But what is common is the clinical presentation and the causes or factors which contribute to mortality. Thus, in this article we will discuss various causes and trends leading to mortality in covid-19 patients. In people with underlying health problems or comorbidities, it is thought to proceed more quickly and severely, leading to death. This study looked at the comorbid diseases and causes of death in patients of various ages who were infected with COVID-19. A search of the digitized literature was conducted, and relevant data was gathered from peer-reviewed articles.

Keywords: Covid-19, SARS-CoV-2, Mortality, Infection, Intensive Care Unit

Corresponding author: Rohit Dabas

e-mail✉: rohitdabas4@gmail.com

INTRODUCTION

A Covid-19 virus pandemic, often known as coronavirus disease, is currently sweeping the globe [1]. Both developed and developing nations are suffering from a wave of the virus, despite a vast difference in the level of population and healthcare infrastructure. The virus is reported to be mutating and spreading continuously every day, thus the serious problem of the pandemic. Also, known by its official name i.e., SARS-CoV-2 as given by the World Health Organization [2] in the year 2020 the pandemic has reported to infect a huge population all over with a high mortality rate [3]. The very first case of the viral disease was reported in the province of Wuhan of China [4] and from there it continued to spread throughout the globe. Different countries reported different statistics of the case numbers and death counts; there was no evidence a particular geographical area or group/community had a more serious level of pandemic, but instead the infection had infected people

of all ages, ethnic backgrounds, and genders. Already having suffered one fatal wave of the virus by the globe and present suffering of the second wave by many nations, it's still difficult to comment whether a third wave would precipitate or not. Thus, a serious need to prepare for the worst outcome is a pre-need. Clinicians and various researchers have reported that the disease's clinical presentation is diverse and maybe unique in each individual and they may vary from mild to severe respiratory failure with multiple organ failure., the most common symptoms are high grade fever [5] cough [6] breathlessness of difficult breathing, and loss of taste and smell sensation [7-9] which have a period of variability of their appearance ranging from 1-14 days after infection [10]. The infected patients may be categorized as symptomatic(who clearly show symptoms and signs of infection) or as asymptomatic cases (who don't show any usual found symptoms and signs)and it is found by various researches that they still contain an active covid infection and are susceptible for about another 20-25 days [11,12]. The current scenario in terms of diagnosis has become quite advanced and results can be obtained easily with various procedures but the gold standard technique remains to be rT-PCR technique. Whereas, the preventive options include practice of social distancing, frequent hand washing, employing quarantine measures, use of protective equipment like masks and face shields and getting vaccinated for which various vaccines are available. Treatment of infection depends on the clinical

presentation of an individual and there are no as such strict guidelines regarding it, life saving measures and patient compliance are utmost expected. It is highly recommended to get vaccinated with the both doses of the vaccine, and the vaccine is readily available for everyone above 18 years of age. As we are thorough with the fact that disease-related mortality and morbidity are inescapable, despite existing preventative and treatment alternatives, one must be aware with the causes and factors contributing to it. A variety of methods are widely used to predict mortality [10]. These figures vary by region and over time, and are influenced by factors such as the number of tests done, the quality of the healthcare system, treatment options available, the length of time since the outbreak began, and demographic features such as age, sex, and overall health. Initially believed to be exclusively a respiratory disease; Covid-19 virus has the ability to infect a wide spectrum of body cells and systems. There is no medical guarantee that one can escape mortality but one can surely prevent it to some extent. This article will discuss the onset of covid infection, mortality & the risk factors associated with it and the various bodily systems affected & complications that may contribute to mortality, in the SARS-CoV-2 viral disease. The relevant information to write this review was obtained from medical researches and findings of esteemed peer individuals by carrying out a thorough survey on a medical search engine like PubMed, etc.

Onset of the infection
The infection starts after an individual inhales the virus aerosols or droplets i.e., mainly via respiratory route from an infected individual [13]. Viral infection follows a definite pathogenesis and the five stages of the virus's life cycle within the host are attachment, penetration, biosynthesis, maturity, and release. After binding to host receptors (attachment), viruses enter host cells via endocytosis or membrane fusion(penetration). SARS-CoV has been found to have high attachment to a functional receptor called angiotensin converting enzyme 2 (ACE2) inside the host's body [14] and for it the virus uses an unique surface glycoprotein termed as spike [15]. After the virus gets attached to the host protein, the spike protein is cleaved by proteases, and after a series of other events i.e. biosynthesis of the viral machinery starts, which further multiply and lead to infection in the whole system. After the infection has fully occurred there are two possible outcomes i.e. the individual suffers from a milder form of disease and can easily manage it. And the other if the infection keeps on spreading rapidly it leads to a state of compromised immunity. If adequate measures are still not taken, one may suffer from a critical circumstance which may be either severe complications or even death. During the period of infectivity, the individual can still spread the infection to others, thus it is strictly advised to seek treatment and stay in isolation.

Mortality and risk factors associated with it
Mortality is used to describe the number of deaths in a particular population and in a particular span of time. The statistics related to mortality differ from region to region and over time, and are impacted by factors such as the amount of testing carried out, the efficiency of the health sector, therapeutic opportunities available, the duration since the outbreak began, and demographic characteristics such as age, gender, and general wellbeing. Various risk variables, such as sex, age, and co-morbidities such as hypertension, diabetes, cardiovascular disease, chronic lung disease, and so on, are taken into account for covid infection since they may directly or indirectly affect mortality.

Age
Mortality rates in covid disease are also proportional to age, with younger persons experiencing lower rates and the elderly experiencing greater rates [16]. It is commonly found that as people get older; their natural immunity begins to deteriorate, making them more susceptible to diseases. COVID-19 sufferers, both middle-aged and elderly, were shown to be more susceptible to the illness, more likely to be admitted to the ICU, and more likely to die. Also older people are said to have higher expression of ACE-2 receptors, causing higher viral attachment and infection. Changes in lung structure, which result in changes in physiologic performance, lung reserve, airway clearance, and defensive barrier function, may be to blame for age-related changes in the aged population [17]. And ageing is a natural and irreversible phenomenon making age an unmodifiable risk factor for the disease.

Sex
In most nations, men have a greater COVID-19 case fatality rate than women and are far more likely to be admitted to the intensive care unit (ICU) [18]. Also, it is found that males have a higher level of angiotensin-converting enzyme 2 (ACE2) expressions, making them more susceptible to SARS-CoV-2 infection and worse clinical results [19] but in our country India the scenario was found to be reverse i.e. women were more affected than males. Also, sex is an unmodifiable risk factor.

Comorbidities
COVID-19 is thought to have an increasingly rapid and severe progression in those with underlying health issues or comorbidities, often resulting to death [20]. Comorbidities are conditions/diseases which lead to compromised immune status, i.e. makes individual more susceptible to any form of infections or diseases and more severe clinical outcomes; as compared to an individual with normal status. The most prevalent comorbidities seen in patients are hypertension, cardiovascular and cerebrovascular diseases, and diabetes [21, 22]. Less common comorbidities include HIV and hepatitis B infection, cancer, respiratory ailments, renal disorders, and immunodeficiency's. From various researches it was observed that people of any age who suffer from underlying illnesses such as hypertension or diabetes have a poor prognosis in covid infection and diabetics

have higher rates of morbidity and mortality, as well as a higher rate of hospitalizations and ICU admissions [23]. Additionally, diabetics who had poor blood glucose control had a higher overall mortality risk than diabetics who had better glucose control. Poor blood glucose control was linked to a significantly higher risk of complications and death. COVID-19 is more likely to cause serious sickness in those who have respiratory problems [24]. Patients with moderate to severe asthma are especially vulnerable because the virus affects their respiratory tracts, resulting in asthma attacks and acute respiratory distress [25]. Also, poor disease progression has been linked to chronic obstructive pulmonary disease (COPD). COVID-19 patients with prior COPD had a significant mortality rate [26]. Lastly, it has been stated that COVID-19 infection is more likely to be more severe in individuals such as cancer patients on chemotherapy; smokers; transplant recipients; and patients who take steroids on a long-term basis.

If one has one or more than one positive risk factors, it directly exposes the individual to be at more risk. Out of all the risk factors it's the old age and the presence of co morbid conditions which pose the highest risk. Also, both of these are unmodifiable and irreversible risk factors, so much cannot be done. Both the pandemic waves marked mortality in individuals with these factors mostly.

Commonly affected bodily systems in Covid-19 infection

The SARS-CoV-2 virus is a highly contagious virus with a high transmission rate, and its clinical manifestations may invest in several bodily systems and its clinical presentation may also vary in each individual. The expression of ACE2 is found to be high in the lungs, heart, neurons, kidneys, and bladder, thus accounting for the various manifestations majorly in these system cells. The management and treatment approach is different depending on the system affected. And the prognosis of the sufferer depends on the clinical presentation, risk factors associated and various individual factors. The complications contributing to mortality in various systems are:

Respiratory System

The lungs are the primary organs of respiration and the organs that are most severely impacted by covid-19 infection. The virus can manifest inside both the upper and lower respiratory tract [27]. The virus has a unique surface glycoprotein known as spike, [28] that allows it to adhere to the angiotensin conversion enzyme-2(ACE2) receptors in the host lungs [29]. The infection to lungs can cause various life threatening modalities like acute respiratory distress syndrome, pulmonary fibrosis [30] pneumonia [31], etc which can cause mortality. These pathologies are often not experienced as symptoms in early stages, but almost at an end stage when the infection has reached a critical irreversible point and no effective treatment can now undone the damage caused. This indicates a poor prognosis and can even precipitate

mortality. The main pathogenesis that contributes to death in the respiratory modalities is believed to be a hyper immune reaction leading to a hyper inflammatory state due to release of excessive cytokines [32].

Cardiovascular System

The viral infection may also contribute to mortality by causing various cardiovascular complications too. The damage to the cardiac tissue is always irreversible accounting for its severity; once the cardiac tissue dies it cannot be revived again with any form of medical or surgical treatment. The high prevalence of the virus causing cardiac manifestations is also attributed to presence of ACE2 receptors in the heart too [33, 34]. High levels of D-dimer[35] which indicate blood clot formation and blood vessel damage are indicative of cardiac damage and major cardiac system complications that can lead to mortality are pulmonary embolism, thrombus formation and ischemic injuries[36,37]. The most common complications of the cardiovascular system are venous thromboembolism, atrial fibrillations, heart inflammation, etc [38, 39]. Also, acute myocardial injury can be there [40]. These directly or indirectly cause mortality in patients. In the second wave in our country, there was a massive count in individuals who succumbed to death due to cardiovascular causes rather than the covid infection being a direct cause, this included the young as well as the older age groups.

Nervous System

Many studies have given some evidence that the whole of the nervous system is affected in the covid disease, both the peripheral and central nervous system, [41] as the neural cortex and brain stem both have ACE2 receptors. The neurological presentation and complications in Covid comprise of include seizures, encephalopathy, stroke, loss of taste and smell sensation [42,43]. It is the loss of taste and smell which is first noticed by the layman. The other manifestations which are precipitated either suddenly or much later i.e. encephalopathy and stroke are the complications which bring about mortality in the most cases if the nervous system is affected due to Covid-19 disease.

Renal System

In the renal system cell the ACE-2 receptors are also abundant, crediting for the virus to cause a fatal infection. There are various complications like acute and chronic kidney injury, hyperkalemia and rarely kidney failure [44].The incidence of renal complications is not as much prevalent as other system complications, but renal failure and end stage kidney disease are reported to precipitate in individuals suffering from covid and even cause mortality [45].

Other systemic co infection: Mucormycosis

It is a fungal infection which is usually seen in immunocompromised individuals, but during the second wave of the covid pandemic in India, it became a complication of the Covid-19 disease. The occurrence

of mucormycosis was attributed to extensive use of steroids for the management of covid infection. Also called the black fungus, its cases rose so quickly that it was declared an epidemic in India. The presenting symptoms and preventive strategies are similar to covid-19 but the management is entirely different. Also the risk factors associated with mortality are similar as Covid-19 too. The pathogenesis contributing to death in covid-19 patients is said to be compromised immune status, vascular invasion, subsequent dissemination, and tissue necrosis of the bodily cells.

CONCLUSION

In this article we discussed the Covid-19 disease causing virus SARS-CoV-2 and how it contributes to mortality in individuals. Although, majorly presenting as a respiratory disease, the virus can still affect other bodily systems and lead to death. Each affected bodily system presents its own symptoms and complications and may contribute to mortality. And the most severe manifestations from the viral infection are seen in cardiovascular, nervous system, other than respiratory system The pathogenesis of the infection may initially be the same in each bodily system, but as it progresses each system presents with its unique symptoms and complications that bring about mortality. Also we discussed about a fungal infection associated with Covid-19 i.e. mucormycosis. The worst affected individuals are those who have an underlying disease or older populations, mainly due to their compromised immune status and the immune system is severely suppressed in the covid infection. It's the severity of the disease presentation and individual risk factors that may or may not cause mortality. It must be noted that even though management options and treatment lines to some extent for the disease are available, there is still no definite cure and the risk of mortality cannot be ruled out even after following safety practices. Thus, prevention is what is recommended and safe practices advised related to the infection must be practiced. Also, every individual must get vaccinated.

REFERENCES

1. Zimmer C. The Secret Life of a Coronavirus–An oily, 100-nanometer-wide bubble of genes has killed more than two million people and reshaped the world. 2021; 298.

2. Prieto-Ramos F, Pei J, et al. Institutional and news media denominations of COVID-19 and its causative virus: Between naming policies and naming politics. Discourse Commun 2020; 14:635-652.

3. World Health Organization. COVID-19 weekly epidemiological update, 22 December 2020.

4. Page J, Hinshaw D, McKay B. In Hunt for Covid-19 origin, patient zero points to second wuhan market– the man with the first confirmed infection of the new coronavirus told the WHO team that his parents had shopped there. Wall Str j mag 2021; 26.

5. Islam MA, Kundu S, Alam SS, et al. Prevalence and characteristics of fever in adult and paediatric patients with coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis of 17515 patients. PloS One 2021; 16.

6. Islam MA, Alam SS, Kundu S, et al. Prevalence of headache in patients with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of 14,275 patients. Front Neurol 2020; 11.

7. Saniasiaya J, Islam MA, Abdullah B. Prevalence of olfactory dysfunction in coronavirus disease 2019 (COVID-19): A Meta-analysis of 27,492 Patients. Laryngoscope 2021; 131:865-78.

8. Saniasiaya J, Islam MA, Abdullah B. Prevalence and characteristics of taste disorders in cases of COVID-19: A meta-analysis of 29,349 patients. Otolaryngol Head Neck Surg 2021; 165:33-42.

9. Agyeman AA, Chin KL, Landersdorfer CB, et al. Smell and taste dysfunction in patients with COVID-19: A systematic review and meta-analysis. Mayo Clin Proc 2020; 95:1621-1631.

10. Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection: a narrative review. Ann Intern Med 2020; 173:362-7.

11. Lai CC, Shih TP, Ko WC, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020; 55:105924.

12. Bloom BR, Nowak GJ, Orenstein W. "When will we have a vaccine?"—Understanding questions and answers about Covid-19 vaccination. N Engl J Med 2020; 383:2202-2204.

13. Wang CC, Prather KA, Sznitman J, et al. Airborne transmission of respiratory viruses. Science 2021; 373.

14. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003; 426:450-454.

15. Dehingia N, Raj A. Sex differences in COVID-19 case fatality: do we know enough?. Lancet Glob Health 2021; 9:e14-15.

16. Colaneri M, Seminari E, Novati S, et al. Severe acute respiratory syndrome coronavirus 2 RNA contamination of inanimate surfaces and virus viability in a health care emergency unit. Clin Microbiol Infect 2020; 26:1094.

17. Liu K, Chen Y, Lin R, et al. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect 2020; 80:e14-18.

18. Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun 2020; 11:6317.

19. Gemmati D, Bramanti B, Serino ML, et al. COVID-19 and individual genetic susceptibility/receptivity: role of ACE1/ACE2 genes, immunity, inflammation and coagulation. Might the double X-chromosome in females be protective against SARS-CoV-2 compared to

the single X-chromosome in males?. Int J Mol Sci 2020; 21:3474.

20. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med 2020; 2:1069-76.

21. Paudel SS. A meta-analysis of 2019 novel corona virus patient clinical characteristics and comorbidities.

22. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395:1054-1062.

23. Singh AK, Gupta R, Ghosh A, et al. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr Clin. Res Rev 2020; 14:303-310.

24. Zhao Q, Meng M, Kumar R, et al. The impact of COPD and smoking history on the severity of COVID-19: A systemic review and meta-analysis. J Med Virol 2020; 92:1915-1921.

25. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States, March–June 2020. Morb Mortal Wkly Rep 2020; 69:993-998.

26. Zhao Q, Meng M, Kumar R, et al. The impact of COPD and smoking history on the severity of COVID-19: A systemic review and meta-analysis. J Med Virol 2020; 92:1915-21.

27. Verdecchia P, Cavallini C, Spanevello A, et al. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med 2020; 76:14-20.

28. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol 2020; 5:562-569.

29. Verdecchia P, Cavallini C, Spanevello A, et al. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med 2020; 76:14-20.

30. Sadhukhan P, Ugurlu MT, Hoque MO. Effect of COVID-19 on Lungs: Focusing on Prospective Malignant Phenotypes. Cancers. 2020; 12:3822.

31. Wadman M, Couzin-Frankel J, et al. A rampage through the body.

32. Quirch M, Lee J, Rehman S. Hazards of the cytokine storm and cytokine-targeted therapy in patients with COVID-19. J Med Internet Res 2020; 22:e20193.

33. Zheng YY, Ma Y, Zhang J, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol.

34. Kloor D, Osswald H. S-Adenosylhomocysteine hydrolase as a target for intracellular adenosine action. Trends Pharmacol Sci 2004; 25:294-297.

35. Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with COVID-19 pneumonia. Eur Respir J 2020; 56.

36. Abou-Ismail MY, Diamond A, Kapoor S, et al. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res 2020; 194:101-115.

37. Zhongming Z, Linong L, Xiaona Y, et al. NIH study uncovers blood vessel damage & inflammation in COVID-19 patients' brains but no infection.

38. Romiti GF, Corica B, Lip GY, et al. Prevalence and impact of atrial fibrillation in hospitalized patients with COVID-19: a systematic review and meta-analysis. J Clin Med 2021; 10:2490.

39. Long B, Brady WJ, Koyfman A, et al. Cardiovascular complications in COVID-19. Am J Emerg Med 2020; 38:1504-1507.

40. Guerrero JI, Barragán LA, Martínez JD, et al. Central and peripheral nervous system involvement by COVID-19: a systematic review of the pathophysiology, clinical manifestations, neuropathology, neuroimaging, electrophysiology, and cerebrospinal fluid findings. BMC Infect Dis 2021; 21:515.

41. Carod-Artal FJ. Complicaciones neurológicas por coronavirus y COVID-19. Rev Neurol 2020; 70:311-322.

42. Toscano G, Palmerini F, Ravaglia S, et al. Guillain–Barré syndrome associated with SARS-CoV-2. N Engl J Med 2020; 382:2574-2576.

43. Kunutsor SK, Laukkanen JA. Renal complications in COVID-19: A systematic review and meta-analysis. Ann Med 2020; 52:345-353.

44. Elezkurtaj S, Greuel S, Ihlow J, et al. Causes of death and comorbidities in hospitalized patients with COVID-19. Sci Rep 2021; 11:1-9.

45. Morales-Franco B, Nava-Villalba M, Medina-Guerrero EO, et al. Host-Pathogen Molecular Factors Contribute to the Pathogenesis of Rhizopus spp. in Diabetes Mellitus. Curr Trop Med Rep 2021; 22:1-2.