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Review article

Factors Associated with COVID-19 Morbidity and Mortality: A Narrative Review

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Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been declared as a pandemic on March 11th 2020 by the WHO. Morbidity and mortality of COVID-19 has been shown to be high among patients with underlying diseases. In this narrative review, searching a number of electronic databases (PubMed, Google Scholar, Scopus, and Science Direct), 127 related articles written in English were retrieved and of which 73 articles related to risk factors affecting morbidity and mortality of COVID-19 were extracted and summarized. Factors such as old age, male gender and working in health setting were associated with higher morbidity and mortality. Hypertension was the most frequent reported condition among those with severe disease. It also appeared to increase the mortality and duration of hospitalization. Diabetes, respiratory chronic illnesses (COPD, asthma), impaired liver and renal function, and malignancies were also mentioned as the risk factors for severe disease, longer hospitalization, poor prognosis and outcome. Some laboratory findings such as elevated D-dimer, CRP, and LDH as well as severe lymphopenia were associated with severity, mortality and poor outcomes in hospitalized patients. All in all, a considerable number of comorbidities and biomarkers are associated with severity and presentations of COVID-19 disease, affecting its morbidity and mortality rates.

Keywords: COVID-19, Morbidity, Mortality, Risk factors, SARS-CoV-2

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Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The novel virus was discovered during an outbreak of viral pneumonia in Wuhan city, Hubei Province, China in December 2019. The symptoms include fever, dry cough, dyspnea, myalgia, and fatigue. Radiographic imaging usually indicates lung involvement with ground glass opacities. In laboratory findings, there is usually an elevated White Blood Cell (WBC) count with low lymphocyte fraction along with high C-reactive protein (CRP). However, severe cases result in organ damage (shock, acute respiratory distress syndrome, and myocarditis) and eventually lead to death (1-3).

The main route of SARS-CoV-2 transmission is person to person mainly through respiratory droplets spreading by coughing or exhaling; however, recently there is some evidence of possible airborne transmission in closed environments (4). Studies showed that the asymptomatic patients have the potential to transmit the virus as much as the symptomatic ones (5,6).

Ever since the COVID-19 emergence, the number of reported cases and related deaths has increased dramatically worldwide. The recent studies have shown that people with similar history of exposure who have underlying diseases are more predisposed to COVID-19 and they are at risk of developing severe illness (7,8). Therefore, the Case Fatality Rate (CFR) is higher in these cases. In total, the CFR was 49.0% among critical cases. Based on the report from Chinese Center for Disease Control and Prevention, the CFR was 14.8% in those aged 80 years and older, 10.5% for cardiovascular diseases, 7.3% for diabetes, 6.3% for chronic respiratory diseases, 6.0% for hypertension, and 5.6% for cancer in China (7).

To prevent and control the current epidemic, it is necessary to identify the risk factors for COVID-19 infection. As mentioned above, the majority of patients were individuals with comorbidities such as cardiovascular diseases, hypertension, diabetes, cerebrovascular diseases, respiratory diseases, and malignancies. Such risk factors are more evident in severe cases of pneumonia and ARDS. Furthermore, due to the rapid spread of this virus, it is essential to characterize the high risk groups so as to reduce the mortality of disease by implementing preventive measures among this vulnerable population. In this review, the risk factors and underlying diseases among individuals with COVID-19 were described in an attempt to enhance the current knowledge regarding the individuals at risk of developing severe diseases.

Literature search

In this narrative review, factors contributing to mortality and morbidity of severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 infection are explained. This study was conducted from March 2020 to April 2020. Inclusion criteria were all the available literature in English language identified by keyword searches in PubMed, Scopus, Embase and Google Scholar databases. The used search terms were “Coronavirus 2019”, “COVID-19”, “New Coronavirus”, “SARS-CoV-2”, “Cardiovascular Diseases”, “Hypertension”, “Pulmonary Diseases”, “COPD”, “Asthma”, “Chronic Bronchitis”, “Diabetes”, “Cancer”, “Malignancy”, “Immunosuppressed”, “Risk Factors”, and “Comorbidities”. A total of 127 articles were retrieved. The most related studies were selected by two independent researchers based on the title and abstract. Studies on non-human subjects with incomplete or inconclusive results were excluded. Overall, 73 articles were included after reading the full text based on inclusion criteria.

Risk factors related to morbidity and mortality

Demographic factors

Age

The mean age of people affected by SARS-CoV-2 ranged between 47 to 60 years in recent studies (1,8-12). People older than 50 years contributed to 67% and 48.8% of overall COVID-19 positive cases in two studies (1,12). Moreover, the fatality and ICU admission rates are often higher in older patients (Average of 60 years and higher) (9-11,13). In a study conducted among 44,672 COVID-19 patients in China, fatality rate was reported to be 14.8, 11.6 and 1.3% in people aged ≥ 80, 60-79 and 50-59 years, respectively (14).

In a study by Guan *et al*, among 7,736 cases tested positive for SARS-CoV-2, patients older than 65

years accounted for 27% of severe cases, and 31% of them were patients aged 55-64 years old. Only less than a half of ICU admitted patients (42%) were young adults (8). Based on the recent CDC report from 4,226 patients positive for SARS-CoV-2, the highest fatality rate (Ranging from 10% to 27%) belongs to patients aged ≥ 85 years, while it declines in younger ages (3-11% in 65-84 and 1-3% in 55-64 years olds) (15).

Gender

Although it has not yet scientifically proven, in several studies the proportion of female patients was lower than male ranging from 27 to 45.7% (1,8-12). Likewise, the fatality rate in women is significantly lower than that of men (14). In studies by Huang *et al* and Wang *et al*, men consisted 85 and 60% of ICU admitted patients, respectively (1,11). Moreover, 60 and 66% of non-survivors were male in Zhou *et al*'s and Yang *et al*'s studies, respectively (9,10,15).

Occupation

Given the origin of COVID-19 which was first argued to be from wild life and transmitted via seafood, the occupational exposure was suggested for the first cases working in seafood market in Wuhan (16). However, as the proportion of cases increased, the person-to-person transmission became the main route of transmission and the Healthcare Workers (HCWs) became the next population at risk for COVID-19. In a case series of 138 hospitalized patients, 40 patients (29%) were HCWs from whom 77.5% were working in general wards, 17.5% in emergency department, and 5% in ICU (11,17). During the last decade, it seems that COVID-19 is the first emerging virus associated with occupational exposure (18).

Viral loads

Viral load of SARS-CoV-2 can be an indicator of disease severity and eventual prognosis. Based on a study that compared the mean viral load in nasopharyngeal swab samples of COVID-19 positive patients (19), severe cases showed significantly higher levels than mild cases. According to Zou *et al*, viral load is immense at the onset of symptoms and the CT value (Inversely related to detected nucleic acid) appeared to be lower in patients with severe cases (5,20). Based on the Handbook of COVID-19 Prevention and Treatment, following infection, as the serum IgG and IgM levels increase, viral load decreases (21).

Comorbidities

Comorbidities play important role in morbidity and mortality of COVID-19 patients. In recent studies, 23.7-51.3% of patients infected with this virus had underlying diseases such as chronic pulmonary disease, diabetes, hypertension, cardiovascular diseases, cancer, cerebrovascular disease, Chronic Kidney Disease (CKD) and immunodeficiency (1,8-13). Moreover, a broad range of severe, ICU admitted, and deceased patients were reported to have at least one of these underlying diseases (1,9-11,13).

Factors related to immune system

The immunosuppressive medications are known to be effective treatments for patients receiving transplantation, chemotherapy, or suffering from autoimmune diseases; however, the outbreak of COVID-19 raised the concern among health workers as to whether immunocompromised patients are more susceptible to severe pulmonary diseases than general population same as with influenza (22). According to D'Antiga, although such patients are at higher risk for SARS-CoV-2 acquisition, the risk of severe acute respiratory disease among them is not more than general population; therefore, vital transplantation or chemotherapy treatments should not be delayed because of this outbreak (23). On other hand, Xu *et al* suggested patients with lung cancer have a higher risk of developing serious respiratory illnesses compared to non-cancer patients. Therefore, they are more vulnerable to SARS-CoV-2 infection. However, factors such as frequent hospital visits, old age, poor personal hygiene, physical activity, and other underlying diseases should not be neglected in this population (24).

According to Guillen *et al*, the differential diagnosis of an immunocompromised patient may be challenging. In this study, a 50-year-old man recipient of kidney transplant due to end-stage renal failure presented with atypical symptoms, *e.g.* fever, diarrhea, and fatigue. C-Reactive Protein (CRP) and WBC were also within the normal ranges. Ignoring the epidemiologic risk

factor, these symptoms could easily be mistaken with pneumonia of bacteriological source due to high dose immunosuppressants. However, a nasopharyngeal swab specimen performed on day 5, when the patients' fever persisted, tested positive for COVID-19 (25). On the other hand, in a study by Li *et al*, two patients who received heart transplant presenting similar symptoms (fever, chills, fatigue, poor appetite and diarrhea) had elevated CRP and WBC and typical bilateral ground-glass opacities in chest CT scan (26).

Factors related to cardiovascular system

Current literature indicates that preexisting cardiovascular disease and hypertension in COVID-19 patients can lead to a poor prognosis and critical situations. Hypertension is one of the key risk factors in COVID-19 disease and therefore is mentioned in many studies. It increases both morbidity and mortality in patients suffering from this novel virus (1,8,9,11-14). In fact, an estimated 12.8-31.2% of confirmed cases had underlying hypertensive diseases (1,8,9,11-14). Hypertension has been documented in 15-58.3% of inmates with severe conditions in different studies (1,11). In one study, hypertension contributed to approximately half of deaths due to this virus and existed in a quarter of survivors (9).

Other cardiovascular diseases such congestive cardiac failure and Coronary Artery Disease (CAD) are also reported to be more prevalent among COVID-19 patients ranging from 2.5-15% (1,8,9,11-14). Such diseases are responsible for roughly 25% of ICU admissions or deaths (1,9,11). A study among 44,672 COVID-19 patients showed 6.0% fatality rate for hypertension and 10.5% for cardiovascular diseases (14). The underlying pathophysiology has been attributed to the Renin-Angiotensin System (RAS) that plays a significant role in inflammatory response (27). Angiotensin-Converting Enzyme 2 (ACE2) is an enzyme that lies in the external layer of cell membrane in the lungs, heart, arteries, kidney and intestine (28). Recent studies have shown that 2019-nCoV uses ACE2 as an entry point into cells and decreases the level of ACE2 through binding ACE receptors and viral S proteins (29). Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) inhibit the generation of Ag2 which is a vasoconstrictor peptide used for treatment of hypertension. On the other hand, these RAS blocker drugs cause an augmentation in the rate of ACE2 which provides an opportunity for SARA-CoV-2 to spread in the lungs and heart which may cause ARDS and myocarditis (30,31). Therefore, the hypertensive patient taking these drugs may be more susceptible to SARS-CoV-2 infection. However, a previous study showed that RAS blocker drugs could be effective in patients with viral pneumonia through decreasing the release of cytokines that induce the inflammatory response (30).

The high troponin T (TnT) level is associated with higher morbidity and mortality in COVID-19 patients (32). The raised TnT level is also associated with higher WBC count, higher neutrophil count, and lower lymphocyte counts. The increased level of high-sensitivity cardiac troponin I (hs-TnI) is closely associated with myocardial injury. According to recent studies, patients with higher mortality rate presented higher levels of this biomarker (1,9,10,13,33). It has been shown that there is a correlation between plasma TnT level and two COVID-19 mortality-related biomarkers, namely, plasma high-sensitivity CRP and plasma NTproBNP. The data from 187 COVID-19 patients indicated 69.4% mortality rate among those with elevated TnT (32).

In another study (34), plasminogen level is considered as a risk factor for morbidity among COVID-19 patients. Patients with Chronic Heart Failure (CHF) have higher levels of plasmin activity (35). Plasmin is a fibrinolytic enzyme producing a split through furin site in the S protein of SARS-CoV-2 and facilitating the entry of the virus into the cell leading to a poor prognosis in COVID patients (36,37).

Myocardial injury indices such as LDH and creatinine kinase (38) could also be high in COVID-19 patients (1,8,9,11,12,38-40). Elevated LDH has been reported in 23-98% of total patients (1,8,9,12,38-40), in 55% of severe cases (40), and in 82-98% of non-survivors (9,39). Creatinine kinase elevation was also observed in 4.5-33% of confirmed COVID-19 patients (1,9,12,38,41) and 21% of deaths (9).

In a study conducted by Liu *et al*, one patient who developed fulminant myocarditis, had elevated levels of myoglobin, cardiac troponin 1, brain natriuretic peptide, and CK-MB. Therefore, these biomarkers could be used as indexes for disease severity in

patients with COVID-19 (39). However, further studies are warranted to explore and determine the prognostic value of these biomarkers in COVID-19 patients.

Factors related to metabolic diseases

Previous studies have shown that diabetic patients are more vulnerable to SARS-CoV-2 infection (12,17) and an estimated 5.3-20% of COVID-19 patients were diabetic (1,12,14,17,42). In a study among 1,099 COVID-19 patients, 16.2% of patients with severe disease had diabetes mellitus (43). However, in a review of laboratory findings in patients with COVID-19, increased level of blood glucose or diabetes were not considered as risk factors for severe disease (44).

Overexpression of ACE2 in pancreas cells as a result of treatment with ACE inhibitors and ARBs could increase the likelihood of COVID-19 among diabetic patients (45,46). The ACE2 overexpression leads to the rise in furin level which is a cellular protease that cleaves the S1 and S2 regions of the viral protein and facilitates the virus entry into the cell (47).

A recent study suggested that the impaired viral clearance in diabetic patients could also increase the probability of being infected by COVID-19. However, further evidence is essential (48). In fact, the impaired phagocytic and cytotoxic activity in diabetes could be potential underlying reasons for inefficient immune system in the patients and higher chance of virus acquisition. In addition, the initial lag in Th1 cell-mediated activity could result in hyper-inflammatory response and cytokine storm. Moreover, insulin has been demonstrated to diminish ACE2 expression and therefore reduces the chance for virus to enter the cell (49,50).

Factors related to respiratory system

Although in the current literature, respiratory diseases were reported as a predisposing factor for COVID-19, they are not as frequently reported as the CAD and hypertension (22). In studies from China, chronic pulmonary diseases were reported in 1.1-8.0% of COVID-19 patients and only 6-8% of them had poor outcomes (1,2,11-14,16,40). In another study, only 10% of deceased patients had chronic lung diseases (41). In a recent study at the hospital in Washington, 43.5% of COVID-19 patients (among 21 patients) had underlying chronic obstructive pulmonary disease (COPD) and asthma (42). Further multi-sites epidemiological studies with larger sample size are recommended to precisely characterize the prevalence of underlying respiratory illnesses in COVID-19 patients. Despite the low prevalence of COPD in COVID-19, it is one of the strongest predictors for disease severity and ICU admission and similar to hypertensive and cardiovascular patients, it has a poor outcome (43).

Factors related to gastrointestinal system

Among 1,099 patients infected with COVID-19 in China, 5.6% of patients were reported having nausea or vomiting and 3.8% of patients had diarrhea (43). The first case with COVID-19 in a stool specimen was detected in United States (51). In another study among 73 hospitalized COVID-19 patients, up to 50% of the stool samples were positive (52).

Inflammatory Bowel Diseases (IBDs) including Crohn's Disease (CD) and Ulcerative Colitis (UC) have been shown to be associated with adverse outcomes in patients with COVID-19 (53). In IBD, the expression of ACE2 increases in the terminal ileum and colon and it is higher in CD than UC (54). Therefore, in these patients, fusion of the coronavirus envelope with host cell membrane is facilitated through up regulating activity of furin (55). Moreover, the intake of immune suppressors (*e.g.* azathioprine, methotrexate) in these patients can increase the chance of infection by blocking the intracellular signal which is necessary for protecting the host cells (56). However, these medicines could also be beneficial by suppressing the production of interleukin IL-2, IL-6, TNF, and interferon and preventing the cytokine storm in COVID-19 (57,58).

Most of the studies from China indicated an estimated 4% of underlying kidney diseases in COVID-19 patients (8,9,11,39). On the other hand, CKD has been reported in nearly half of the patients with severe COVID-19 in a hospital in Kirkland, Washington (59). In another study, nearly 5 out of 21 (23.8%) patients who needed ICU admission had CKD (60). The results, however, cannot be generalized due to the variety in patients' characteristics. High serum creatinine was reported in around 2-10% of

confirmed COVID-19 cases (1,9,12,38,41) and in 9% of deceased subjects (9).

It is of great importance for healthcare workers to keep in mind the atypical symptoms of COVID-19 such as gastroenteritis (61). In a report by Ferrey *et al*, a 56-year-old male on hemodialysis with the history of cardiovascular diseases primarily presented with diarrhea and vomiting and developed ARDS after 6 weeks. The atypical presentation of diarrhea and vomiting delayed the diagnosis by 5 days. Therefore, home dialysis, if possible, is recommended during the current outbreak (61).

Factors related to liver function

Alaninaminotransferase (ALT), Aspartate aminotransferase (AST), albumin, and Total Bilirubin (T-Bil) are the key indicators of liver function. In critically ill COVID-19 patients, ALT, AST and T-Bil ranges are reported to be higher than normal in comparison to mild cases. Furthermore, progressive decrease of albumin was reported in severe cases (40,62). According to Zhang *et al*, although these changes were statistically significant in critical patients, it is not yet clinically reliable (40).

Data from the Fifth Medical Center of PLS General Hospital in Beijing, China showed that only 2-11% of confirmed cases had underlying liver disease, yet 14-53% of persons were seen with raised ALT and AST levels (63). Zhang *et al* compared liver injury in community-acquired pneumonia (CAP) and COVID-19 patients (40); the results showed that the rise in ALT, AST, and T-Bil levels is not significantly different from normal cases. In comparison with CAP patients, COVID-19 patients had a higher mean level of albumin and globin (35.51 to 38.79 and 26.96 to 29.17, respectively). Respectively, in 13 and 17% of COVID-19 and CAP patients, Gamma-Glutamyl Transpeptidase (GGT) level and in 22 and 18% of them, LDH level was high, respectively (40). About 50% of COVID-19 patients and 30% of CAP patients showed increased International Normalized Ratio (INR) (40) due to liver failure in producing coagulation factors.

Similar studies (1,8,9,12,39,40) have shown raised AST and ALT in approximately 15-37% of infected patients. According to Zhang *et al* who compared severe patients to non-severe ones, 39% of severe patients had an increase in AST and 26% an increase in ALT level (40). In non-survivors, high ALT and AST levels were detected in 27-48% and 52% of patients, respectively (9,39).

Taking into account the high prevalence of liver diseases such as viral hepatitis and alcoholic/non-alcoholic fatty liver in general population, further studies are necessary to evaluate the effect of these diseases on COVID-19 prognosis and clinical outcome (63).

Factors related to cerebrovascular disease

Several studies indicated around 1-14% of Cerebrovascular Diseases (CVDs) in COVID-19 patients; however, the ratio rose up to 22% in severe cases (8,10,11,39).

Factors related to malignancy

Patients with malignancies appeared to be more vulnerable to the SARS-COV-2 infection (64). Taking immunosuppressive medicines and anticancer treatments such as chemotherapy and surgery might cause a poor prognosis in these patients (12,65). In a retrospective study in China, 1590 COVID-19 cases were monitored and 18 (1%) had an underlying cancer disease which was higher than the cancer prevalence in Chinese general population (0.29%). It is also reported that the patients with cancer are more predisposed to severe clinical events. The most common cancer was lung cancer (28%) (65). In another study, among 28 cancer patients with laboratory confirmed COVID-19, 53.6% had severe events, 21.4% were admitted to ICU, 35.7% had life-threatening outcomes and 28.6% of the patients died (66).

Laboratory findings

According to Liu *et al*, albumin, LDH, and CRP levels are significantly associated with high Murray score of lung injury. They studied the Area Under Curve (AUC) for different characteristics among 12 COVID-19 patients and concluded that based on approximate AUC of 1 for albumin, LDH and CRP, they could be an indicator of disease severity (67).

D-dimer level is an indicator of coagulation function. In previous studies, approximately 15-68% of confirmed COVID-19 patients had elevated levels of D-dimer (9,12,38,39,41); it was also documented

in 35-92% of deaths (9,39). Wu *et al* suggested Disseminated Intravascular Coagulation (DIC) as the potential reason for death as the difference in median level of D-dimer between ARDS and non-ARDS groups was lower than that of survived and non-survived cases (38).

Several studies among hospitalized patients with COVID-19 (1,8-13,39,68) have shown abnormalities in various biomarkers such as CRP, LDH, procalcitonin, AST, and D-dimer. High CRP level has been reported in about 84-86% of COVID-19 patients (12,68) and in approximately 60% of severe patients (8). Unlike serum CRP level, procalcitonin levels were often normal in COVID-19 patients. In most of the studies, high D-dimer level was detected in severe disease. Therefore, Yu *et al* recommended testing serum CRP, procalcitonin, ferritin, D-dimer, lymphocyte count, and inflammatory cytokines like IL-6 to assess the prognosis in COVID-19 (21).

Conclusion

SARS-CoV-2 infection is a global concern which is spreading rapidly. It is now well known that the comorbidities have a significant role in increasing the risk of morbidity and mortality in patients with COVID-19. The most prevalent underlying diseases are hypertension and cardiovascular diseases, followed by diabetes, respiratory tract diseases, cerebrovascular diseases, immunosuppression, malignancies, gastrointestinal disease, and impaired liver and renal function. It is recommended that healthcare professionals be informed about atypical symptoms that may be present especially among immunosuppressed patients. Measuring serum inflammatory and coagulation indices such as CRP and D-dimer and biomarkers such as AST and ALT could be an optimal method for disease prognosis. Further, multi-site epidemiological studies with larger sample size are recommended to produce reliable data regarding the prevalence of underlying diseases and their impact on prognosis and eventual outcome of patients with COVID-19.

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Conflict of Interest

The authors declared no conflict of interest.

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