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CLINICAL COURSE AND MANAGEMENT OF COVID-19 IN PATIENTS WITH PRE-EXISTING CARDIOVASCULAR DISEASE

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ABSTRACT
Since the beginning of the Coronavirus outbreak in December 2019, there have been many comorbidities and complications associated with this respiratory illness. Among these are cardiovascular diseases (CVD). Multiple studies have reported an exacerbation of pre-existing cardiovascular conditions in COVID-19 patients, as well as increased morbidity and mortality. Other studies reported an association of COVID-19 with the incidence of cardiovascular diseases. Either way, the inflammatory process involved in the pathogenesis of COVID-19 infection has been reported as a potential cause of myocardial injury, especially in critically ill patients. This review aimed at investigating the pathogenesis and impact of COVID-19 on patients with pre-existing cardiovascular diseases. Beyond establishing an association, we also focused on the mechanisms of myocardial injury in COVID-19 patients and the management approach. We searched PubMed and Google Scholar for this review from May 1, 2016, through May 1, 2021. We selected publications reporting the pathogenesis, association, and outcome of the disease process in COVID-19 patients with cardiovascular diseases and finalized 14 critically appraised articles for this review. After a careful analysis, most studies reported an exacerbation of the disease process in covid-19 patients with pre-existing cardiovascular diseases. This exacerbation was associated with an exaggerated inflammatory response to the coronavirus, which caused a myocardial injury. Few studies indicated that myocardial injury is not limited to COVID-19 patients and could also occur in any critically ill patient. In conclusion, COVID-19 patients with cardiovascular conditions are at increased risk for complications and mortality and, therefore, should be monitored closely and treated promptly.

KEYWORDS: cardiovascular disease, comorbidities, COVID-19.

INTRODUCTION
The Coronavirus disease (COVID-19) was declared a pandemic on March 11, 2020, by the World Health Organization.[1] By March 31, 2020, the disease had spread to more than 200 countries, with 662,037 confirmed patients and 37,819 deaths.[2] Covid-19 is infectious and can be fatal. It is caused by Severe Acute Respiratory Syndrome Coronavirus 2, known as SARS-CoV-2. The clinical manifestations range from mild flu-like symptoms, pneumonia, and acute respiratory distress syndrome (ARDS).[3,4] Multiple risk factors are associated with the disease severity, exacerbation, outcomes, and prognosis. Some of these risk factors are old age and pre-existing comorbidities.[5,6] Elderly patients with COVID-19 and pre-existing comorbidities like cardiovascular disease, diabetes, cerebrovascular diseases, cancer, and chronic kidney disease were more susceptible to a severe disease process and a high likelihood of poor prognosis.[1,4,5,7] The myocardial injury observed in COVID-19 patients with cardiovascular diseases is associated with a systemic hyperinflammatory response.[3,8–10] Though this hypothesis is still under investigation, the hyperinflammatory response in COVID-19 patients plays a massive role in the severity and outcome of the disease. The cytokine storm elicited by the virus initiates a series of inflammatory and coagulation cascade that damages the myocardium. This myocardial injury exacerbates symptoms, especially in cardiovascular diseases like hypertension, coronary artery disease, and arrhythmia.[3,8,9] These patients showed more severe lung injury, multiple enzyme release, inflammation storm, and hypercoagulability.[2] To achieve the most efficient treatment and management of symptoms in COVID-19 patients with cardiovascular

disease, it is imperative to understand the pathophysiology of this clinical association. Accurate knowledge of the disease mechanism will help develop potential therapies and achieve a better prognosis. This study assesses the clinical course of COVID-19 in patients with pre-existing cardiovascular diseases (CVD), the pathophysiology, possible complications, probable treatment, and management plan.

MATERIALS AND METHOD

We searched Google Scholar and PubMed using the keywords; cardiovascular disease, comorbidities, and COVID-19. We screened the articles using our inclusion and exclusion criteria. Inclusion criteria include English articles published between May 2016 through May 2021, publications focusing on COVID-19 and cardiovascular diseases, clinical trials, randomized controlled trials, books and documents, meta-analysis, and adults (18 years and older). Exclusion criteria include non-English articles, articles older than five years, articles not aligned to the aim of the study, pediatric population (younger than 18 years). We screened the reports generated by our search terms and inclusion/exclusion criteria. Afterward, we extracted the papers, searched the selected articles' reference lists, and agreed on those with information relevant to our study objective. After the selection and screening process, we ended up with 14 critically appraised research articles.

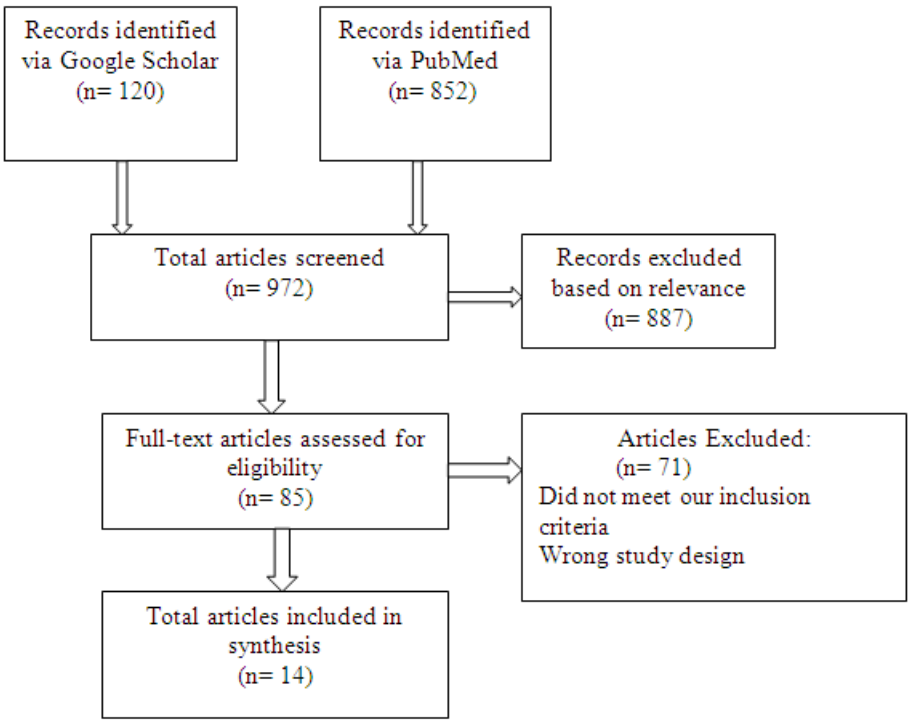

Figure 1:

DISCUSSION

The outcome of COVID-19 infection is affected by many factors, including the presence of various comorbidities.[11] A meta-analysis conducted on several studies which included patients with pre-existing chronic illnesses who contracted SARS-COV-2 revealed that CVD (atherosclerotic cardiovascular diseases like myocardial infarction, stroke, and peripheral arterial disease) was associated with the highest severity and mortality compared to other comorbidities.[7] Cardiovascular disease (CVD) was also identified as an independent risk factor that predicted the progression of COVID-19 infection to critical illness early in the infection.[10] According to the World Health Organization, patients who died from COVID-19 or were in critical conditions were more likely to be the elderly or had one or more morbidities such as hypertension, diabetes, cardiovascular disease, and cerebrovascular disease.[12] These comorbidities are independent causes of millions of annual deaths globally, with cardiovascular diseases at the lead at 17.9 million deaths.[12] People with pre-existing conditions have inadequate immune systems that make them susceptible to being infected, reach critical conditions, and even die of a secondary disease like COVID-19. Risk factors for the prognosis and severity of COVID-19 are therefore crucial for risk-stratifying and precautionary measures. Such information is critical for the timely identification and management of high-risk patients.[13] The planning measures can range from forecasting the need for beds and ventilators to effective patient triage by healthcare providers.[13] A meta-analysis of observational studies conducted by Sabatino et al. reported that pre-existing cardiovascular comorbidities or risk factors were associated with cardiovascular complications in COVID-19 patients, leading to a poor prognosis and increased mortality.[5] Shoar et al. also reported, through a meta-analysis of comparative studies, that a significant level of

cardiovascular-related conditions was prevalent in hospitalized COVID-19 patients who died from the disease.[14] Cardiovascular instability measured by tachycardia, dyspnea, hypoxemia, presence of cardiovascular disease and or risk factors on presentation, as well as a tremendous increase in cardiac biomarkers such as troponin-I, BNP, and CK, correlated with a higher risk of mortality.[14] Drastic elevation of troponin-I, up to 3 times above the upper reference limit, was suggested to be associated with a 3-fold increase in mortality rate as elevated troponin-I levels were strongly associated with new myocardial injury, coronary artery diseases, and heart failure in patients with COVID-19.[14] There was an increase in mortality rates in those with pre-existing cardiovascular conditions. For example, non-survivors had a history of chronic cardiovascular disease (OR = 2.7, p = 0.0004), including chronic heart failure (OR = 27.8, p < 0.0001) or cerebrovascular disease (OR = 4.4, p = <0.00001).[14] The prevalence rates for CVD risk factors are hypertension ranged from 13% to 41%, diabetes from 5% to 58%, and pre-existing CVD from 1% to 22%.[13] Furthermore, most studies showed an independent positive association between the severity of COVID-19 illness and hypertension, diabetes mellitus, and CVD.[13] Almada-Pititto et al. reported a positive association between age and severity of the COVID-19 infection; the more the age, the higher risk of disease severity.[1] This pattern was consistent across national survey databases in China, the US, and Italy. Older age is associated with a compromised or reduced immune reaction, limited organ reserve, and comorbidities.[1] Males are more at risk of severe COVID-19 infection than women.[1] Also, men tend to die more from COVID, mainly those greater than 50 years of age;[2,14] they tend to have more comorbidities, wash hands less frequently, and have an immunologic disadvantage.[1,13]

Mechanisms of increased mortality in COVID-19 patients with CVD

COVID-19 has several cardiovascular manifestations such as acute myocardial injury, myocarditis, acute coronary syndrome, thromboembolism, heart failure, and arrhythmia, although viral pneumonia is the most common clinical manifestation.[15] The development process of atherosclerotic CVD is complicated and involves inflammation, oxidative stress, and prothrombotic state.[1] Though the mechanisms of myocardial injury in COVID-19 patients are still under investigation, multiple postulations have been made. Amongst these are impaired immune function, exacerbated inflammation, and increased expression of ACE 2 (Angiotensin-converting enzyme) receptors.[1,9] COVID-19 enters human cells by binding to the angiotensin-converting enzyme 2 (ACE 2), expressed in various body cells and tissues, including cardiac epithelial cells, intestinal, respiratory, and kidney tissues.[1,8,11,15,16] ACE 2 serves as a receptor to the virus; it binds to the receptor through its viral surface spike (S) protein. This enzyme catalyzes the conversion of angiotensin II to angiotensin 1-7, a peptide that counters the pro-inflammatory, pro-oxidative, fibrotic, and vasoconstrictive functions of angiotensin II.[1,8,11,15,16] The binding of the virus to ACE 2 inhibits the function of the enzyme, thereby promoting pro-inflammation, vasoconstriction, and endothelial dysfunction, which leads to injury to the cardiac myocytes and prothrombotic state.[1] The ACE 2 receptor pathway influences the severity of COVID-19 patients with CVD history.[1,8] A possible pathophysiological explanation for increased mortality in COVID-19 patients with chronic medical conditions such as CVD is increased allostatic load.[7] Chronic conditions are usually associated with dysregulation of the immune system, hypothalamic-pituitary-adrenal axis, and sympathetic nervous system. These patients have reduced immunity, increased susceptibility to severe COVID-19 complications, and death due to the stress these chronic conditions cause to the body's regulatory system. This stress promotes the accumulation of pro-inflammatory cytokines, which affect the cellular immune system.[7] In a comparative study conducted among hospitalized COVID-19 patients, serum levels of laboratory biomarkers such as cardiac troponin I, lactate dehydrogenase (LDH), brain natriuretic peptide (BNP) or proBNP, and creatine kinase (CK) were elevated among non-survivors who had CVD suggesting a new myocardial injury or worsening of pre-existing heart disease.[14] SARS-COV-2 can bind to myocardial ACE 2 receptors, causing myocardial injury and increasing cardiac enzymes.[1,2] Due to already existing pathological changes in myocytes of patients with CVD, there is increased susceptibility to COVID-19 related myocardial injury. This myocardial injury may explain the higher values of cardiac enzymes seen in COVID-19 infected patients with CVD in a study comparing the clinical characteristics of CVD and non - CVD patients with COVID-19 infection.[2] In a descriptive study conducted among CVD and non-CVD patients by Jixiang Zhang et al., patients with CVD were more likely to have elevated C-reactive protein (CRP), increased neutrophils, and reduced lymphocytes, which indicates a robust immune response.[10] An increased level of inflammatory biomarkers like CRP is the hallmark of cardiac disease. It plays a significant role in the progression and outcome of CVD.[10] Studies have shown that increase in pro-inflammatory cytokines like IL-6, IL-10, serum amyloid A, and increased inflammatory indicators like erythrocyte sedimentation rate (ESR), CRP, serum ferritin, which occurs more in COVID-19 patients with CVD, signifies an increase in cytokine storm occurrence in these patients. Cytokine storm is associated with myocardial damage[2,10,16] and rapid deterioration of COVID-19 patients with CVD.[2,10] Also, elevated leukocytes and decreased lymphocytes which are independent predictors of cardiovascular events, have been linked to the development of atherosclerosis.[10] Decreased levels of total protein, albumin, red blood cells, and hemoglobin, which indicates reduced immunity and increased risk for superinfection, have been noted in COVID-19 patients

with CVD.[2,10] In severe COVID-19 infection, pneumonia may lead to impaired gaseous exchange in the alveoli, leading to hypoxemia. Hypoxemia promotes increased anaerobic metabolism, leading to increased intracellular acidosis and free radicals that damage the cell membrane. The influx of calcium ions induced by hypoxia then causes injury and death of the cardiac myocytes.[17]

There is also an increase in D-dimer and fibrinogen in CVD patients with COVID-19 than non-CVD patients, which means they may be more prone to hypercoagulability. This hypercoagulable state is associated with an increased risk of cardiovascular events like acute myocardial infarction and pulmonary embolism.[2]

Complications in COVID-19 patients with CVD

The presence of established cardiovascular disease or risk factors were significant predictors of complications in COVID-19 patients. These patients were likely to have a more robust and lethal inflammatory response.[10] In addition, COVID-19 patients with CVD showed more severe clinical symptoms, like lung injury, and had more prominent radiologic abnormalities than those without CVD.[2] There is a higher probability for COVID-19 patients with CVD to develop liver function abnormality, elevated blood creatinine, and lactic dehydrogenase.[10] The mortality of patients with pre-existing CVD was significantly higher than that in patients who had no CVD. The risk of severe disease and increased mortality from covid-19 was at least two times higher in patients with CVD than those without comorbidities.[1,5,7,10,15,17] This risk increased even more in patients with two or more CVDs.[10] In a study by Jolanda Sabatino et al., cardiovascular complications were seen in 14.09%, myocardial injury in 10.34%, angina in 10.15%, arrhythmias or palpitations in 18.40%, acute heart failure in 1.96%, and acute myocardial infarction in 3.54% of patients.[5]

Treatment/Management

There was little information about the treatment of covid-19 patients with pre-existing comorbidities and CVD, in the articles reviewed. However, a meta-analysis by Saeed Shoar et al. suggested that in addition to antivirals and antibiotics, steroids and mechanical ventilation are more likely to be used in COVID-19 patients with comorbidities.[14] As patients with pre-existing CVD were more likely to have more severe disease,[5,13,14] patients with CVD and covid-19 were more likely to receive corticosteroid treatment and mechanical ventilation in addition to other treatment modalities.[14] Antiviral medication like Remdesivir help prevents and decrease the severity of disease, especially in patients with pre-existing conditions.[9] The interleukin-6 receptor antagonists, Tocilizumab and sarilumab, may be clinically relevant for critically ill COVID-19 patients.[9] Interferon and convalescent serum are other treatments that have been proposed.[9]

There is clear evidence that CVD increases the severity and complications of covid-19 infection, and some of the treatment modalities used in the management of CVD also raise other concerns. For example, Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are used in the treatment of cardiovascular disorders, but there is no consensus on whether they increase the expression of ACE2 at the cell surface.[9,11] Some authors believe that the use of ACEIs and ARBs increases the risk of developing a severe and fatal SARS-CoV-2 infection, given that SARS-CoV-2 entry into cells is mediated by ACE2.[1,11] Other authors believe that hypertensive patients may have reduced expression of ACE2 because the binding of SARS-CoV-2 to ACE2 causes downregulation of residual ACE2.[11] In support of this opinion, some recent clinical studies have found no association between the RAAS blockers and increased mortality from COVID-19.[1,7,16] As a result, patients are advised against stopping their ACEIs, ARBs, or other renin-angiotensin-aldosterone system antagonists, except on clinical grounds independent of COVID-19, given the lack of evidence available on their potential benefit or harm.[9]

CONCLUSION

In conclusion, pre-existing cardiovascular diseases are the most common comorbidity seen in critically ill COVID-19 patients. CVD influences the disease process, severity, morbidity, and mortality of people with COVID-19. This clinical association is influenced by an exaggerated inflammatory response, old age, initiation of the coagulation cascade, and immunological factors. If not critically manages, there is an increased risk in mortality and morbidity. Therefore, it is crucial to monitor these patients closely and treat/manage promptly to prevent complications and achieve a good outcome.

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