Review Article

SARS-CoV-2: Review of Conditions Associated With Severe Disease and Mortality

Abstract

The 2019 Coronavirus Virus Disease (COVID-19) represents a global public health challenge in the twenty-first century. As of June 2020, the virus had spread across 216 countries across the globe. This paper aims to analyze and identify those existing comorbidities among COVID-19 patients that represent potential risk factors for COVID-19 complications, severe illness, and death. Multiple database resources were searched. The resources include the University of Saskatchewan library USearch, Google Scholar, PubMed, Medline, and the Google search engine. Thirty-seven articles, which included 15 different types of chronic diseases, were selected. Among the reviewed diseases and conditions, cancer, diabetes, lymphopenia, hypertension, kidney disease, smoking, chronic obstructive pulmonary disease (COPD), and organ transplant were found to represent potential risk factors for COVID-19 complications, severe illness, and death. Other conditions that require further research as to whether they predispose subjects to severe illness and death include coronary artery disease, cerebrovascular disease, valvular heart disease, gastrointestinal diseases, HIV/AIDS, asthma, and liver disease. In conclusion, this article explains the association between diseases mentioned above and the severity of COVID-19 and clearly shows the population at risk. This paper will help government bodies and decision-makers prioritize resources for these populations to reduce mortality rates and overall quality of life.

Keywords: *Chronic, COVID-19, mortality*

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Introduction

In December 2019, the city of Wuhan in the province of China became the epicenter for a respiratory illness outbreak of unknown etiology. It was later identified as a novel coronavirus (2019 Coronavirus Virus Disease [COVID-19]) disease.[1] Since then, the disease has rapidly spread across the world, affecting approximately 216 countries and territories, with some countries having a higher number of cases and higher mortality rates than others.[2]

The severity and mortality among COVID-19 patients have been associated with potential risk factors and comorbidities.[3] This rapid review's objective is to analyze and identify those existing comorbidities among COVID-19 patients that represent potential risk factors for COVID-19 complications, severe illness, and death.

Methods

A literature review was conducted to explore the potential association between existing comorbidities in patients infected with COVID-19 and the severity and complications of the disease. Multiple database resources including the University of Saskatchewan library USearch, Google Scholar, PubMed, Medline, and the Google search engine were utilized. In the end, 37 articles were retrieved, which included 15 types of diseases.

Association of Diseases with Severity of Covid-19

Cancer and COVID-19

As compared to other strains of Coronavirus, more COVID-19 deaths were reported to have resulted from multiple organ dysfunction syndromes rather than respiratory failure.[4] This may be attributed to the widespread distribution of angiotensin-converting enzyme,[4] which is the functional receptor for SARS-CoV-2 in multiple organs.[5,6] Cancer patients are more susceptible to infection than cancer-free patients because of their systemic immunosuppressive state caused by malignancy and anticancer therapy, such

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as chemotherapy and surgery.[7-10] Thus, these patients may be at an increased risk for serious COVID-19 illness and have a poorer prognosis. To illustrate, a cohort study with 1590 cases from 575 hospitals in China found that the proportion of cancer patients in COVID-19 cases is much higher than the incidence of cancer in the overall Chinese population.[11] Most notably, cancer patients were found to have a higher risk for severe events such as admission into the intensive care unit, invasive ventilation, and death, compared to cancer-free patients.[11]

Furthermore, another literature report came to a similar conclusion that the immunosuppressive status of cancer patients caused cancer patients to be at a higher risk of COVID-19 infection than the general population.[12] The same study also claimed that the immunosuppressive condition caused by malignant tumors and anti-cancer therapies such as chemotherapy or surgery significantly increased cancer patients' susceptibility to severe complications of COVID-19.[12] It was found that cancer patients are 3.5 times more likely to develop COVID-19 severe infections than patients without cancer.[12] Moreover, having cancer history brings the highest risk for severe complications, and it is associated with COVID-19 poor prognosis.[12]

Based on the above findings, the researchers provided strategies for how cancer patients respond to the COVOID-19 crisis. Firstly, a deliberate delay of adjuvant chemotherapy or elective surgery to treat stable cancer in endemic areas should be considered.[11] Secondly, patients with cancer or cancer survivors should be given better health security provisions.[11] Thirdly, when cancer patients are infected with SARS-CoV-2, more intensive surveillance or treatment should be considered, especially in older patients or those with other comorbidities.[11]

Kidney disease and COVID-19

In a large prospective cohort study in Wuhan, China, researchers found a high prevalence of kidney disease in COVID-19 hospitalized patients.[13] A potential reason for the high incidence of kidney disease at admission to the hospital is that some COVID-19 patients had a previous history of chronic kidney disease.[13]

Such patients with functional deficiencies in populations of innate and adaptive immune cells are known to have a higher risk for pneumonia and upper respiratory tract infection.[14,15] Furthermore, after the lungs get infected with COVID-19, the virus can penetrate the blood, accumulate in the kidney, and cause sustained damage of organ's resident cells.[13] The study also suggests that kidney disease is associated with higher hospital mortality.[13] One possible reason for this is that COVID-19 patients with existing kidney disease have a higher risk of developing acute kidney injury (AKI) during hospitalization, which can lead to poorer prognosis and significant mortality.[13]

Similarly, in Arentz's research in Washington State, it showed that out of 21 critically ill COVID-19 patients, 18 of them had confirmed comorbidities. The most common was chronic kidney disease (48%).[16] Hence, these findings indicate that early identification of those with kidney disease, interventions to provide adequate care, and nephrotoxin avoidance may help improve the prognosis of COVID-19 patients.[13]

Smoking and COVID-19

The main invasion route of the COVID-19 virus is through mucosal tissues: nose, mouth, and upper respiratory tract.[17] Exposure to cigarette smoke triggers inflammatory processes in the lung, heightened mucosal inflammation, expression of inflammatory cytokines and tumor necrosis factor α, increased permeability in epithelial cells, mucus overproduction, and impaired mucociliary clearance.[18] A recent systematic study from Vardavas and Nikitara reported that "smoking is likely associated with negative development and adverse effects of COVID-19".[19] The research has shown that differences in COVID-19 disease prevalence and severity are associated with the higher expression of ACE2 among smoking people.[20] Conversely, Lippi, and Henry's brief meta-analysis recorded no correlation between smoking status and COVID-19 severity.[21] However, we cannot ignore the fact that tobacco smoke exposure is the leading risk factor for lung disease.[18] Also, smoking is a significant risk factor for bacterial and viral infections.[22] Moreover, other suggested risk factors for severe COVID-19 illness (lung and cardiovascular diseases, diabetes, etc.) are common among smokers.[17]

According to another report, the poor prognosis of COVID-19 patients with a history of smoking is significantly higher than that of patients without a history of smoking.[19] Smokers were 1.4 times more likely to have severe COVID-19 symptoms and approximately 2.4 times more likely to be admitted to an ICU, need mechanical ventilation, or die than non-smokers.[19]

Chronic obstructive pulmonary disease and COVID-19

Chronic obstructive pulmonary disease (COPD) is associated with a high risk of morbidity and mortality in community-acquired pneumonia (CAP). At the same time, COVID-19 is relatable as it is a systemic respiratory illness that may progress to severe hypoxemia.[23]

According to a meta-analysis conducted to analyze the association between COPD and increased odds of severe COVID-19 infection, it was advised that clinicians should always monitor COPD patients with suspected infection.[23] The results from the study showed that the odds of increased severity of COVID-19 infection are five times higher in COPD patients (OR = 5.69; 95% CI: 2.49–13.00; 12 = 0.0%; Cochran's Q, P = 0.95).[23] Therefore, to reduce COVID-19 exposure or severity, patients with

COPD should practice protective measures against contact with suspected or confirmed cases of COVID-19.[23]

Bone marrow/organ transplantation and COVID-19

As the management of COVID-19 in the transplant population remains unclear and complicated, bone marrow/organ transplantation patients require utmost care and attention. Posttransplant patients are usually under immunosuppressive therapy; the immunosuppressive agents they take, including cyclosporin-A and mycophenolate mofetil, have been reported to increase the risk of opportunistic infection, including viral infection.[24]

According to reports among the transplant population, comorbidities increase the risk of severe pneumonia in the COVID-19 infected population.[25] However, in the history of transplantation, immunosuppressive agents have never been reported as a risk factor to increase the chances of COVID-19. Haung *et al*.[25] dispute the claim that the discontinuation of immunosuppressants and steroid treatment might help faster recovery from COVID-19 pneumonia among the posttransplant population due to the fact that patients in their study developed a nosocomial bacterial infection during hospitalization, which warrants more careful use of steroids in COVID-19 disease.[25]

Cerebrovascular disease and COVID-19

According to a retrospective, observational case series, neurological manifestations fell into three categories: central nervous system manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system manifestations (taste impairment, smell impairment, vision impairment, and nerve pain), and skeletal muscle injury manifestations.[26] Most neurologic manifestations among patients in this case series occurred early in the illness (with a median time to hospital admission being 1–2 days).

The patients with severe infection had little or no COVID-19 symptoms and more underlying disorders like hypertension.[26,27] In addition, they were older and more likely to develop neurologic manifestations, especially acute cerebrovascular disease, conscious disturbance, and skeletal muscle injury. In the United States, cerebrovascular diseases are regularly associated with high morbidity, mortality, and a financial burden.[27]

Although more extensive studies are needed, these studies explain that for those with severe COVID-19, rapid clinical deterioration, or worsening could be associated with neurological events such as stroke, which would contribute to its high mortality rate.[26] However, clinicians must consider the state of the present COVID-19 epidemic during the diagnosis of neurological manifestations. Also, coupled with the current COVID-19 pandemic, understanding cerebrovascular disease patients who are at high risk for COVID-19 will place priority in resource allocation.[27]

Lymphopenia and COVID-19

COVID-19 patients with lymphocytopenia have demonstrated more severe disease than patients with normal lymphocytes level.[28] Lymphocytopenia alone is a prominent feature among patients severely affected with SARS-CoV,[29] which is explained by the necrosis or apoptosis of lymphocyte when there is invasion of viral particles.[28] It is suggested that the severity of the disease is determined by lymphopenia in patients with COVID-19.[30] A study by Zhang *et al*.,[30] analyzing the absolute number of different subsets of lymphocytes among Intensive Care Unit (ICU) patients, showed that there was a dramatic decrease in the total number of T-cells, CD4+ T cells, CD8+ T cells, total B cells, and natural killer cells among severely ill patients.

Lymphocytopenia in COVID-19 patients with severe disease may be caused by T-cell exhaustion, and a state of T-cell dysfunction resorts from the using up of T cell during many chronic infections and cancer.[31] The expression of inhibitory receptors characterizes it, and IL-10, an inhibitory cytokine, not only prevents T-cell proliferation but also can induce T-cell exhaustion.[31] It is characterized by the expression of inhibitory receptors, and IL-10, an inhibitory cytokine, not only prevents T-cell proliferation but also can induce T-cell exhaustion.[31] A study by Diao *et al*.[31] demonstrated that COVID-19 patients have very high levels of serum IL-10 following SARS-CoV-2 infection, which may be responsible for the apoptosis of T cells in these subjects.

Lastly, lymphocytopenia in COVID-19 patients with high levels of circulating cytokines can be explained by pre-existing chronic diseases and reveals a connection between the existence of these chronic diseases and the development of severe disease after infection.[31]

Coronary artery disease and COVID-19

There is often poor prognosis in patients with the acute coronary syndrome who are infected with the SARS-CoV-2.[32] This phenomenon is because, in acute coronary syndrome (ACS), there can be a reduction in cardiac functional reserve resulting from myocardial ischemia or necrosis.[32] Therefore, when an individual with ACS is infected with SARS-CoV-2, there may be resulting cardiac insufficiency, which can lead to a sudden worsening of these patients' conditions.[33]

A study by Zheng *et al*.,[32] in Wuhan, China, reported that some patients with COVID-19, who had previous ACS, showed that there was an association between history of ACS and severe illness and high mortality after SARS-CoV-2 infection. In patients with underlying coronary artery disease and cardiac insufficiency,

SARS-CoV-2 infection might act as a precipitating factor to deteriorate the condition and lead to death.[6]

It remains unclear whether cardiomyopathy in some aged patients was pre-existing or resulted from the impact of SARS-CoV-2 infection.[16] There is a need to conduct more research on the correlation between the pre-existing coronary artery disease, cardiomyopathy, and the development of severe illness after SARS-CoV-2 infection.

Valvular heart disease and COVID-19

Patients with pre-existing structural and valvular cardiac diseases tend to have a more severe illness from SARS-CoV-2[34]; this may result from the effects of dysfunctional valves on the pulmonary system.[35] For example, a patient with prolonged mitral stenosis may experience lodging blood in the left atrium, causing atrial hypertension. This hypertension can find its way up to the lungs, leading to pulmonary hypertension.[36]

As the current literature has limited information on the impact of COVID-19 in patients with structural heart disease (SHD), it is imperative to extrapolate that these patients are at high risk for poor prognosis based on their old age and several comorbidities.[37] Further research still needs to be conducted to provide specific descriptions on the impact of pre-existing structural heart disease on the outcome of SARS-CoV-2 infection in patients.

Diabetes and COVID-19

Diabetes has become a suspected risk factor associated with severe COVID-19 illness and death. A reason for this may be the abnormalities in the immune system associated with high blood glucose.[38] The irregularities in innate cellular immunity play a role in the pathogenesis of increased infections in diabetic patients.[39] Moreover, diabetic cells become more adherent to microorganisms, which later become more virulent in a high glucose environment.[39]

In a recent study analyzing the impact of diabetes and hyperglycemia among laboratory-confirmed COVID-19 patients, it was found that patients with diabetes and/or uncontrolled hyperglycemia had a longer length of stay in the hospital when compared with patients without diabetes and/or hyperglycemia.[40] The same study concluded that the mortality rate was considerably higher among patients with diabetes and/or uncontrolled hyperglycemia than among patients without diabetes and/or hyperglycemia.[40] Furthermore, the study found that COVID-19 patients with uncontrolled hyperglycemia had a high mortality rate.[40]

Similarly, another study analyzing the risk for ICU admission and mortality in COVID-19 patients with diabetes concluded that diabetes represents a high risk for ICU admission and mortality among COVID-19 patients.[41] This study found a significant increased risk for ICU admission among diabetic patients (OR: 2.79, 95% CI: 1.85–4.22, $P < 0.0001$, $I_2 = 46\%$).[41] The study also analyzed patients for secondary outcomes, finding diabetic patients to be at a higher risk for mortality (OR: 3.21, 95% CI: 1.82–5.64, $P < 0.0001$, $I_2 = 16\%$).[41]

Since research has shown that COVID-19 patients with diabetes and/or uncontrolled hyperglycemia are at higher risk for severe illness and death compared with patients without diabetes and/or uncontrolled hyperglycemia. Clinicians must pay particular attention to COVID-19 patients with diabetes and/or uncontrolled hyperglycemia to ensure adequate treatment for diabetes and hyperglycemia.

Hypertension and COVID-19

Hypertension has been identified as a potential risk factor for severe COVID-19 illness and death. A study that analyzed the clinical characteristics of patients who died of coronavirus associated complications in China found that among patients who died of COVID-19-induced pneumonia, hypertension was the most common chronic comorbidity.[3] Similarly, in a case series, it was reported that the rate of hypertension was higher among COVID-19 patients admitted to ICU than among COVID-19 patients that were not admitted to ICU.[35]

Furthermore, another recent case series analyzing the characteristics, comorbidities, and outcomes of hospitalized COVID-19 patients in New York reported that hypertension was one of the most common comorbidities among COVID-19 hospitalized patients.[42] Relatedly, a study evaluating the outcome in hypertensive patients with COVID-19 and its association with the use of renin-angiotensin system blockers (RASB) concluded that hypertension is one of the comorbidities that represents an increased risk for in-hospital death among COVID-19 patients.[43] Lastly, a retrospective cohort study exploring clinical course and risk factors for mortality of adult inpatients in China found hypertension as the most common comorbidity in COVID-19 adult patients.[6]

As hypertension has been identified as one of the comorbidities associated with severe COVID-19 illness and death, special attention must be paid to COVID-19 patients with existing hypertension.[43]

Gastrointestinal disease and COVID-19

There is limited information about gastrointestinal disease patients and the potential risk for COVID-19 complications. A recent review has reported that irritable bowel disease (IBD) patients could be at higher risk for COVID-19 complications.[44] A possible reason for this may be the chronic condition itself and the use of immunosuppressant as a treatment.[44]

Although more research is needed to evaluate the potential risk of COVID-19 complications among patients with gastrointestinal disease, health authorities in developing

countries must pay special attention due to the lack of basic sanitation in part of the population.[44]

HIV/AIDS and COVID-19

Research dedicated to understanding the impact of COVID-19 on the health and well-being of individuals living with HIV is a new area being explored. According to a recent article, a weakened immune system from AIDS was not associated with the development of COVID-19.[45] These findings may be because some AIDS patients use protease inhibitors, which may impact the development of COVID-19.[46-48]

On the other hand, in a case study conducted in 2020, an AIDS patient diagnosed with COVID-19 presented with fever and chest lesions symptoms upon admission to the hospital.[45] The progression of the patient's symptoms was reported to be similar to that of a moderate COVID-19 patient.[49,50] A possible reason for this may be that the presence of a weakened immune system decreases the body's immune response to COVID-19, which could increase the damage to the respiratory system of AIDS patients.[51] Additionally, the presence of a weakened immune system was thought to be associated with the delayed clearing of the SARS-CoV-2.[49] However, this was not the outcome for the AIDS patient within the case study; these findings may be due to the use of LPV/r and arbidol.[45]

Health impacts of COVID-19 and HIV were also explored in a case series based on five HIV patients. In this study, none of the five patients died from COVID-19; however, they were reported to have experienced health challenges, which included lung infections, viral pneumonia, admissions to intensive care, and noninvasive assistance for breathing.[48] Other studies have suggested that individuals aged 18–49 living with HIV are at risk for COVID-19.[52] The risk of dying from complications associated with COVID-19 might be higher for younger individuals living with HIV.[53]

However, more information is needed to understand the full extent of the health impact that COVID-19 can have on patients living with HIV or AIDS.[45] This is supported by findings that suggest that factors that influence personal behaviors might also contribute to an increased susceptibility of contracting COVID-19. For example, the severity of patients' symptoms was reported to affect their use of personal protective equipment (PPE).[54] More specifically, individuals with mild to moderate AIDS symptoms may not be as likely to wear PPE as those with severe symptoms.[54]

Asthma and COVID-19

According to the current research, asthma patients may be disproportionately represented among adult patients hospitalized for COVID-19.[55,56] These findings might be associated with hospitalization due to asthma exacerbations, which can be brought on by the presence of SARS-CoV-2.[55] Concern over the impact of COVID-19 on the health and wellness of individuals living with asthma has increased due to finding substantial commonalities in the clinical presentation of asthma exacerbation and COVID-19.[57,58] In light of this, children experiencing difficulties with breathing or intensified coughing episodes were recommended to be tested for COVID-19,[57,58] especially since asthmatic children infected with SAR-CoV-2 could develop pneumonia or acute respiratory disease due to the presence of their existing condition.[59]

Attention to the potential risk associated with COVID-19 and asthma was confirmed when the CDC placed moderate and severe asthma as a condition associated with higher susceptibility for contracting COVID-19.[59] Unfortunately, the literature is currently unclear about the extent of the risk for COVID-19 that is faced by children living with asthma.[55] This is because most of the research associated with risk determinants is based on data from the adult population.[57,60,61] More research must be gathered within the younger asthmatic population, especially since adult data regarding asthma and COVID-19 suggest that asthma is a risk factor for adverse health outcomes.[55]

Liver disease/cirrhosis and COVID-19

Presently, the impact of COVID-19 on the health and the well-being of patients living with liver disease is not fully understood.[62] Due to this lack of clarity surrounding the potential impact of COVID-19 on impaired liver conditions, liver disease has not been listed as a risk factor for severe disease outcomes associated with COVID-19.[62]

Findings from a 2020 study suggest that liver disease is not related to the worsening of COVID-19 disease progression or death.[62] However, studies with larger sample sizes are needed to better understand the possible health impact that COVID-19 could have on patients with pre-existing chronic liver diseases.[62] With this being said, because COVID-19 is a relatively new public health concern, many questions remain regarding liver disease and COVID-19.[63] For instance, it is unknown whether individuals living with pre-existing cirrhosis who have contracted COVID-19 are at a higher risk for deterioration in liver functioning or developing acute-on-chronic liver failure.[63]

Overall, more information is needed to better understand the full impact that COVID-19 may have on the disease progression and overall health outcomes of individuals impacted by COVID-19 and living with liver disease.

Discussion

Our review suggests that COVID-19 is both a suspected and a confirmed risk factor influenced by various pre-existing health conditions. The CDC[64] supports these findings by suggesting that preventive actions against COVID-19 are necessary and essential for patients with an existing health

condition. Some of these health conditions included asthma, chronic kidney disease, chronic lung disease, diabetes, severe heart conditions, and liver disease.[64] Similarly, the Government of Canada[65] reports that health disease, hypertension, lung disease, diabetes, and cancer are health conditions that are associated with a high risk for severe illness form COVID-19. Nonetheless, individuals with or without a pre-existing health condition need to be cautious and practice healthful behaviors such as social distancing, washing hands, and travelling with hand sanitizers.[65]

Somewhat surprisingly, one study suggested that a weakened immune system in AIDS patients was not associated with the development of COVID-19. Interestingly, these findings were reported to be linked to the use of drugs related to treatment. This suggests that the type of therapy utilized to treat the pre-existing health condition could reduce the severity of COVID-19 progression. Thus, clinicians need to pay special attention to the quality of care provided to patients with health conditions and COVID-19. Nevertheless, individuals with HIV and COVID-19 were found to suffer health challenges, and the risk of death might be higher in specific populations. Notably, more research is required to document how COVID-19 impacts health conditions. According to the World Health Organization,[66] for instance, there is currently no peer-reviewed literature that evaluates the risk of COVID-19 and smoking.[66] This is troubling because, in 2015, more than 1.1 billion individuals were reported to smoke tobacco.[67]

Nevertheless, the WHO[68] asserts that because COVID-19 mainly attacks the lungs and smoking makes it more difficult for individuals' respiratory function, smoking will make it more challenging for the human body to withstand COVID-19. The impact of COVID-19 on health conditions is complex amongst cancer patients, and care should be modified to address the patient's unique challenges. For instance, recent research suggests that COVID-19 exposure in cancer patients can be dangerous and even lethal.[69] Researchers suggest that the approach for cancer patients needs to be adaptive and tailored to the needs of the patient, the available health resources, and the expertise of the health professionals.[69]

This report provides insights into health conditions that may be a high risk for severe illness for COVID-19 outcomes. Presently, there is a gap in the literature, and consequently, there is a need for more research to fully understand the extent to which COVID-19 impacts different health conditions. For example, researchers report the need for further research to understand how gastrointestinal symptoms are associated with COVID-19 and possible fecal-oral transmission.[70]

Notably, a limitation of this study was the limited access to research regarding COVID-19 and health conditions. The limited research is because COVID-19 is a novel disease, and research is gradually building over time. Further work is needed to understand the severity of COVID-19 illness amongst patients with various existing comorbidities and the impact that treatments and preventative measures have on disease progression.

Conclusions

The general population's safety is essential and some may argue that everyone should be included, but the thing is that nobody is excluded; there is only prioritization. The association between existing health conditions and the severity of COVID-19 gleans by focusing on which populations are at risk. Considering the weak economy and tight budgets that has resulted due to the COVID-19 pandemic, policymakers will need to focus their country's resources on these populations while other ways of preventing COVID-19 are being sought. When this group of people are selected, the funds can be directed to test the populations at higher risk for severe COVID-19 illness to reduce mortality rates and improve the overall quality of life.

Finally, at this time, simple testing kits should be made available to the public, in a similar way that test kits are available for HIV/AIDS, ovulation, or pregnancy. This is because as we wait for vaccines or other effective treatments, we need to control the spread to the barest minimum, and the only way to do that is to have everyone test for the disease.

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Conflicts of interest

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