COVID-19 and the World with Co-Morbidities of Heart Disease, Hypertension and Diabetes

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Abstract

Newly emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) pandemic has now spread across the globe in past few months while affecting 26 million people and leading to more than 0.85 million deaths as on 2nd September, 2020. Severity of SARS-CoV-2 infection increases in COVID-19 patients due to pre-existing health co-morbidities. This mini-review has focused on the three significant co-morbidities viz., heart disease, hypertension, and diabetes, which are posing high health concerns and increased mortality during this ongoing pandemic. The observed co-morbidities have been found to be associated with the increasing risk factors for SARS-CoV-2 infection and COVID-19 critical illness as well as to be associated positively with the worsening of the health condition of COVID-19 suffering individuals resulting in the high risk for mortality. SARS-CoV-2 enters host cell via angiotensin-converting enzyme 2 receptors. Regulation of crucial cardiovascular functions and metabolisms like blood pressure and sugar levels are being carried out by ACE2. This might be one of the reasons that contribute to the higher mortality in COVID-19 patients having co-morbidities. Clinical investigations have identified higher levels of creatinine, cardiac troponin I, alanine aminotransferase, NT-proBNP, creatine kinase, D-dimer, aspartate aminotransferase and lactate dehydrogenase in patients who have succumbed to death from COVID-19 as compared to recovered individuals. More investigations are required to identify the modes behind increased mortality in COVID-19 patients having co-morbidities of heart disease, hypertension, and diabetes. This will enable us to design and develop suitable therapeutic strategies for reducing the mortality. More attention and critical care need to be paid to such high risk patients suffering from co-morbidities during COVID-19 pandemic.

Keywords: SARS-CoV-2, COVID-19, Heart Disease, Hypertension, Diabetes, Pandemic, Co-morbidity

Introduction

Coronavirus disease 2019 (COVID-19), caused by newly emerged, single-stranded enveloped RNA virus namely severe acute respiratory syndrome coronavirus - 2 (SARS-CoV2), affects primarily the respiratory tract1. The COVID-19 pandemic has been regarded as a serious pandemic that has adversely affected the health, social and economic status of the whole world, irrespective of the economic status of the countries2-4. COVID-19 has now spread to more than 210 countries across the globe, accounting for more than 0.85 million deaths out of 26 million confirmed cases reported till 2nd September, 2020, and thus has created huge panic, havoc, and fear among worldwide population. Efforts to develop vaccines, drugs, therapies, immunomodulatory agents and strategies to enhance immunity against SARS-CoV-2 infection are continuously being made along with adopting appropriate mitigation strategies to safeguard the health of the humans and save their lives from COVID-19 pandemic5-14.

The infection of SARS-CoV-2 affects all individuals irrespective of age. Men are more affected when compared to women, but that might be due to the higher chance of exposure15. However, the COVID-19 is indiscriminately affecting everyone; the co-morbidities are being suspected to pose a higher risk for decreasing the survival rate of the SARS-CoV-2 affected individuals. Various kinds of pee-existing diseases have been identified as co-morbidities in SARS-CoV-2 infection, which increases susceptibility, pose risks of more severity outcomes and deaths in COVID-19 patients by modulating virus-host interactions and host-immune responses, and also have some age-dependent effects16-20. These include hypertension, diabetes, heart disease, chronic lung, kidney and liver diseases, malignancies, pro-inflammatory and pro-coagulative states, cerebrovascular diseases, smoking and others. The two life style associated conditions of overweight and obesity are identified as potential risks factors towards contributing to severe illness associated in COVID-19 patients18,21. The most common co-morbidities that have been identified with SARS-CoV-2 infection are heart diseases, hypertension, and diabetes20,22,25, which are the commonly found clinical conditions worldwide. Presence of diabetes and hypertension were found to be associated with a 2-fold while
CVDs were associated with 3-fold increased requirement of intensive care and greater risk of severe disease, suggesting the importance of these co-morbidities as prognostic markers.

Identification of various risk factors linked to COVID-19 deaths would aid in enhancing the treatment efficacy and lower down the mortality rates during COVID-19 pandemic. Medicines to treat heart diseases, anti-hypertension drugs for alleviating hypertension and glucose-lowering agents along with subscribing anti-viral treatments can reduce the risks of higher severity in COVID-19 patients having co-morbidities, however few of the associated limitations of their administration and potential interactions with anti-viral therapies need to be carefully evaluated.

In New York, among 5,700 COVID-19 patients, the most commonly reported co-morbidities comprised of hypertension (56.6%), obesity (41.7%), and diabetes (33.8%)\(^2\). Out of 1,023 deaths in China due to COVID-19, the higher fatality rate was associated with CVD, diabetes, chronic respiratory disease, and hypertension\(^2\). A systematic review that included 1,576 cases showed that the most prevalent co-morbidities in SARS-CoV-2 infected patients were hypertension (21.1%), diabetes (9.7%), CVD (8.4%), and respiratory system disease (1.5%)\(^2\); the combination of these co-morbidities were associated with mortality. Acute cardiac injury, pre-existing cardiovascular diseases (CVDs), hypertension, diabetes have been revealed

Fig. 1(a). COVID-19 and ACE2

**ACE2 and COVID-19**

- Angiotensinogen
- *Renin*
  - Angiotensin I
  - *ACE*
  - Angiotensin II
  - *ACE2*
  - Angiotensin I - VII

ACE2 enzyme Structure

Other Functions of ACE2

- Blocks blood pressure
- Controls organ damage
to be linked to COVID-19 clinical severity and survival of patients in a meta-analysis study by Momtazmanesh et al.26

Although this is clear that CVD, hypertension, and diabetes are substantial co-morbidities for the incidence and fatality of COVID-19, our understanding of how these pre-existing conditions increase the incidence and fatality is limited. The present article summarizes the evidence of the association between these conditions on COVID-19 incidence and mortality and discusses the possible mechanisms of how these conditions could increase the menace of infection as well as mortality in SARS-CoV-2 infection.

**COVID-19 and Heart Diseases**

Some patients having SARS-CoV-2 infection exhibited CVD problems27 and heart diseases as co-morbidities along with COVID-19 which influence prognosis and fatal outcomes during this ongoing pandemic20. Individuals who have suffered from heart failure (HF) are at higher risk of getting gripped by infections, which precipitate acute HF and increases mortality rates in such patients. In fact, about 40% of the mortality in COVID-19 cases was attributed to cardiac conditions including HF in Wuhan28.

Present era of COVID-19 pandemic is also playing critical role with co-morbidities of heart diseases and thus posing a challenge in managing heart disease patients in clinical practice, which need to be followed up with adopting appropriate guidelines for management and treatment of these critical patients29-32. It is suggested that early glucocorticoid anti-inflammatory therapy and immunoglobulin therapy may be of significant value to COVID-19 patients with heart diseases27. Long et al.33 evaluated the cardiovascular

**Fig.1(b). COVID-19 and ranges of Cytokines**

<table>
<thead>
<tr>
<th>Cytokines and COVID-19</th>
<th>Normal Ranges</th>
</tr>
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<tbody>
<tr>
<td>IFN-γ</td>
<td>10.2 pg/ml</td>
</tr>
<tr>
<td>IL-1</td>
<td>0-5 pg/ml</td>
</tr>
<tr>
<td>Troponin T</td>
<td>0-0.4 ng/dl</td>
</tr>
<tr>
<td>IFN-IP 10</td>
<td>156.4 pg/ml</td>
</tr>
<tr>
<td>NT-pro BNP</td>
<td>125 pg/ml</td>
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<table>
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<tr>
<th>Healthy Heart</th>
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complications in COVID-19 patients such as injury in the myocardium, myocarditis, dysrhythmias, acute myocardial infarction, failure of heart, heart attack, and thromboembolic events in veins. The virus binds and enters through ACE2 and results in systemic inflammation, which leads to multiorgan dysfunction. The cardiovascular system of the body gets further complicated by pulmonary difficulties and systemic inflammations. One of the major characteristic feature of COVID-19 that contributes to the pathophysiology is the overproduction of inflammatory cytokines [interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α)]. This will result in systemic inflammation, lead to multiple organ dysfunction syndrome, thereby disturbing the cardiovascular system.

Modes of CVD complications in COVID-19 have been reviewed by Bansal. Direct myocardial injury, systemic inflammation, altered ratio of myocardial demand and supply, rupture of plaque resulting in myocardial thrombosis, adverse effects of various therapies, electrolyte disturbances especially hypokalemia were proposed as possible mechanisms for cardiovascular complications. Mononuclear infiltration in the myocardium, and associated cardiomyocyte necrosis leading to acute lung injury and acute respiratory distress syndrome (ARDS) result in strain on right side of heart and right ventricular (RV) dilation and dysfunction. The resultant elevated positive end expiratory pressure (PEEP) in the patient on ventilation can also deteriorate heart function.

SARS-CoV-2 infection is linked to acute myocardial infarction and other cardiovascular emergencies. Recent studies and case reports identified that COVID-19 can lead to acute cardiac injury and is associated with myocardial damage leading to increased complexity in patient treatment. COVID-19 patients were found to show higher levels of troponin I, natriuretic peptides, diffuse myocardial dyskinesia, reduced left ventricular ejection fraction (LVEF) and high levels of IL-6. Hence, the study reported that such patients might build up severe cardiac complications including myocarditis and heart failure. Babuapoor-Farrokhran et al. observed myocarditis, cardiac arrest, acute HF in patients suffering from COVID-19 and suggested SARS-CoV-2 infection and cardiac diseases to be interrelated.

Various signaling pathways are regulating the cardiovascular functions, and the major among them is a notch signaling pathway, which is also involved in the regulation of biological reactions against viral infections. A recent study observed the possible ways to prevent COVID-19 is by targeting the notch signaling pathway. Case reports have revealed COVID-19 significant effects on heart and vessels. SARS-CoV-2 interacts with cardiovascular system via a direct or indirect mode. The virus binds to ACE2, a membrane-bound zinc metallopeptidase, which is located in lungs as well as in the heart, which in turn is involved in the cleavage of angiotensin. ACE2 receptor expression gets elevated in post-myocardial infarction and diabetic patients thus posing increased risk for severe COVID-19 illness. The regulation of crucial cardiovascular functions and metabolisms like regulation of blood pressure and sugar levels are being carried out by ACE2. Hence, SARS-CoV-2 affects cardiovascular system directly by targeting ACE2 (Fig. 1A). Apart from that, the alternative mechanism includes the effect on SARS-CoV-2 infection by immune system indirectly through the myocardial vessels. Severe illness during COVID-19 entail a cytokine storm that pave way to coronary plaque instability, as like has been reported in SARS-CoV infection. Besides, SARS-CoV or SARS-CoV-2 infected persons show lymphopenia which is linked for atherosclerosis development and unfavorable CVD outcomes. Another study by Huang et al. has suggested that, the involvement of cardiac organ is an impediment that has been connected to COVID-19, even while pneumonic symptoms / signs are lacking. The patient with COVID-19 without symptoms of viral infections revealed cardiac concerns with elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity troponin T detection.

The infections due to SARS-CoV-2 can lead to pulmonary as well as systemic inflammation, which can cause the dysfunction of multiple organs that may be a higher risk for the patients. The progression of COVID-19 includes the wet lung disease and failure of respiratory organ, sepsis and heart disease as their dangerous complications. Chronic hypertension, other cardiovascular co-morbidities, dyspnea, chest tightness and consciousness disorder have been
observed to be more common in deceased patients compared to recovered patients. The departed patient samples showed higher levels of the enzymes like creatinine, cardiac troponin I, alanine aminotransferase, NT-proBNP, creatine kinase, D-dimer, aspartate aminotransferase and lactate dehydrogenase, and differed profiles of cytokine levels when compared to the patients, who were recovered from the disease (Fig. 1B).

COVID-19 patients with underlying cardiovascular conditions appear to face a higher risk of complications. The American Heart Association has suggested that acute coronary events and strokes are common complications of viral infections. Influenza is linked to higher risk, while influenza vaccination in clinical trial reduced cardiovascular risk. Individuals suffering from CVD are being advised by the American College of Cardiology for the influenza vaccination, in order to protect themselves from respiratory diseases that are related to the flu. In China, CVD and hypertension were associated with an increased COVID-19 case fatality rate.

Patients with cancer and/or CVD are at greater risk with worse outcomes with COVID-19. C-reactive protein levels were recorded higher in COVID-19 than in recovered patients. Amrane et al. analyzed development of COVID-19 in anti-coagulated patients and reported that it might be associated with acute viral infection. Person suffering from COVID-19 and acute coronary syndrome are adopted in catheterization laboratory to check viral spread. Heart diseases were found to be most prevalent co-morbidities in COVID-19 patients dying in Brazil.

Dong et al. reported that end-stage heart failure in COVID-19 lead to an increased mortality rate and strong indication of SARS-CoV-2 induced cardiac injury. The Tongi Medical College performed screening for SARS-CoV-2 infection by nucleic acid and chest CT scan testing. COVID-19 patients in heart failure had prominent troponin I level, higher C-reactive protein ranges and brain natriuretic peptide and level of troponin I level increased before the death of the patient. The older age, poor general condition severe myocardial injury can be considered as the risk factors for COVID-19 infection.

To understand the relation between COVID-19 and CVD, it is important to comprehend pathobiology of SARS-CoV-2. SARS-CoV and SARS-CoV-2 entry involves the ACE2 receptor, which is expressed in nearly all body organs including on surfactant producing type 2 alveolar cells, ciliated and goblet cells of airways, the intestinal epithelium, cardiac cells, vascular endothelia, acini and islets of the pancreas. Co-expression of ACE2 and Transmembrane Serine Protease 2 (TMPRSS2) in same cell type is required as the viral entry process needs to undergo priming of Spike (S) protein. TMPRSS2 play an important role in proteolytic cleavage of viral S protein and in viral binding with ACE2. High expression of ACE2 is observed in pericytes. Pericytes are located outside endothelial cell of capillary and part of venules which might indicate for SARS-CoV-2 infection of pericytes leading to increased thrombogenicity, and hypercoagulation seen in COVID-19 patients and a higher probability for acute coronary syndromes (ACS).

Moreover, myocardial ACE2 expression was significantly up-regulated in patients with heart failure with an increase of 3 fold compared to the patient with a healthy heart. This increase may give explanation of the higher infectivity of SARS-CoV-2 and higher mortality in patients with heart disease. These findings are relevant with another study which reported that the SARS-CoV-2 can directly replicate in cardiomyocytes and pericytes, causing viral myocarditis.

Higher cytokines levels are cardiotoxic and lead to intense myocardial injury. Elevated levels of interleukin-1 (IL-1), chemotactant proteins, interferon-gamma and inducible protein of interferon have been revealed in COVID-19 patients resulting in activation of helper T cell response. The triggered helper T cell initiates the differentiation of monocyte to macrophage, and then macrophage is recruited to the intimal layer of an artery. Modified lipid inside the plaque is enveloped by the macrophage to form foam cells. This foam cells altered the efferocytotic capacity (ability to clear apoptotic cells), which resulted in vast accumulation of cholesterol that leads to the formation of the necrotic core inside the lesion. Plaque with the necrotic core is unstable and prone to rupture. This plaque rupture in the form of thromboembolism blocks the blood flow to the heart and responsible for ACS and cerebral ischaemic events. This life-threatening condition
may express the severity of COVID-19 infection, particularly concerning heart disease.

Zaim et al. 76 suggested that COVID-19 can cause fatal outcomes in younger healthy individuals. Respiratory failure, severe hypoxia, septic shock, and multiple organ failure have been reported in younger individuals leading to mortality due to COVID-19. A recent study has suggested that myocardial injury is an important prognostic factor of COVID-19. The tiny veins of the lungs have been found to expand at a higher ratio in individuals affected with COVID-1976.

One meta-analysis study reported varying proportions of the prevalence of cardiovascular co-morbidities among different CoVs-associated diseases (COVID-19, SARS and MERS cases)77. Zaman et al. 78 highlighted few of the salient issues with regards to practical approaches related to cardiovascular health care support and services for COVID-19 patients.

**COVID-19 and Hypertension**

The increased pressure in blood vessels has been characterized as hypertension, according to WHO. The higher incidence of hypertension might be due to immunodeficiency and long-drawn-out antiretroviral therapy, and conventional risk factors of older age, male gender, and high body mass index79. Essential hypertension (EH) is associated with cytomegalovirus (CMV) infection80, and gestational hypertension is associated with herpes simplex virus infection, during pregnancy81. Pulmonary arterial hypertension is associated with some viral infections viz., human immunodeficiency virus (HIV), human herpesvirus-8, hepatitis B, and C82. However, in COVID-19, pulmonary hypertension is probably a significant factor for morbidity and mortality linked with it83. A study reported that the most common underlying risk factors in COVID-19 patients included hypertension, CVDs, diabetes, smoking, chronic obstructive pulmonary disease (COPD), malignancy, and chronic kidney disease (CKD)84.

Hypertension is also one of the most common cardiovascular co-morbidities and appears to significantly elevate mortality risk in COVID-19 patients85. Lippi et al. 86 reported that hypertension might be linked to a higher risk for severe and fatal outcome in COVID-19 affected persons. It has been reported that co-morbidities in COVID-19 include hypertension in nearly 21%, diabetes in nearly 11%, CVD in about 7% patients, as per pooled data from Chinese studies87. Since these studies have not yet assessed the benefit to risk ratio in COVID-19 patients receiving rennin-angiotensin system blockers (RASB). These patients having co-morbidities connected to COVID-19 require special care as they give the highest risk of death cases. The exact mechanisms responsible for the poor prognosis in hypertensive COVID-19 patients need to be explored. However, one hypothesis is that the excessive activation of renin-angiotensin system (RAS) may promote the progression of lung injury in hypertensive COVID-19 patients via promotion of cytokine storm, smooth muscle cell contraction and vasoconstriction88. There is no solid evidence that proves the hypothesis suggesting that the use of ACE inhibitors (ACEI) or angiotensin receptor blockers (ARB) could be harmful in COVID-19 patients owing to increase in virus infectivity89.

ACE inhibitors / ARB in hypertension-COVID-19 co-morbid patient results in reduced angiotensin 2 due to ACE inhibition and increased angiotensin 1-7 due to increased activity of ACE2. This results in drop in cytosolic pH producing more favorable environment for SARS-CoV-2 endocytosis90. Further angiotensin 1-7 acts on Mas receptors thus can cause increase in sympathetic activity in the brainstem91,92. This can also aggravate cardiovascular morbidity in such co-morbid patients93. Cardiovascular and renal diseases also complicate pathogenesis and disease severity of COVID-1994. Coronary artery disease and CKD further aggravate COVID-19 prognosis92. Though the utility of GLP-1Ra and SGLT-2i in such conditions may be well known but under co-morbid situations with COVID-19 their role in preserving cardiovascular and renal function need to be evaluated92,93. Some of them may have beneficial effects on oxidative-inflammatory-apoptotic pathway thus preventing oxidative stress, inflammation and apoptosis thereby attenuating vascular ischemia/reperfusion injury94. Another mechanism for increased severity and mortality is believed to be increased susceptibility of the COVID-19 co-morbid patients to infections of microbial pathogens including bacteria and fungi95-97.
Nevertheless, not having sturdy proof regarding advantage or harm, it is sensible to utilize ACE inhibitors and ARBs for therapeutic purposes\textsuperscript{87}. There is dysfunction of renin-angiotensin system (RAS) in COVID-19 patients. It is still unknown that RAS inhibitors like ACEIs and ARBs render better disease outcomes. Severity of disease gets lowered as well as level of IL-6 is reported to be low in peripheral blood in patients administered ACEI or ARB therapy. Also, there is an increase in CD3 and CD8 T cell counts in the peripheral blood and decrease in reaching peak viral load using ACEI/ARB therapy as against giving antihypertensive drugs. This results in improving COVID-19 outcomes in patients suffering from hypertension, supporting the benefit of using ACEIs or ARBs\textsuperscript{98}. Thus, treatment with ACEI/ARB is known to be linked to a lower mortality risk in comparison to non-ACEI/ARB therapy, among patients hospitalized with hypertension linked to COVID-19\textsuperscript{99}.

Similarly, RAS inhibitors can modulate ACE2 mRNA expression and ACE2 function in tissues promoting SARS-CoV-2 proliferation and enhancing its infection capability\textsuperscript{100}. Even though RAS is linked to lung damage and a high cardiovascular and renal risk using ACE2, it helps in SARS-CoV-2 entry into cells, as expressed in lung, cardiovascular system, kidney and other tissues, and thus these do not support a harmful impact of RAS blockers in SARS-CoV-2; therefore can be continued in constant patients facing the COVID-19 epidemic\textsuperscript{101}.

Renin hydrolyzes angiotensin I into inactive angiotensin 1-9, angiotensin II into angiotensin 1-7 that further act on Mas receptor and cause a variety of effects, including cardiovascular defense, vasodilation, anti-proliferation, and anti-oxidative stress. Thus, homeostasis is maintained by functioning of ACE-Ang II-AT1R axis and ACE2-Ang1-7-MAS axis. The angiotensin I and angiotensin II levels, as ACE2 substrates, got remarkably increased, after ARB treatment which can persuade ACE2 expression and augment its activity. Some other studies stated that RAS blockers may potentiate SARS-CoV-2 infectivity and clinical course severity. Thus, it was opined to avoid RAS blockers for COVID-19 treatment. More consistent ACE2 up-regulation was seen for ARBs, and ACE2 modulation by ACEIs was more variable. Apart from this, the type and dosage of drugs used also play a key role\textsuperscript{99}.

In hypertension, inflammatory dysregulation is another likely pathogenic association to COVID-19. Systemic IL-2, IL-6, IL-7, granulocyte colony-stimulating factor, C-X-C motif chemokine 10 (CXCL10), chemokine (C-C motif) ligand 2 (CCL2) and TNF-α levels have been found to increase in COVID-19 patients. Pro-inflammatory cytokines are produced in greater amount (IL-17, IL-7, IL-6, IFN-C, TNF-α) as a result of dysregulation of CD4 and CD8 cells during hypertension\textsuperscript{101}.

**COVID-19 and Diabetes**

Diabetes has been considered as the risk factor that has been independently found to involve in the complications and mortality that occurred during SARS-CoV outbreak during the years 2002-2003\textsuperscript{105}. Diabetes in the patients increased the risk of being hospitalized for approximately about three-fold and even to four-fold to be admitted in the intensive care unit in influenza A (H1N1) outbreak, which occurred during the year 2009\textsuperscript{106}. The hypothesis of diabetogenic potential of COVID-19 has been explored by various workers\textsuperscript{107-109}. Co-morbid diabetes has been associated for a two-fold increase in risk of having a severe disease or even death in case of COVID-19 patients in China\textsuperscript{110}. Diabetes prevalence was found to be
approximately 14.5% in laboratory confirmed patients and linked with COVID-19 severe symptoms\textsuperscript{111}. The study by Liu et al.\textsuperscript{112} differs from previous studies, profound impact of diabetes was not revealed on prognosis of COVID-19 patients although negatively impacted course of clinical disease. However this was attributed to lower sample size in this study\textsuperscript{112}.

Although the current evidence suggests that individuals with diabetes are affected with a severe type of COVID-19, the mechanism associated with the difference in pathology is not clear\textsuperscript{111}. Therefore, further knowledge on the interaction between diabetes and COVID-19 can help us to develop suitable therapeutic strategies for reducing mortality. It has been speculated that blood glucose and body mass index might play a crucial role in poor prognosis linked to COVID-19 patients having diabetes\textsuperscript{113}. Type 1 diabetes patients are at risks of severe COVID-19. Infection of SARS-CoV-2 may worsen diabetes via precipitating acute metabolic complications by negatively affecting β-cell function, which could lead to diabetic ketoacidosis, hyperglycaemia and new-onset diabetes\textsuperscript{16}.

Another outbreak of CoV is caused by MERS-CoV, during the year 2012. The diabetic patients have been found to have higher risk during this outbreak too. Approximately, about 50% of the people with the critical illness were found to have diabetes\textsuperscript{114}. Dipeptidyl peptidase-4 (DPP-4) is a transmembrane glycoprotein, type II that is expressed in many cells and tissues including immune cells of the body. This glycoprotein has been found to have a critical role in metabolism of glucose as well as insulin. The glucagon-like peptide (GLP-1), as well as a glucose-dependent insulinotropic polypeptide, may be degraded by DPP-4 that results in the declined secretion of insulin and abnormal metabolism in the visceral adipose tissue\textsuperscript{115}. The postprandial glucose is regulated through the GLP-1 degradation by the DPP-4. The interaction between DPP-4 and coronavirus has been studied by using the mouse model, in which the results showed that the mouse was susceptible to MERS-CoV\textsuperscript{116}. In the case of COVID-19, the DPP-4 has been found to reduce the risk of respiratory complications that is related to diabetes. A study by Akbar\textsuperscript{117}, has suggested that the diabetic patients with the elevated glycemic levels were found to have a higher risk at the rate of 60% for being hospitalized during the pneumonia-related infections. This has been observed due to the decline in innate and humoral immune responses in diabetic patients\textsuperscript{107,117}.

Diabetes could be a significant risk factor leading to hospitalization and increased mortality of the COVID-19 patients. The 22 out of 32 deceased COVID-19 patients were observed to have diabetes as their co-morbidity\textsuperscript{103}. Few studies have reported that about 12% to 16.2% of hospitalized patients due to COVID-19 have been observed to suffer from diabetes\textsuperscript{99,104}. The severity of the patients increases for two folds in case of individuals with diabetes\textsuperscript{104}. A clinical survey conducted on the confirmed COVID-19 patients in China and the reports suggested that diabetes has been observed to be the most common co-morbidity in about 16.2% of the severe cases. A potential mechanism that might enhance susceptibility and severity of COVID-19 in diabetic patient has been discussed in several studies. Jing Liang et al.\textsuperscript{118} investigated the laboratory findings of SARS-CoV-2 patients having type 2 diabetes mellitus. Findings indicated that the affected patients exhibited decreased levels of lymphocytes, uric acid, albumin, and body mass index along with an increase in C-reactive protein levels. The decreased levels of uric acid, albumin, and body mass index can be linked to the oxidative stress response and nutritional consumption\textsuperscript{118}.

Increased ACE 2 in lung, kidney, heart and pancreas has been seen in diabetic mice\textsuperscript{119}. An elevated level of furin, a cellular protease which cleaves S1 and S2 domain of viral spike protein, is also presented in diabetes mellitus patients. The increase of ACE 2 receptor and furin level might facilitate the viral entry resulting in higher binding affinity, which leads to an increase in the susceptibility of COVID-19 inpatient with diabetes\textsuperscript{119-121}.

A few studies have provided information regarding diabetes and its positive association with worsening COVID-19. The diabetic patients are easily susceptible to the COVID-19 since the body mechanisms of diabetes affected individuals are not more efficient to clear the viral entry with the weakened immune cell functions and high
susceptibility to the inflammation\cite{115,122}. Recently, a study showed that SARS-CoV-2 clearance was prolonged in diabetic patients\cite{123}. Delayed recruitment of neutrophils and macrophages might impact the viral clearance\cite{123}.

Deterioration of adaptive immunity in diabetic patients is marked by delayed activation of Th1 cell-mediated immunity and dysregulation of inflammatory markers. Excessive release of inflammatory biomarkers (C-reactive protein, IL-6, TNF-α) may lead to cytokine storm that can result in multi organ failure (Fig. 2)\cite{122,124-126}. Diminished T cell function is also consistent with the finding in severe COVID-19 patient where a significant decrease of CD4+ and CD8+, an augmentation of proinflammatory CCR6+ Th17 in CD4 T cells, high concentration of cytotoxic granules in CD8+ was observed in peripheral blood. These factors may play a role in severe immune injury in COVID-19 patient with DM as co-morbidity\cite{127,128}.

Studies have suggested that the patients with diabetes have been found to have a lower recovery rate in SARS-CoV infections, which is the previous outbreak caused by a novel CoV\cite{129,130}. Studies done in Wuhan have reported that COVID-19 treatment has resulted in the worsening of hyperglycaemic condition in around 10% of the individuals with diabetes. The clinical consequences led to the increase in cardiovascular abnormalities that resulted in severe illness of COVID-19 patients with diabetes\cite{93,129,131}. Studies have reported prevalence of CVD, hypertension and diabetes in severely affected SARS-CoV-2 infected patients as 7%, 21% and 11%, respectively\cite{103}. A bidirectional connection has been recently reported between diabetes and COVID-19, as a phenomenon of new-onset diabetes and severe metabolic problems in pre-existing diabetes like changes in glucose metabolism, diabetic ketoacidosis and hyperosmolarity requiring very high insulin administration. A hypothesis of a potent diabetogenic consequence of SARS-CoV-2 has been suggested, which need further explorative studies to further reveal novel modes of disease\cite{132}. Pancreatic damage can occur in COVID-19 and stress hyperglycaemia in patients that may require insulin\cite{133}.

Diabetes patients getting COVID-19 have severe disease course and higher mortality\cite{134}. Disease severity is due to compromised immune response, elevated inflammatory response and hypercoagulable state\cite{134}. Management of diabetic patients is also affected in COVID-19\cite{92}. Administering ACE inhibitors and ARB in such
patients has raised some concerns including effects on pulmonary functions\textsuperscript{134}. As ACE2R is SARS-CoV-2 target, hence anti-diabetic drugs inducing expression of such receptors can predispose to infection besides increasing severity\textsuperscript{92}. Sodium-Glucose-Transporter-2 inhibitors (SGLT-2i), Glucagon-Like-Peptide-1 Receptor Agonists (GLP-1RAs), pioglitazone and even insulin could persuade an over-expression of ACE2 receptor\textsuperscript{135}, thus increase risk and aggravate severity of COVID-19\textsuperscript{92}. Dipeptidyl Peptidase 4 (DPP4) receptors are also exploited by coronaviruses\textsuperscript{7}, hence DPP4 inhibitors and GLP-1 receptor analogues which are having role in diabetes therapy need to be investigated for concomitant therapy of diabetic COVID-19 patients\textsuperscript{92,136}. Similarly, antihyperglycemic effects of hydroxychloroquine along with anti-inflammatory and antiviral (anti-SARS-CoV-2) effects also favour its use in COVID-19 patients with diabetes\textsuperscript{136,137}. Movement restrictions can aggravate emergency situations of co-morbid patients hence telemedicine can be helpful\textsuperscript{134}. Future studies should focus on individual, regional, ethnic variations in prevalence and course of disease\textsuperscript{134}.

CONCLUSION AND FUTURE PROSPECTS
The literature survey, including the available recent studies, has found to support the statement, that the co-morbidities increases the susceptibility, risk of mortality and decreases survival rate in COVID-19 patients by worsening the clinical outcomes in terms of higher disease severity. The individuals without co-morbidities are being found to have higher chances of recovery rate, and the rate of mortality has been found less. Hence, we can conclude that heart disease, hypertension and diabetes are positively associated with worsening of disease severity during SARS-CoV-2 infection. In such scenario, patients suffering from different co-morbidities require prioritising attention and critical health care support in managing their diseases conditions during COVID-19 pandemic which could aid in saving their lives to some extent. In addition, special prevention and control strategies are required to be adopted strictly to minimise risk of SARS-CoV-2 transmission to uninfected population at risk especially patients suffering with different co-morbidities to avoid complicating disease conditions.

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CONFLICT OF INTEREST
The authors declares that there is no conflict of interest.

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All datasets generated or analyzed during this study are included in the manuscript and/or the Supplementary Files.

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