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Review Article

Pulmonary and Extra-Pulmonary Complications of COVID-19: A Literature Review

Muhammad Ibrahim,[1] Ahmed Ayaz,[2] Ainan Arshad,[2] Erfan Hussain,[2] Bushra Jamil[2]

[1]Karachi Grammar College, [2]Aga Khan University, Karachi, Pakistan

Abstract

Although scientific innovation in the modern age has led the way for crucial breakthroughs in the field of medicine, human beings have not yet been able to tame burgeoning infectious threats. Initial studies had shown that elderly patients and those with a higher comorbidity burden had a worse prognosis when compared to their younger and healthier counterparts. The former were also at a higher risk of developing pulmonary complications such as Acute Respiratory Distress Syndrome (ARDS) and cytokine storm to devastating effect. Later on, it was discovered that this virus can also affect several extra-pulmonary organs and cause cardiac, neurological, thrombotic, dermatological and gastrointestinal complications. The purpose of this review article is to summarize current evidence on short and long term complications of COVID-19 in a system-wise manner to serve as a guide for all healthcare providers around the world for early detection, prevention and timely management of such complications.

Key Words: Covid-19, pneumonia, cytokine storm, complications

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Corresponding Author: Dr. Ainan Arshad **Email:** ainan_arshad@hotmail.com

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Introduction

Although scientific innovation in the modern age has led the way for crucial breakthroughs in the field of medicine, human beings have not yet been able to tame burgeoning infectious threats. First emerging in Wuhan, China, today the novel coronavirus has had devastating effects all around the world, carving a course of carnage its wake. This virus, also known as SARS-CoV-2, seems to be an extremely sophisticated pathogen which can cause asymptomatic or mild infection, but also has the capability of imposing severe multi-organ damage when it comes across vulnerable hosts.

As of 14th June 2021, the virus has killed almost 3.9 million people and led to more than 181 million confirmed cases around the world.[1] Perhaps the most frightening aspect of this disease is how easily it is spread through droplets in air and a mere conversation between two unmasked people has the potential to spread devastation throughout an entire population.

Initial studies had shown that this deadly virus colonized the nasopharynx and the most common presenting symptoms were fever, fatigue, cough, sore throat, myalgias, anorexia and dyspnea.[2,3] Respiratory complications such as Acute Respiratory Distress Syndrome (ARDS), super infection and cytokine storm were also reported. It was learnt that older patients and those with a greater number of comorbid conditions were affected more severely by this disease as compared to their younger and healthier counterparts.[4]

As more data was amassed over the next few months, it was discovered that the virus can also cause several extra-respiratory problems such as cardiac, neurological, thrombotic, dermatological and gastrointestinal complications in patients.[5–9] While researchers have published individual findings with regards to these complications from their respective specialities, there is no comprehensive resource amalgamating all these new findings. The purpose of this review article is to summarize the current evidence on short and long term complications and outcomes of COVID-19 in a holistic manner and to serve as a guide for all healthcare providers around the world for early detection, prevention and timely management of such complications.

Discussion

Respiratory Complications

Respiratory complications have been the most commonly reported complication of the Sars-CoV-2 virus infection.[10,11] Severe cases may also develop acute respiratory distress syndrome (ARDS) as seen in almost one-fifth of the cases. Moreover 33% of these have the risk of developing respiratory failure and require mechanical ventilation.[2,12]

Furthermore, recent studies have shown that ARDS may be caused or further worsened to multi-organ failure and even death by a condition called Cytokine Release Syndrome, which is brought into being by excessive and persistent inflammation when the human body cannot bring about a sufficient immune response to COVID-19.[13,14] Hence, we infer that CRS can be caused by COVID-19 and we can recognize it by a surge in levels of inflammatory cytokines.[15,16] Potential treatments and timely controls for the cytokine storm have been identified in several studies around the world, and they include the administration of Tocilizumab and the use of immunomodulators and cytokine antagonists.[9,17] These treatment options may help decrease the fatality rate of patients suffering from CRS, but further research on their effectiveness is required.

Recently, a number of case reports have reported invasive pulmonary aspergillosis in a few COVID-19 recovered patients. Interestingly, the patients treated with Tocilizumab seemed to be at an increased risk of developing this rare, but alarming complication after recovering from COVID-19.[18] In addition to the classic ground-glass pulmonary opacities seen in COVID-19, medical practitioners should look out for thin-walled cavities occupied by fungal ball-like lesions in such patients. Furthermore, elevated IGE levels and neutrophil counts have also been reported.[19–21]

Cardiovascular Complications

Multiple studies around the world have indicated that patients with existing cardiac conditions are more susceptible of developing severe symptoms of COVID-19. At the same time, COVID-19 can also worsen damage to the heart. A meta-analysis of 1527 patients from six studies conducted by Li and his colleagues reported that the ratios of hypertension and cardiocerebrovascular disease in those with COVID-19 were 17.1% and 16.4%, respectively. Furthermore, the likelihood of cardiovascular disease and hypertension was approximately two times and three times, respectively, greater in severe ICU cases as compared with severe non-ICU cases. The analysis also concluded that the chance of myocardial injury is about thirteen times greater in severe, ICU admitted patients than non-severe, cardiac patients.[22] A study on 99 diagnosed COVID-19 patients in Wuhan, China further shows that this virus can cause cardiac damage. Out of the 99 patients, the first fatality was by way of cardiac arrest. This 61-year-old man had no earlier underlying disease, but was suffering from sepsis and lung and heart failure. Furthermore, three out of eleven of the patients that died in the study suffered from hypertension previously.[10] Another study conducted in South Asia showed that those with existing hypertension and ischemic heart disease had a greater risk of mortality than their healthier counterparts[(11)]. A Washington study of[21] critically ill patients, conducted by Arentz et al, showed that 42.9 percent of patients had congestive heart failure before admission, hence showing that comorbidities increase the risk of developing severe disease. [23]

On average, cardiovascular complications in COVID-19 infections amount to an incidence of approximately eight to twelve percent.[24] The above data clearly shows that not only do cardiac comorbids increase the risk of severe onset of Sars-Cov-2, but the virus can also exacerbate damage to the heart. Hence, we recommend that clinicians focus on continuous monitoring and aggressive management of patients with existing cardiac comorbidities and those who show signs of developing cardiac complications.

Neurological Complications

Neurological manifestations are yet another recently discovered aspect of COVID-19. Researches classify these manifestations into those of the Central Nervous System (CNS) and Peripheral Nervous System (PNS).[25] Although approximately thirty five percent of patients show these manifestations, they are more common in patients suffering from severe disease because of cerebral hypoxia caused by respiratory failure.[26,27]

Several CNS manifestations have been reported, with headaches being the most common. They have a prevalence of up to 23 percent and a mean prevalence ratio of eight per-cent.[28] Dizziness remains another common symptom, with 13 out of 138 patients displaying it in a study by Wang et al.[29] In patients with more poor prognosis, manifestations such as delirium was also observed; one study reported a state of confusion in nine percent of patients.[10] Other less common symptoms such as ischemic stroke, epilepsy, ataxia, acute necrotizing encephalopathy (ANE), and acute disseminated encephalomyelitis (ADEM) were also observed.[30,31]

The PNS manifestations that have been reported in literature are comparatively less severe, with the common ones being ageusia and anosmia.[32] These 2 symptoms are usually seen at the initial stages of the disease or in individuals with no other symptoms.[33] It is therefore recommended that anyone experiencing these symptoms should get tested for COVID-19 and self isolate as a precautionary measure as they may be possible carriers of the virus. Other PNS manifestations that have been reported include muscle pain and Guillain-Barre synd-

rome.[32] Several case studies have also reported the onset or worsening of complications such as myasthenia gravis and cerebral venous sinus thrombosis.[34,35]

It is imperative that medical practitioners are made aware of the wide spectrum of neurological COVID-19 manifestations for early diagnosis and isolation of patients. It can be concluded that severe neurological manifestations are less common and associated with severe disease, while mild symptoms such as anosmia are fairly common in COVID-19 patients.

Thrombosis and Coagulopathy

An increased rate of thromboembolic events is fairly common among patients with COVID-19[(36,37)]. Acute limb ischemia and abdominal and thoracic aortic thrombosis are two very similar and common complications. Both of them can occur in patients receiving already receiving thromboprophylaxis, and patients suffering from these complications usually have elevated D-Dimer levels and may have high C-Reactive Protein levels.[38–40]

Symptoms for the former include acute limb pain, focal hypothermia, skin mottling and necrosis of the toes, while symptoms for the latter include unilateral distal limb ischemia, bilateral distal limb ischemia, bilateral lower extremity weakness, bilateral lower extremity loss of sensation, and acute periumbilical abdominal pain.[38,41,42] Other manifestations include mesenteric ischemia, myocardial infarction, venous thromboembolism, acute cerebrovascular accident and disseminated intravascular coagulation.[43–45]

It is important that early recognition and treatment of these manifestations takes place, as these complications can be fatal if not adequately treated.

Gastrointestinal Complications

Gastrointestinal complications are yet another facet of COVID-19 that were initially not seen, but have now started coming to light in more recent studies. These complications were usually evident through increased levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST). One study reported that thirty three and twenty-eight percent patients had higher ALT and AST levels, respectively, while another showed injury to the liver in almost 15 percent of patients.[46] Another study that examined eighty-two COVID-19 fatalities concluded that the occurrence of liver damage could be as high as seventy eight percent.[47]

Several studies indicate that liver damage can occur from the pathogen directly infecting liver cells. According to one study, about two to ten percent of patients had SARS-CoV-2 RNA present in blood and fecal samples along with nausea, vomiting, diarrhea and abdominal pain.[48] Tan et all further indicated the likelihood of the virus directly infecting liver tissue by showing that 7a, a COVID-19 specific protein, could bring about cell apoptosis in the liver and organs like the kidney and lungs by making use of the caspase dependant path.[49] Another study, however, suggested that the virus may not always precisely attack liver cells, but could also cause pulmonary injury by inflicting damage on bile duct cells.[8] Other studies suggest that cytokine storms induced by increased immune response could also contribute to liver damage.[50,51]

While pulmonary complications are frequent in patients suffering from SARS-CoV-2, no direct fatal effect of the pathogen on the liver has been observed. To further understand the pulmonary complications of this disease, changes in patients already suffering from liver disease and in patients suffering from severe COVID-19 must be closely monitored.[52]

Dermatological Complications

Dermatological complications of COVID-19 infection include urticaria, vesicles, maculopapular rashes and distal limb ischemia[(5)]. While many of these manifestations are known to resolve on their own, they can help in the early diagnosis of COVID-19. In a study conducted in Lombardy, Italy, about twenty percent of patients displayed cutaneous symptoms such as erythematous rash, extensive urticaria and vesicles resembling chickenpox. However, there was no connection with the disease's severity, and itching was usually minimal or not present [(53)].

A study of 375 Spanish patients reported maculopapular rashes in forty seven percent of patients, pseudo-chilblain and urticaria in nineteen percent, vesicles made of monomorphic vesicles in nine percent and livedo reticularis or necrosis in 6 percent. What's unique about this study is that they have attributed these observed symptoms with different demographics. They concluded that pseudo-chilblain was typically correlated with less severe disease, and usually took place in younger people. On the other hand, necrotic lesions were present in aged individuals suffering from more severe disease. This group had a mortality rate of ten percent. Furthermore, vascular lesions were seen in cases with intermediate severity, with patients being middle aged, and urticaria and maculopapular lesions were seen in disease with greater severity.[54]

A study conducted in France, however, is not in line with the majority of the studies. It shows that only 4.9 percent of screened patients presented with cutaneous manifestations.[55] Many believe that since patients in France were only screened if they are suffering from pulmonary problems or if they needed hospitalization, it is possible that many unreported asymptomatic or non-severe patients might have been suffering from

dermatological manifestations in the country, but were under-reported. All the above studies show that dermatological manifestations are quite common, and could aid in the early diagnosis of COVID-19 patients that don't present with the typical symptoms reported earlier.

Outcomes of COVID-19

Readmissions

It seems that even after recovering from the immense suffering brought about by the horrific SARS-CoV-2, some patients are not relieved from its effects even after hospital discharge. Several studies have shown that many patients are being readmitted to hospitals after being discharged. Between nine and twenty percent of patients were readmitted to hospitals within sixty days of being discharged.[56,57] Another study reported that the mean number of days before readmission was ten, with the interquartile range being between six and fifteen days, while another reported that the median number of days before readmission was five.[58,59] Elderly patients and those suffering from chronic conditions such as hypertension, chronic lung disease and diabetes were more likely to be readmitted than their younger and healthier counterparts. The most common reasons for the readmission were respiratory distress, sepsis, pneumonia and cardiac failure.[59,60] Readmission from bacterial pneumonia was the most common, with one study showing that 34 out of 61 re-admitted patients were suffering from it.[61]

Another frightening observation was that the time spent in the hospital during readmission was generally longer and more burdening on hospital resources than that spent during the initial hospitalization. Keeping in mind the above data, it is extremely important for hospitals to aggressively monitor trends in readmission as there is still a dearth of literature available on this topic. Risk stratification must be used to identify high risk patients who have a higher potential for readmission in the future and effective strategies must be developed to prevent the readmission of such patients.

Effects of steroid use

Due to being easily accessible and affordable, Corticosteroids serve as a viable treatment option for hyper inflammation and ARDS in COVID-19[(62)]. Many clinical trials have reported corticosteroids having a positive effect in treating severe COVID-19. The RECOVERY trial reported that the employment of dexamethasone reduced twenty eight day mortality in patients needing oxygen or mechanical ventilation as compared to normal care.[63] A systematic review of 44 studies also showed that there is an overall beneficial effect of steroid use in patients.[64]

However, there is also well documented evidence of the harm associated with steroid use, which includes the suppression of the hypothalamic pituitary adrenal axis, delayed viral clearance and opportunistic infections.[65,66] This evidence has also been collected in researches done during the onset of the MERS and SARS Coronaviruses.[67,68] Studies published by Ma et al and Sarkar et al show that corticosteroid treatment in COVID-19 patients can lead to longer hospitalization, longer use of antibiotics and greater viral shedding.[69,70]

Hence, it is safe to say that while corticosteroid treatment is a viable option, close care and attention needs to be paid to the duration, timing and doses of the medicine to ensure minimal adverse effects.

Mental Health

Human beings are social animals, and being in quarantine or isolation due to the ongoing pandemic has not fared well for us. The pandemic has caused a surge in mental health issues around the globe such as anxiety, depression, stress, insomnia, and anger.[71]

A systematic review completed by Vindegaard et al yielded some very important conclusions. Patients were found to have a very high level (96%) of post traumatic stress symptoms and depressive symptoms. Furthermore, research also showed increased incidence of anxiety, stress, depression and worsened sleep quality in those working in the healthcare sector. Lower self-being was also reported in the general population, while those with already present psychiatric problems showed a worsening of symptoms.[72]

Because the pandemic has had such an immense strain on healthcare facilities, mental health has generally been overlooked around the globe. However, it is imperative that this sector is given its due importance and proper strategies are devised to minimise the deterioration of mental health at a national level due to the adverse effects of the pandemic.

Conclusion

Although respiratory complications such as ARDS are the most commonly observed manifestations among patients suffering from COVID-19 infection, this virus is also responsible for a myriad of complications in other organs such as the liver, heart, brain and skin. This article provides a comprehensive system-wise review of all common and rare manifestations of COVID-19, and we hope that it can act as a guide for all medical practitioners for early detection, prevention and timely management of such complications.

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Table 1: *System-wise summary of the pulmonary and extra-complications of COVID-19.*

S.NO.	Organ System	Description
1	**Respiratory**	• Bilateral pneumonia and pulmonary opacities reported in 75% and 50% of admitted patients, respectively • 17% of admitted patients can develop ARDS which can further complicate into Cytokine release syndrome.[10,11]
2	**Cardiac**	• Patients with existing cardiac conditions are more susceptible of developing severe symptoms of COVID-19. • At the same time, COVID-19 can also worsen damage to the heart. • cardiovascular complications in COVID-19 infections amount to an incidence of approximately eight to twelve percent.
3	**Neurological**	• Neurological manifestations can be classified into those of the Central Nervous System (CNS) and Peripheral Nervous System (PNS). • Approximately thirty five percent of patients show these manifestations. • they are more common in patients suffering from severe disease because of cerebral hypoxia caused by respiratory failure. • Common CNS manifestations include headaches while common PNS manifestations are ageusia and anosmia.[32]
4	**Thrombosis and Coagulopathy**	• Acute limb ischemia and abdominal and thoracic aortic thrombosis are two very similar and common complications. • Both of them can occur in patients receiving already receiving thromboprophylaxis. • patients suffering from these complications usually have elevated D-Dimer levels and may have high C-Reactive Protein levels.[38–40]
5	**Gastrointestinal**	• Gastrointestinal complications were usually evident through increased levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST). • Liver damage can occur from the pathogen directly infecting liver cells. • About two to ten percent of patients can have SARS-CoV-2 RNA present in blood and fecal samples along with nausea, vomiting, diarrhea and abdominal pain.[42-48]
6	**Dermatological**	• Dermatological complications of COVID-19 infection include urticaria, vesicles, maculopapular rashes and distal limb ischemia. • twenty percent of admitted patients can display cutaneous symptoms such as erythematous rash, extensive urticaria and vesicles resembling chickenpox.
7	**Re-admission**	• Between nine and twenty percent of patients were readmitted to hospitals within sixty days of being discharged. • The mean number of days before readmission was ten, with the interquartile range being between six and fifteen days. • the median number of days before readmission was five[58,59]
8	**Steroid use**	• Corticosteroids serve as a viable treatment option for hyper inflammation and ARDS in COVID-19. • Clinical trials have reported corticosteroids having a positive effect in treating severe COVID-19. • However, there is also well documented evidence of the harm associated with steroid use, which includes the suppression of the hypothalamic pituitary adrenal axis, delayed viral clearance and opportunistic infections((65,66)**.**
9	**Mental health**	• Research showed increased incidence of anxiety, stress, depression and worsened sleep quality in those working in the healthcare sector. • Lower self-being was also reported in the general population, while those with already present physciatric problems showed a worsening of symptoms.[72]

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