REVIEW

Indicators of Critical Illness and Predictors of Mortality in COVID-19 Patients

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Abstract: COVID-19 is an emerging disease all over the world and spreading at an unpredicted rate, resulting in significant influences on global economies and public health. Clinical, laboratory, and imaging characteristics have been partially described in some observational studies. Not enough systematic reviews on predictors of critical illness and mortality in COVID 19 have been published to date. In this review, we had illustrated the prognostic predictors of COVID-19 by gathering published information on the risk factors related to the outcomes of SARS-CoV-2 infections.

Keywords: COVID 2019, SARS-CoV-2, predictors, critical illness, mortality

Introduction

In Wuhan city, the capital of Hubei in December 2019 in China, an outbreak representing in pneumonia of unidentified origin had occurred. In 7 January 2020, scientists of china could isolate a new strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), from the affected patients,[1] that causes the disease; coronavirus disease 2019 (COVID-19) as stated by WHO in February 2020.[2]

Although the outbreak mostly have started from a zoonotic transmission in a large seafood market that also traded in live wild animals, it soon became obvious that efficient person-to-person transmission was also possible.[3] The clinical spectrum of COVID-19 disease appears to be wide, ranging from asymptomatic infection, mild upper respiratory tract illness, severe viral pneumonia with respiratory failure or death. The evaluation of risk factors for the severity of the disease and possibility of death is a very important issue for prediction of the possible outcome.

Age and Gender as Predictors for Critical Illness in COVID-19 Infection

A study conducted by Zhou et al[5] confirmed that increased age of patients with COVID-19 was associated with death. The decrease in T-cell and B-cell functions depending on age and the additional production of type 2 cytokines, could lead to a lack in control of viral replication and load and more exacerbation in proinflammatory responses that may lead to increase the severity of the disease and poor outcome.[6] Petrilli et al[7] described characteristics of 4103 patients in New York City with laboratory-confirmed Covid-19 disease, 1999 of them needed hospital admission while 650 of them needed ICU, respiratory support, were discharged to hospital and/or died. They found that older age was one of the most important predictors of hospitalization and a vital predictor of severe outcomes.

Nasiri et al[8] showed that sex affected the mortality rate, where the mortality of females with COVID-19 was significantly lower than males [Odds Ratio (3.4); 95% CI 1.2–9.1, P value = (0.01)], on the other hand, there was not any significant difference between male and female regarding ICU admissions. Earlier coronavirus epidemics of SARS and MERS resulted in a similar form of higher mortality in males than females. Karlberg et al[9] also showed that the difference in mortality rates according to sex distribution of the affected cases was higher in younger males (0–44 years old) (RR=2), compared to those of age group (45–74years old) (RR-1.45). Also, another study conducted by Alghamdi et al[10] showed that regarding MERS, the number of diseases in males was double that of females (52% vs 23%).

Associated Co-Morbidities as Important Risk Factors in COVID-19 Infection

Patients with coronary heart disease have also been found to have severe acute cardiac events and poor outcomes in respiratory viral infections including influenza.[11] A study conducted by Zhou et al showed that increasing level of high-sensitivity cardiac troponin I(cTnI) during hospitalization was presented in more than half of cases who died with COVID-19.[5]

Li et al[12] reported the clinical characteristics of 25 cases died with COVID-19. The clinical profile of these patients showed that the most important risk factors for death in these patients represented in, age and underlying diseases. Regarding the underlying diseases associated with death, the most recorded one was chronic hypertension then diabetes mellitus, chronic cardiac diseases, cerebral infarction, kidney disease, chronic obstructive pulmonary disease, malignant tumors and acute pancreatitis. Li et al[12] demonstrated that respiratory failure was the leading cause of death in all the patients, which confirmed that lungs of the patients are the most important target organ of SARS-CoV-2. Multiple organ failure could be observed in those patients, the heart came after the lung as the most common damaged organ then the kidney and the liver. The results of that study verified that the death of the patients with COVID-19 may be to a large extent related to impaired cardiopulmonary function. All the patients' albumin levels, 80% and 68% of patients' RBC and Hb levels were decreased, which indicates that malnutrition is one of the causes of severe COVID-19.

Measures of inflammation process were found to be much more important than co-morbidities and demographic characteristics in the hospitalized patients with COVID-19.[7] Exaggerated inflammatory response were well defined as severe sepsis.[13] Even though the extent of inflammation caused by COVID-19 is similar to or different than that caused by sepsis is unknown. Some case reports recommend that patients with critical COVID-19 disease are showing complications from hypercoagulability,[5] as pulmonary emboli,[14] and microscopic thrombi.[15] So, it is notable that obesity was the chronic condition that had the strongest association with critical illness, with odds ratio higher than any other cardiovascular or pulmonary disease because obesity is recognized to be a pro-inflammatory condition.[16,17]

Guan et al[18] observed that among patients with COVID-19, the circulatory and endocrine co-morbidities were common. Patients with one or more co-morbidities were associated with worse clinical outcomes. Of the 1590 cases, 399 (25.1%) had at least one co-morbidity. The prevalence of specific co-morbidities was; hypertension (269; 16.9%), other cardiovascular diseases (53.7%), diabetes (130; 8.2%), cerebrovascular diseases (30; 1.9%), hepatitis B infections (28; 1.8%), chronic obstructive pulmonary disease (24; 1.5%), chronic kidney diseases (21; 1.3%), malignancy (18; 1.1%) and immunodeficiency (3; 0.2%). At least, single co-morbidity was commonly seen in severe cases than in non-severe cases (32.8% vs 10.3%).

In hospitalized COVID-19 patients, the prevalence of kidney impairment (abnormal urine analysis and kidney dysfunction) was high. After adjustment for confounders, kidney impairment was related to higher risk of in-hospital mortality so; Clinicians should increase their attention to kidney impairment in hospitalized COVID-19 patients. Early discovery and effective intervention of kidney impairment can help to reduce mortality of COVID-19 patients in clinical practice.[19] Petrilliet al.[7] reported particularly strong association of chronic kidney disease with the risk of hospitalization. Also they declared the importance of hypoxia even with supplemental oxygen in distinguishing among patients who will develop critical illness and those who will not.

Abnormal Hematological and Biochemical Markers in COVID-19 Infection

Blood picture of patients with COVID-19 characterized by normal or low count of WBCs and decreased level of

lymphocytes.[20] Increased levels of WBCs and neutrophils were found in 68% and 72% of patients. Similarly, elevation of procalcitonin (PCT) levels were observed in 90.5% of patients.[12]

D-dimers are fragments produced when plasmin cleaves fibrin to break down clots. They are routinely used to exclude the diagnosis of thrombosis. However, plasma d-dimer increases by any pathologic or non-pathologic process that increases fibrin production or breakdown.[21] A study conducted by Zhou et al[5] found d-dimer more than 1 μg/mL is associated with mortality of COVID-19. High levels of d-dimer have been associated with 28-day mortality in patients with sepsis or infection identified in the emergency department.[22] Petrilli et al.[7] reported striking findings regarding the predictive value of inflammatory markers to distinguish future critical from non-critical illness. Early elevation in d-dimer level had the strongest association with prolonged hospitalization and the need for mechanical ventilation or death.[7] Many studies have reported that d-dimer levels are associated with severity and clinical outcome of community-acquired pneumonia.[23] The other mechanisms include the pro-inflammatory cytokine responses that considered one of the mediators of atherosclerosis disease that contribute to plaque rupture by the local inflammation, induce procoagulant factors, and haemodynamic changes, which trigger to thrombosis formation and ischemic diseases.[24]

Also, angiotensin converting enzyme 2 (ACE 2), that considered the receptor for SARS-CoV-2, is expressed on vascular endothelial cells and myocytes.[25] Therefore, there is at least theoretical possibility of direct affection of the heart by the virus.

C-reactive protein is a useful marker and gauge of inflammation; it plays an important role in host defense against invading pathogens as well as in inflammation.[26] Early rise in the C-reactive protein also had the strongest association with mechanical ventilation or mortality.[7]

Serum amyloid A (SAA) is a plasma protein that transports lipids during inflammation.[27] Li et al[12] showed that the increased levels of SAA and CRP before death in 85% and 100% of patients, suggestive of that there is a serious inflammatory cascade in patients having COVID-19. In intend to monitor biochemical indicators which are important in monitoring the severity of the disease and its progress, Li et al[12] consulted the results of laboratory test for all the dead patients, among which 16patients had repeated measurements. The SAA maintained a high level in all the patients, this result indicated that raised SAA levels are closely related to the poor prognosis of patients. The first test level of neutrophils was (93.8%), CRP (84.6%), PCT (100%), cTnI (88.9%), d-dimer (91.6%) and lactate dehydrogenase (LDH) (100%) were increased than the last test, but the levels of lymphocytes were decreased (87.5%), suggesting that the increasing of neutrophils, CRP, d-dimer, PCT, cTnI, and LDH levels can be used as markers of disease severity and progress, similarly the decline of lymphocytes counts.

Nasiri et al[8] identified common laboratory findings associated with a poor outcome including lymphopenia (50.1%), raised C-Reactive Protein (72%), and increased levels of LDH (41%). Also, thrombocytopenia was found in 11.1% of the cases. The Studies performed by Huang et al,[4] and Lippi et al[28] have suggested that thrombocytopenia and lymphopenia in patients with COVID-19 are associated with prolonged hospitalization and worse outcomes. Patients with SARS were indicated to have a higher percentage of lymphopenia (68–90%) and thrombocytopenia (20–45%) than those of COVID-19.[29] Thrombocytopenia and lymphopenia have been previously associated with a greater risk of mortality in SARS and influenza.[30,31]

Liver changes were one of the most common finding in the COVID-19 infected subjects (13.3%). However, a significant AST rising was found in number of subjects (19.7%) also level of ALT (14.6%). In some previous viral infections including SARS, changes and impaired liver function have been noticed as collateral damage, perhaps caused by direct damaging of the hepatic tissue by the pathogen.[32] Although this could be the same situation with COVID19, an iatrogenic trauma because of medications as the used lopinavir in COVID-19 therapy can play a role.

The method and level of the virus replication and its duration of life are important factors in evaluating the root of transmission and guiding protocols for patients' protection and isolation. As coronavirus RNA detection is more sensitive than the isolation of the virus itself, most studies gave care to use qualitative or quantitative viral RNA tests as a possible marker for infectious coronavirus. About SARS-CoV, the viral RNA was obtained from the respiratory specimens from about third of patients affected by the virus for at least 4 weeks from the onset of the disease.[33] The same regarding MERS-CoV RNA, where the duration of viral detection in the lower respiratory specimens continued as long as 3 weeks.[34]
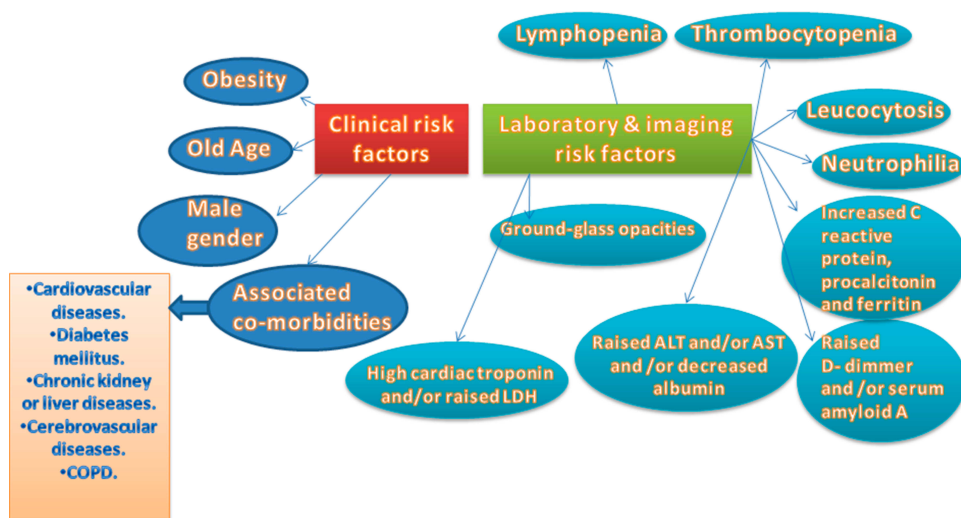
Figure 1 Risk factors of critical illness and mortality predictors in COVID-19.

A study conducted by Zhou et al[5] found that duration of SARS-CoV-2 RNA in survivors could reach for a median of 20 days even though it could still till death in non-survivors. This result has an important role in the decision of patient's isolation and guidelines regarding the length of treatment protocols. Usually in serious influenza virus infection, continued viral replication was associated with worse outcome that may be fatal, also the delay in starting with suitable antiviral treatment had an important effect on viral replication and detection.[35]

In patients with COVID-19, the serum level of ferritin was significantly elevated in non-survivors compared with survivors during the clinical stages of the disease, and raised with case deterioration.[5] Shoenfeldreported that the H-chain of the ferritin had a role in activating macrophages to raise the secretion of inflammatory cytokines. So, understanding of the pathogenesis of the hyperferritinemic syndrome including the infection with COVID-19 became obvious.[36]

Chest Imaging Findings as Risk of Critical COVID-19 Infection

Many studies noted chest X-ray and CT abnormalities in their study populations including unilateral pneumonia,[38] bilateral pneumonia,[4,5,37–39] bilateral infiltrates,[40] and ground glass opacities.[5,37,39,41,42] Cao et al found a mortality rate of 17/102 patients. They found that ground-glass opacity was associated with mortality, present in 41.2% of cases who died versus 12.9% of those who lived.[43] Summary of the risk factors of critical illness and mortality predictors in COVID-19 were presented in (Figure 1).

Conclusions

COVID-19 is an emerging disease all over the world and spreading at an unpredicted rate, resulting in significant influences on global economies and public health. The present review assessed the risk factors related to the outcomes of SARS-CoV-2 infections which were included old age, male gender, and obesity, associated co-morbidities in the form of cardiovascular diseases, diabetes mellitus, chronic kidney disease, liver disease, cerebrovascular diseases and COPD. Laboratory parameters associated with critical COVID-19 disease were lymphopenia, thrombocytopenia, leucocytosis, increased neutrophils, increased C reactive protein and ferritin, increased D dimer, raised ALT and/or AST, decreased albumin, increased cardiac troponin and elevated LDH. Finally, ground-glass opacities when present in the CT chest were considered as the most important imaging indicator for COVID-19 severity.

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