COVID-19: Risk Factors Associated with Infectivity and Severity

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Abstract

COVID-19 is highly transmissible; however, its severity varies from one individual to another. Variability among different isolates of the virus and among its receptor (ACE2) may contribute to this severity, but comorbidity plays a major role on disease prognosis. Many comorbidities have been reported to be associated with severe COVID-19 patients. We have collected data from retrospective studies which include clinical and epidemiological features of patients and categorize them into severe/mild, ICU/non-ICU and survivors/dead patients. In this review, we give an update about SARS-CoV-2 structure with emphasis on the possible reasons for the severity of the virus in patients. We also collected information and patients' data to highlight the relation between COVID-19 patients and comorbidities.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak of the pandemic COVID-19 originated form Wuhan city, China, in December 19.[1] Until 9th of October 2020, a total number of 36,754,395 confirmed cases and over a million deaths were reported worldwide.[2] Patients with COVID-19 exhibit common symptoms that can be divided into two groups: systematic disorders and respiratory disorders. Systematic disorders include fever, headache and gastro-intestinal distress, while respiratory disorders include cough, dyspnoea, bilateral ground-glass opacities and pneumonia.[3]

Distinguishably, COVID-19 showed some unshared symptoms with beta-coronavirus diseases such as sneezing and rhinorrhoea.[4,5] The rapid spread and expansion of SARS-CoV-2 lies on the asymptomatic carriers because they unknowingly transmit the virus to others.[6] SARS-CoV-2 is an RNA virus with a genomic size of around 30 kb and categorized under the beta-coronavirus genera under the *coronaviridae* family.[7] The natural host reservoir for SARS-CoV-2 is believed to be bats as the novel virus was found to have 96% sequence similarity with bat's coronavirus.[8] Nevertheless, human infection is unlikely to be directly caused from bats; instead, an intermediate host is essential for crossing the species barrier. The exact intermediate reservoir for SARS-CoV-2 is yet to be discovered.

Abbreviations: 3CLpro, 3-Chymotrypsin-Like Protease; (SR)-rich, Serine-Arginine rich; ACE2, Angiotensin-Converting Enzyme 2; ARDS, Acute Respiratory Distress Syndrome; COVID 19, Coronavirus Disease 2019; CVDs, Cardiovascular Diseases; DM, Diabetes Mellitus; DPP4, Dipeptidyl Peptidase 4; ER, Endoplasmic Reticulum; GA, Golgi Apparatus; IBD, Inflammatory Bowel Disease; ICU, Intensive Care Unit; Ifβ, Interferon β; LKR, Linker Region; MERS-CoV, Middle East Respiratory Syndrome coronavirus; MODS, Multiple Organ Dysfunction Syndrome; MS, Multiple Sclerosis; NsP1, Non-structural Polyprotein 1; PAMP, Pathogen-Associated Molecular Patterns; PRRs, Pattern Recognition Receptors; RdRP, RNA-dependent RNA Polymerase; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TB, Total Bilirubin; TLR2/4, Toll-Like Receptor 2 and 4.

The whole genome is composed of 14 open reading frames encode for 27 proteins[9] (Figure 1). It includes four structural proteins: the spike surface glycoprotein (S), the envelope protein (E), the nucleocapsid protein (N) and the membrane protein (M). Structural proteins are essential for virus attachment, entry, assembly and pathogenesis. The rest of the encoded proteins are both non-structural and accessory proteins.[7] The non-structural proteins are essential in virus transcription and replication whereas accessory proteins play a role in virus pathogenesis as they interfere with the host immune response, however, many of them their functions are still under investigations.[10,11]

N protein has essential roles in viral replication and assembly. It binds to the viral RNA producing helical ribonucleoprotein core and co-localizes with the replicase complex; therefore, it is needed in viral replication and RNA synthesis. In addition, N protein helps in virus assembly by interacting with other structure proteins and aids virion formation and release. One of the factors that increase SARS-CoV-2 pathogenesis is that it uses the N protein as antagonist that inhibits the production of Interferon β (IFβ) as well as serving as an antigen for SARS-CoV-2 to be detected by IgM, IgA and IgG.[12,13] The spike protein shared by coronaviruses is a trimeric transmembrane protein composed of a large ectodomain, a single-pass transmembrane anchor, and a short intracellular tail. The ectodomain is divided into main subunits, S1 and S2, in which S1 domain is responsible for virus-receptor attachment while S2 is responsible for virus-membrane fusion to the host cells.[14,15]

SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptor to enter their hosts. ACE2 receptors are found not only in lung tissue but also in the renal tubular epithelium, the Leydig cells in the testes, smooth muscle cells and the vascular smooth muscle cells of the blood vessels, in addition to expression in the kidney, liver and gastrointestinal tract cells.[16,17] Consequently, the virus has potential to infect multiple organs, mainly the respiratory epithelia and lung tissue. Once the virus attaches and enters the host cell, the process of uncoating begins, releasing the viral genome into cell cytoplasm. The translation begins with the expression of replicase polyproteins pp1a and 1ab, which undergo proteolytic cleavage by 3-chymotrypsin-like protease (3CLpro) and papain-like proteases (PLpro) yielding sixteen non-structural proteins to form the replication-translation complex and RNA-dependent RNA Polymerase (RdRP).[18,19] The synthesized polymerase produces sub-genomic mRNAs by using the transcription regulating sequence that lie on the 5` end of each gene as SARS-CoV.[20,21] Concomitantly, structural proteins S, N, E and M as well as other viral proteins begin to translate.[20,22] Finally, the proteins and the viral genome are assembled into virions in the endoplasmic reticulum (ER) along with the aid of Golgi apparatus (GA) that helps the complete virus exit the
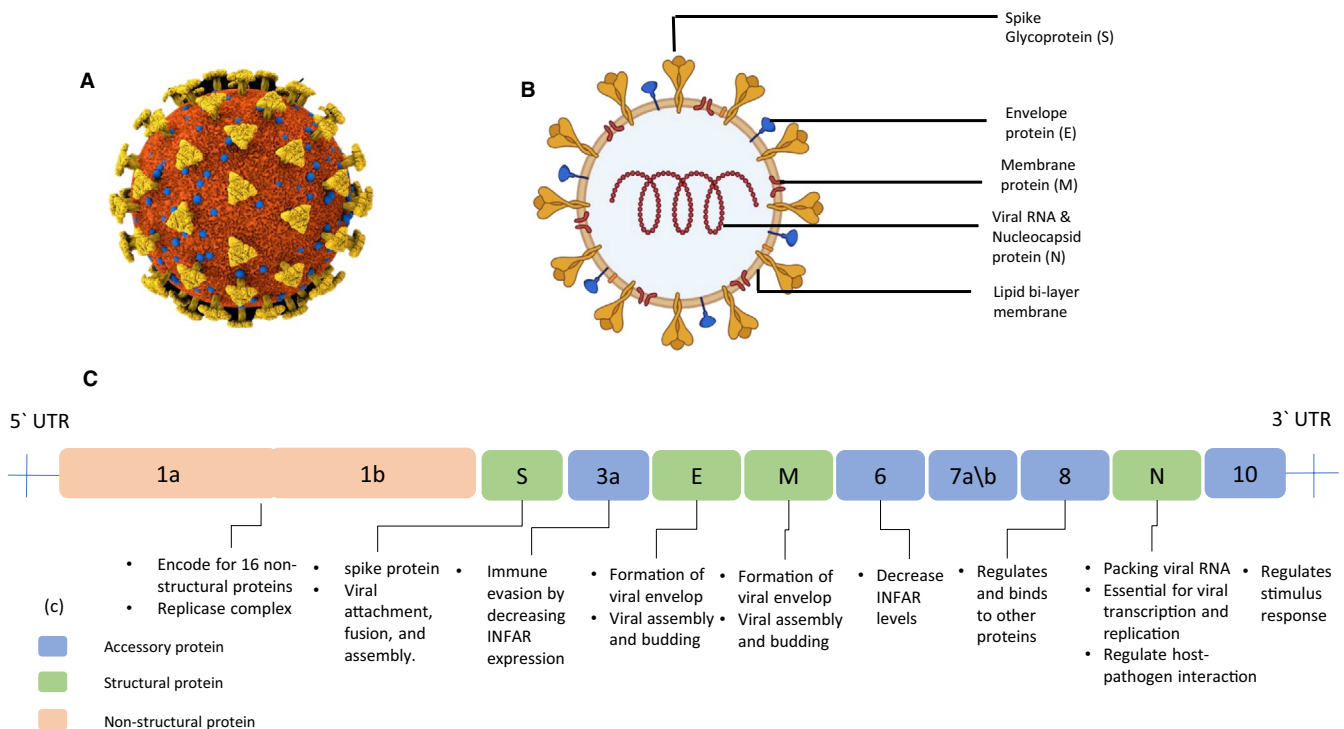

FIGURE 1 Schematic diagram for the SARS-CoV-2 structure and genome. (a) SARS-CoV-2 structure with viral components created with BioRender.com (b) 3D structure for SARS-CoV-2 created with Cinema 4D (c) SARS-CoV-2 genome organization: the viral genome yields structural, non-structural and accessory proteins as shown in the ligand. The proteins functions are illustrated downstream their locations

cell through vesicles.[23] Focussing on any of the previous events can be an effective approach for constraining the viral spread.

So far most of the studies done on SARS-Cov-2 patients are retrospective and meta-analysis studies aiming to understand the clinical features of the patients and assess different factors of poor prognosis. The available prospective studies are testing previously made drugs non-specific antivirals and repurposing them to control the symptoms. There has been several treatment regimens used with hospitalized and ICU patients to alleviate critical complications like acute respiratory dysfunction (ARDS) and multiple organ dysfunction (MODS) among others caused by several factors of disease severity such as viral load, cytokine storm and underlying comorbidities.[24] These were restricted to oxygen therapy, corticosteroids and broad-spectrum antibiotics for possible secondary bacterial infection.[25] In other cases, direct acting antivirals were used such as Remdesivir which is an inhibitor to viral RNA-dependent RNA polymerase that proved efficient against SARS-CoV-1 and MERS virus in-vitro.[26] Chloroquine and hydroxychloroquine used for malaria treatment as well as an immunosuppressor for rheumatoid arthritis was also included in certain guidelines.[27] All these regimens, however, vary by case due to the diverse array of symptoms caused by the virus.[25] Two companies Pfizer-BioNTech and Moderna have launched mRNA vaccines against SARS-CoV-2.[28] They utilize a modified mRNA encoding the spike gene for SARS-CoV-2 locked in perfusion conformation to elicit specific neutralizing antibodies and T cell immune responses.[29] On December 3, the CDC recommended 3 phases for vaccine administration; phase 1a for healthcare personnel, phase 1b was recommended on December 22 to include frontline essential workers and people aged 75 and older. Finally phase 1c to be administered for people aged 65-75 and 16 and younger with underlying comorbidities.[30]

Age has been a contributing factor of disease severity where consistently the older proportion of patients (commonly > 60 years of age) constituted the higher percentage of patients with poor prognosis and ICU admission. Old age is also associated with comorbidities such as hypertension, cardiovascular diseases and diabetes. Even in the younger proportion of patients associated with these comorbidities were also suffering from severe symptoms.[31-33] In this review, we aim to tackle the most important information of SARS-Cov-2 in terms of genetics, mode of infection and lifecycle with a focus on the host immune response and viral immune evasion. Finally, we address the different risk factors in addition to the common and uncommon comorbidities factors such as pregnancy, smoking and nutrient/vitamin deficiency associated with disease severity.

2 | IMMUNE RESPONSE TO SARS-COV-2 INFECTION

The innate immune response is the first line of defence against pathogens including viral infections. For COVID-19 patients, the body becomes sensitized upon attachment of the S1 subunit of the spike protein to ACE2 receptor of the alveolar epithelial cells, which is the same receptor for SARS-CoV.[34] ACE-2 is an enzyme that helps maintaining the balance between two forms of angiotensin namely angiotensin II, which causes inflammation and proliferation of cells, and angiotensin-(1-7) that promotes apoptosis and limit inflammation. ACE2 as a part of an axis called the ACE2/Ang-(1-7) axis is balanced by the ACE1/ angiotensin II axis.[35] ACE2 converts angiotensin II to Ang-(1-7) to maintain balance between angiotensin II mediated vasoconstriction, inflammation, and proliferation versus the vasodilation, anti-inflammatory and apoptotic effects caused by small peptides of Ang-(1-7).[36]

The entry of SARS-CoV-2 reportedly reduces ACE-2 receptors as they appear to enter the cell with the membrane receptor causing it to lose its function and result in an elevated angiotensin II level, leading to impaired lung function.[36,37] The elevation of angiotensin II not only leads to lung dysfunction but has also been associated with old age, obesity, diabetes, CVD and hypertension and heart failure.[38]

Following attachment, the viral RNA which is considered a pathogen-associated molecular patterns (PAMP), produced during the replication process, is recognized by the innate immune system through pattern recognition receptors (PRRs).[39] PRRs are divided into three types according to their localization in the host cell: membrane and cytoplasmic types. The membrane type includes toll-like receptor 2 and 4 (TLR2/4), whereas the cytoplasmic type includes RIG-I, MDA5, TLR3, 7 and 8.[40] RIG-I and MDA5 identify the viral genome in the endosomal compartment; in contrast, the TLR3 and TLR7 identify the RNA when exposed to the cytoplasm.[41] Recognition by any of these receptors triggers a cascade of events involving the MyD88 pathway and cGAS /STING pathway activating the NF-KB transcription factors, which in turn induces the expression of type I interferons (IFN-α /β).[42] Interferons I and III inhibit viral replication and induce the release of non-specific pro-inflammatory cytokines such as IL 1, IL 2, IL 4, IL 6, IL 7, IL 10 and MCP-1, MIP1a, IFN-γ, and TNF-alpha and chemokines (CCL2, CXCL10, CXCL9, IL-8 and IP-10, through neutrophils, macrophages.[34]

The presence of macrophage-induced cytokines such as IL-1 and IL-6 induce the recruitment of cytotoxic T cells and neutrophils.[43] In mild cases of COVID-19, cytotoxic CD8 T cells, which recognize the viral peptide presented on by MHC class I molecules, kill the cells infected with

the virus via perforin and granzymes and provide immunity against secondary infections. As the disease progresses, the number of exhausted CD8 + T cells is higher than the non-exhausted. Humoral immune response by B cells is activated by helper T cells and macrophage-derived IL-6.[43] When the virus or viral particles are presented by MHC class II molecules for a short period on antigen presenting cells such as dendritic cells and macrophage releasing first IgM before neutralizing IgG causing prolonged protection from the virus. In severe cases of COVID-19, autoantigen presentation occurs and CD4 T cells become activated by CD154 and pro-inflammatory CCR6 + Th17 in CD4 T cells, which leads to hyperactivation and release of pro-inflammatory cytokines.[44] Also, the cytotoxicity of CD8 T cells is higher in severe cases. Another important observation is that the number of naïve CD4 T cells increases in comparison with a decrease in memory CD4 T cells in the peripheral blood of severe cases of COVID-19 as well as a decrease in T regulatory cells which all collectively contribute to immune dysregulation.[42]

A cytokine storm also known as hypercytokinaemia leads to dysregulation of the immune response. In mild cases, a balance exists between the pro- and anti-inflammatory immune responses. The release of pro-inflammatory cytokines is high at the start of infection and is then lowered during recovery as interferon I inhibits viral replication and specific adaptive immunity eliminates the infected cells.[45] A delay in the specific acquired immune response, which could be caused by interference with IFN-α /β signals and lymphopenia in severe COVID-19, can cause rapid viral replication that can lead to hyperactivation of macrophages and neutrophils in the lung parenchyma leading to over-production of pro-inflammatory cytokines, chemokines and leukotrienes. This leads to release of free radicals causing tissue damage in lung epithelial and endothelial cells followed by symptoms of pneumonia, acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS), which leads to increased mortality.[43,45]

Elevation in IL-6 has been reported to be associated with cases of ARDS, owed to its recruitment of other immune modulators such as neutrophils and cytotoxic T cells as well as other cytokines.[46] Elevation of IL-6 could be a hallmark for severe COVID-19 prognosis and treatment; however, it is not the sole agent causing complications and mortality.[43] This was evidenced by cases that when administered IL-6 blocking drugs such as tocilizumab or siltuximab, more than half the patients did not recover from hyperinflammation.[47] One hypothesis suggests that this is due to constant release of IL-6 and other cytokines through macrophages as the primary response of infection, which likely causes evasion from blockade.[48]

The release of IL-1b and IL-18 is mainly lead by inflammasome activation.[49] In addition, IL1b also causes local

neutrophil cytotoxicity and pyroptosis, which is a form of cell death by causing an increase in circulating lactate dehydrogenase. The continued release of interleukin 1 from macrophage and especially IL-1b causes lung inflammation and fibrosis and eventually severe respiratory problems.[50]

It was also reported that severe cases exhibit a lowered count of regulatory T cells, which functions to balance the activation of pro-inflammatory function of CD4 T cells, CD8 T cells, B cells and natural killer cells. While the count of T and B lymphocytes is low due to activation of apoptosis and P53 signalling pathway in lymphocytes, their hyperactivation causes the release of multiple inflammatory cytokines such as CCR6 + th17 in CD4 T cells, IL-2R, IL-6, IL-7, IL-8, IL-17, IL-10, IFN-ɣ, MCP-1, MIP-1A, TNF-α, chemokines IP10 and CD8 T cells' cytotoxins, which cause damage to lungs and eventually other organs.[51] In addition, amplification of naïve T helper cells is observed with a decrease in memory B and T cells. In conclusion, severe cases of SARS-CoV 2 report higher counts of neutrophils, c-reactive proteins and pro-inflammatory cytokines and lower count of hyperactivated lymphocytes (CD4 and CD8 T cells). In addition, signs of hyperinflammation include an increasing level of ferritin and erythrocyte sedimentation rate and C-reactive protein.[52]

Coronaviruses use different methods to evade those PRRs hence, guarantee successful replication. In order for the virus to protect its RNA from being recognized by the immune sensors, it either forms a double-membrane vesicle called replication organelle (RO) or it mimics the 5`cap structure of the host mRNA.[10,39] Sometimes, viruses intentionally destroy their own genome to evade the cytoplasmic sensors. This can be achieved by two methods. First, the virus genome encodes for non-structural protein has an endonuclease activity. Second, the virus can undergo the non-sense mediated decay, used continuously by the host cell, by shifting its reading frame concomitantly producing a premature stop codon.[39] Moreover, SARS-CoV and potentially SARS-CoV-2 can halt the cellular translation machinery process using its 5`terminal subunit of the non-structural polyprotein 1(NsP1). NsP1 binds to the 40S subunit of the ribosome subunit hindering it from translocation hence protein synthesis.[53,54]

In addition, the genome of SARS-CoV encodes for eight antagonists that regulate the production of type I interferon (INF), which is used by the host cells to inhibit the virus replication.[55] This can be achieved by downregulating the phosphorylation of STAT1 that will reduce the induction of INF. Moreover, it interferes with the downstream cascade of interferon induction by ubiquitinating hence degradation of RNA sensor molecules.[56] MERS-CoV was found to downregulate the expression of viral antigen presentation-related genes, as a way of adaptive immune system evasion, hence, decrease the detection by the adaptive immune system.[57] Unlike SARS-CoV and MERS-CoV, the O-linked glycan that was predicted in SARS-CoV-2 may serve as a mucin-like domain used by

the virus to hide its recognition sites, that is epitopes from the immune system.[58] Such phenomenon was found to be used by Ebola and hepatitis C viruses for the same immunity-response impairment purposes.[59,60]

In the next section, different risk factors and comorbidities that could affect the severity of COVID-19 will be covered.

3 | RISK FACTORS ASSOCIATED WITH COVID-19 SEVERITY

Studies on COVID-19 continuously report the higher risk of diseases severity and poor prognosis for elderly patients with underlying diseases or comorbidities. A meta-analysis study reported that the most prevalent comorbidities in COVID-19 patients are hypertension (18.6%), cardiovascular diseases (14.4%) and diabetes (11.9%).[32] Other factors such as liver diseases, smoking, pregnancy, autoimmune disease and nutrition are not as common nor as impactful on poor prognosis. In this section, we will cover the relation between each factor and SARS-CoV-2 whether a direct relationship to the virus or an indirect one. Also, we collected data from clinical studies from several scientific databases and sources on each factor and their prevalence in severe/ICU admitted/ Death patients compared to Mild/non-ICU/Survivor patients (Supplementary Table 1).

We used scientific databases (Pubmed and lit. Covid) and searched with terms 'nCov, Covid-19, SARS-Cov-2, clinical features, clinical risk factors, comorbidities', and then, we adjusted filters to include clinical trials, observational studies, multi-center, randomized trials and excluded meta-analysis, systematic reviews and reviews. We further went through the publication to include the ones that had required data such as comorbidities, severe, non-severe groups, ICU, non-ICU groups, survivors and death groups. We also included any additional studies found in references. We then searched for specific meta-analysis publications that included COVID-19 with risk factors that were minimally or not found in the common comorbidities or patient criteria such as pregnancy, nutrient, vitamin deficiency and autoimmune diseases. The outcome results are presented in Supplementary Table 1.

3.1 | Age-associated risk

There has been compiling evidence of the higher risk imposed on elders compared to children in terms of contracting the virus and the fitness of the immune response. The relation between ACE2 expression level and age remains controversial.[61] It was reported that children have a lower baseline expression level of ACE2 in nasal epithelium when compared to older people, used a cohort of 305 patients aged 4 to 60 but did not compare with older patients.[62] While other studies proposed the opposite with a significant decline of ACE2 expression with age and associating the decrease with the age-associated androgen and oestrogen downregulation when analysing the ACE2 expression level in mice models.[63,64] We conclude from these confounding results that perhaps the protective effect of ACE2 decreases with age and its function in angiotensin II conversion diminishes with age while its presence allows for easy entry of SARS-CoV2. Another indisputable fact is the age-associated comorbidities, which are normally associated with an elevated level of angiotensin II leading to an increased risk of severity when compounded with SARS-CoV-2 infection due to the impact of angiotensin II on pro-inflammatory cytokines, vasoconstriction and lung impairment.[38] These results were also further validated by several epidemiological studies where the percentage of SARS-Cov-2 infections were higher in people with older age.[65,66] In terms of immunity, children have a stronger innate immune response with a higher level of lymphocytes, naïve T cells, B cells and natural killer cells, which will strengthen the response to COVID-19. Additionally, they have a lower expression of pro-inflammatory cytokines lowering the risk of developing a cytokine storm.[67] Moreover, due to multiple exposure of children to respiratory diseases and an intense vaccination regime, their bodies develop a trained immunity that may help them combat the disease better than elders.[68] The higher probability of children attracting the virus from 2nd and 3rd generation was also suggested as a contributing factor to milder symptoms.[69] It is important to note that the earlier hypothesis about children not being possible targets of the virus was refuted. The previously mentioned reports show that children are equally to contract the virus but likely show mild symptoms and have shown a better immune response to the virus, while in one case study children from an infected family repeatedly shown negative PCR but cellular immunity demonstrated presence of SARS-Cov-2 antibodies with very mild symptoms.[70,71] As shown in Supplementary Table 1, the difference between the average of age medians is 10 years between severe and in mild. In the next sections, we will cover different chronic diseases that could pose a risk on patients infected with SARS-CoV-2. Although hypertension and diabetes are also age-related diseases, we will tackle studies and theories on how the effect of each disease on the body could affect SARS-Cov-2 prognosis.

3.2 | Hypertension, cardiovascular disease and coagulopathy

There is a correlation between the COVID-19 and myocardial and vascular dysfunction. One arm of this correlation could be the multifunctional ACE2. The renin-angiotensin system (RAS) is a system that maintains vascular homeostasis and controls blood flow and among other functions. ACE

and ACE2 are two essential and sometimes opposing components of this system. Although they share structure similarity, they trigger different events. ACE converts angiotensin I into angiotensin II causing vasoconstriction, while ACE2 which shares structural homology with ACE converts angiotensin II into ang (1-7) promoting vasodilation.[72] After infection with SARS-Cov2, the transmembrane enzyme binds to the spike protein causing an increase in the level of angiotensin II in circulation due to dysfunction of ACE2.[38] In addition to the effect SARS-Cov-2 has on lung injury and inflammation, it also contributes to myocardial and heart damage. Patients with chronic hypertension, cardiovascular diseases (CVD) and cardiac hypertrophy seem to have a reduced ACE2 and Ang 1-7 leading to an increased level of circulating angiotensin II which speeds up the progression to heart failure.[35,36] There is also an increase in Troponin I /T and creatine kinase in hospitalized patients which are markers for cardiac-related diseases.[73] In two meta-analysis study tracking the elevation of troponin I/T or creatine kinase in hospitalized patients as a marker for underlying CVD from clinical trials and case reports, the proportion of patients with underlying hypertension and cardia-cerebrovascular diseases was higher in ICU versus non-ICU admitted patients.[74,75]

The reported over-production of angiotensin II and IL-6 caused by SARS-CoV-2 lead to endothelial activation and hyperinflammation which are contributing factors to coagulation activation and coagulopathy.[76] It is important to mention that about 70% of hospitalized patients have reported coagulation abnormalities like hypercoagulation, venous thrombosis (VT) and disseminated intravascular coagulation (DIC) with VT and pulmonary embolism being the causative factors behind almost 58% deaths.[77] This has also been validated by the elevated D-dimer reported in patients who develop severe symptoms. As a result, the steep and sudden decrease in fibrinogen levels causes an increase in consumptive coagulopathy in deceased patients.[78] The molecular mechanism that leads to SARS-CoV-2 mediated coagulopathy is not yet know. The increased risk of severity has been reported in both animal models and humans and serves as an important prognosis and a recommendation to use anticoagulants to prevent adverse outcomes.[79]

Hypertension and CVD are the most commonly found comorbidities or underlying diseases in retrospective studies when analysing clinical features of COVID-19 patients as is apparent in Supplementary Table I. A large Chinese meta-analysis study with 44,672 cases reported 10.5% increased fatality rate for patients with CVD and 6% for patients with hypertension.[80] Additionally, it was found that COVID-19 patients with no previous chronic diseases could develop cardiac injury. It is important to note that ACE inhibitors and angiotensin receptor blockers are recommended as a first line of treatment for patients with hypertension. There were recommendations for discontinuation of the ACE inhibitors for

risk of altering ACE2 expression and affecting SARS-CoV-2 virulence.[81] Although animal studies showed confounding effects of ACE inhibitors and ARBs on ACE2 expression, human studies have shown intravenous administration of these drugs for patients with hypertension or heart failure had no direct effect of on ACE2 expression or production of angiotensin 1-7 or angiotensin 1-9.[82] One Japanese study observed urinary increase in ACE2 after long-term treatment with ARB Olmesartan but not with ACE inhibitors.[83] A very large population study aimed to test the effect of ACE inhibitors and ARBs on increased risk of infection and/or admission in ICU. The study showed an overall reduced risk of SARS-CoV2 positive PCR with adjusted administration of the drugs, while it proved no significant correlation with the risk of ICU admission.[84] However, a direct correlation between heart dysfunction and COVID-19 induced death is not yet established. Moreover, there is no proof that patients with hypertension or any cardiac-related comorbidities were more susceptible to infection.[75,85] In Supplementary Table I out of 5138 patients, the average of severe case patients with hypertension is about double the average in mild cases. In patients with CVD, the average is approx. 20% in severe and 10% in mild.

3.3 | Diabetes

Both type I and type II diabetes mellitus (DM) are chronic diseases that put the body under immune stress.[86] Diabetes can be considered as a hyperinflammation state, which could lead to rapid worsening of patients with COVID-19 who already have an elevated level of cytokines like IL-6 and IL-1b leading to ARDS and mortality.[87] It is important to note that diabetes is as with hypertension an age-associated disease and in most retrospective studies is present in the older age groups. Patients with DM also exhibit lowered expression of ACE2 and high angiotensin II in circulation, reportedly due to glycosylation of the ACE2.[88] Nonetheless to reverse the effect of increased angiotensin II, patients with DM are prescribed with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers ACEI/ARB as part of their treatment as an anti-hypertensive drug. These drugs increase the level of ACE2 that is used by SARS-Cov-2 as a receptor for entry, leading to a vicious cycle.[89] Diabetes mellitus is also associated with increased levels of serum ferritin and D-dimer, which are two indicators of inflammation. In addition, an increase in blood clot formation or hypercoagulation is elevated in COVID-19 patients.[90,91] Due to the abundance of ACE2 in the pancreatic cells, SARS causes the reduction or dysfunction of the pancreatic islet cells, leading to reduced glycemic control.[92] In addition, the presence of a pro-inflammatory environment or a cytokine storm further reduces the insulin sensitivity in type I and type II DM.[87]

Several trials recorded the percentage of COVID-19 patients with DM in severe and non-severe cases. In several studies in China, diabetes patients represented up to 20% of the COVID-19 patients.[90,93,94] Even higher percentage of COVID-19 induced death and ICU cases suffered from DM was reported, in some cases up to 35%.[95] The data collected from studies in Supplementary Table I also conclude that the percentage of patients with DM is higher (almost double) in severe cases than in mild cases.

3.4 | Liver dysfunction

SARS-Cov-2 has been reported to affect liver functions such as the AST and ALT levels as well as a slight elevation in total bilirubin (TB).[96] The effect of COVID-19 on liver has been controversial, with some studies correlating abnormal AST and ALT levels with severity of infection, while others report no difference between mild and severe cases. A large meta-analysis study with 3428 patient records of liver function analysis pooled from 20 prospective studies reported liver injury incidence marked by AST, ALT and bilirubin elevation at 58% to 78%.[97] Another study specified elevated ALT or AST levels in severe and mild cases, respectively.[98] It is undecided whether the cause of liver abnormalities is due to the viral infection or the inflammation caused by cytokine storm. Although it is comparably low, ACE2 is found in liver and bile duct cells as reported in a recent ACE2 expression profiling study comparing the expression across different cell types.[99] Therefore, the damage observed in liver functions could be owed to SARS-CoV-2 effect on ACE2 expression. However, the expression is about 20 times higher in bile duct cells than in hepatocytes and histopathological analysis of hepatocytes show minimal damage, which leads us back to acute inflammatory reaction and multiple organ dysfunction.[44,100] The cytokine storm caused by the virus in severe cases leads to severe inflammation, apoptosis and necrosis of cells and eventually leads to multiple organ dysfunction syndrome (MODS). Another important issue is the side effects of the drugs used for treatment. Most of the drugs used to alleviate the symptoms contains acetaminophen, which has proven to cause liver damage.[101] The use of different non-specific antivirals such as oseltamivir or lopinavir also affect the liver.[100]

Chronic liver diseases are widespread worldwide and are especially more common in the elderly. People with underlying liver disease and cirrhosis are more vulnerable to severe COVID-19 manifestation due to systemic immunodeficiency. There are currently no reports of increased risk of infection due to pre-existing liver diseases.[102,103] According to data collected in Supplementary Table I, over 30% of the studies did not contain data on liver disease and the average between severe and mild cases show a slight increase with no confirmed causality between severity and liver dysfunction. Until now, there have been no reports of patients undergoing treatment for liver hepatitis B or C having an increased or decreased risk of COVID-19.

3.5 | Autoimmune disease and organ transplantation

The increased level of pro-inflammatory cytokines such as IL-1 and IL-6 and c-reactive protein accompanied by lymphopenia in severe cases of COVID-19 can be found closely related to symptoms in other diseases such as rheumatoid arthritis, systemic Lupus, multiple sclerosis (MS) and inflammatory bowel disease (IBD), which could lead to confusion in diagnosis.[104] There are two major prespectives when looking at the relation between SARS-CoV-2 and autoimmune disease; one is that people with autoimmune diseases are greatly susceptible to viral infection due to decreased adaptive immunity and because of increased intake of immunosuppressants such as corticosteroids as part of their treatment regimen.[105] The other prospective is that these immunosuppressants may help contain the cytokine storm cause by COVID-19, which eventually leads to ARDS and death. The latter has been used to test drugs with immunosuppressive nature normally consumed by rheumatic patients such as chloroquine, hydroxychloroquine and IL-6 blockers in treatment regimens of mild and severe COVID-19 cases with variable results.[106-108] We found that most of the randomized cohort studies assessing clinical features of COVID-19 cases did not include autoimmune disease as a comorbidity, but rather were presented in case-controlled studies and case reports as the main inclusion criteria. One trial following up with 111 patients of previous organ transplantation and undergoing long-term immunosuppressive treatment did not show correlation between immunosuppression and increased risk of infection.[109] A follow-up study with 20 kidney transplants patients who had developed SARS-CoV-2 induced pneumonia. All patients were taken off their immunosuppressive drug tocilizumab (IL-6 blocker) and started antiviral treatment. Out of 20 admitted patients, 14 were severe cases, including five deaths, and six patients were moderate cases.[110]

At the beginning of the outbreak in China and Italy, preliminary data reported lower risk of infection in patients with inflammatory bowel disease (IBD).[111,112] With the increase in COVID-19 spread, severe and fatal cases of IBD (ulcerative colitis or Crohn's disease) infected patients started to appear.[113] A retrospective observational study included 79 IBD patients with COVID-19 to study their clinical features and outcome were reported. This study found that patients with active IBD and treated for flare-ups developed COVID-19 related pneumonia and showed increased ICU admission as well as fatality.[114] In the data gathered in Supplementary

Table I, only six studies contained data on patients with autoimmune diseases, but even then, the number of patients was very small.

3.6 | Pregnancy-associated risk

Monitoring pregnant women with SARS-Cov2 report relatively similar symptoms of fever, coughing and diarrhoea across the sample size but with higher severity compared to non-pregnant women.[115] More importantly, several cases of premature birth were reported experiencing other complications such as premature membrane rupture, irregular contractions, growth restriction and some stillbirths.[116] The newborns manifested shortness of breath, vomiting and rashes, and some had an elevated level of IgM specific to SARS-CoV-2.[66] However, tests for viral RNA from amniotic fluid, serum and breast milk came out negative for SARS-CoV-2.[117] Therefore, there is no proof of vertical transmission from the mother, but there is a suggestion that the viral infection affects the pregnancy and the general health of the newborn. Pregnancies go through different phases in immune response between pro-inflammatory and anti-inflammatory with a strong innate immune response and a decrease in the number of T and B cells. The high level of oestrogen and progesterone tends to cause swollen upper respiratory tract.[117] Another systematic review of pregnant women infected with CoVs (MERS-CoV, SARS-CoV, and SARS-CoV-2) found the increased risk of severe symptoms in pregnant women to be higher in SARS-CoV and MERS-CoV than in SARS-CoV-2. Of the COVID-19 infected women, pregnant women showed a higher rate of premature birth and neonatal ICU admission, with 2.4% rate of stillbirths and 2.4% of neonatal death.[118] However, other studies showed that pregnant women with COVID-19 who are treated had the same pattern of clinical features as non-pregnant women with no reported deaths.[119,120] Overall, the number of studies monitoring infection in pregnant women is limited without a significant pattern for severe prognosis between pregnant and non-pregnant women.[121,122] In a US study, they reported a total of 91,412 women infected with SARS-CoV-2 at the reproductive age. In this study, among the 8,207 pregnant women about 31% were hospitalized and 1.5% admitted to ICU while in non-pregnant women only 5.8% were hospitalized and 0.9% admitted to ICU.[123] Notably, the percentage of pregnant women admitted to ICU was higher in the older age range (34%) compared to younger women (29.3%), and compared to non-pregnant women they were more likely to have comorbidities such as DM (15.3% versus 6.4%), CVD (14% versus 7%) and immunocompromised condition (3.5 versus 2.8).[123] It is important to note that pregnancies are often associated with hypertension, respiratory problems, gestational diabetes and an immunosuppressive state that may complicate their situation when they get infected.[120,124]

3.7 | Health and nutrition

Comorbidities resulting from smoking, obesity and nutrient deficiencies affect the severity level, treatment regimen and complications of the viral infection. Smoking and obesity lead to diseases such as hypertension, cardiovascular and respiratory diseases. Studies comparing intensity of COVID-19 symptoms between patients with different comorbidities and healthier patients. People with comorbidities were more vulnerable and developed more critical symptoms and even a higher mortality rate. Bad habits such as smoking and accumulating saturated fatty acids in morbid obesity lead to a lowered adaptive immunity and an increased innate immunity.[125,126] The WHO released a review including results from 26 observational studies and eight meta-analyses that reported a correlation between smoking and hospitalized COVID-19 patients.[127] The review reports no evidence of increased risk of infection but a prevalence of 1.4%-18.5% of smokers among hospitalized patients.[128] Vitamin D has also been included in the treatment protocol of COVID-19 patients with suggested higher risk in patients with vitamin D deficiency. Vitamin D has been known to enhance adaptive immune response, which would hasten specific immunity against COVID-19 and decrease cytokine storm.[129] With the current restriction of outdoor activity, this could affect the vitamin D intake caused by lack of exposure to the sun. It is worth noting that the number of studies monitoring health habits such as smoking, obesity or nutrient/ vitamin deficiency is not common.

3.8 | Viral load

Although not a host related factor, it is imperative to mention one of the first and most effective factors affecting the prognosis of the disease is the initial viral load. Primarily this was observed with SARS where it was reported that higher expression of ACE2 mRNA was concurrent with higher levels of SARS-CoV RNA in patient plasma and serum.[130,131] Several retrospective studies have recorded high viral load just before or at the time of symptoms onset. These studies monitor the quantitative viral load in serum and plasma and viral shedding in stool. Higher viral load leads to erratic shedding in stool with symptoms appearing on day 3 to 5 followed by a decrease in the viral load.[132] One study reported detectable levels of SARS-CoV-2 in the serum of critically ill patients as opposed to mild and severe patients with positive nasal swabs. This study proposed a correlation between higher load of SARS-CoV2 in serum and a sharp elevation

in IL-6 in critically ill patients (almost 5 times the level in severe patients).[133] It was also reported that quantitative viral load measurements differentiates between patients who survived versus patients who died from SARS-CoV-2.[134]

4 | CONCLUSION

The severity of the SARS-CoV-2 infection is variable among patients. This can be on the virus level, the host genetics level or the host health condition level. Therefore, different isolates of the virus, different ACE2 variants and their abundance, or different comorbidities may participate in this variation in the COVID-19 severity among patients. Once the virus enters the cell via spike protein (S), it induces the activation of the innate immune system and macrophage-derived cytokines are released. The virus then through mechanisms not yet definite such as interference with interferon signalling causes a delay in specific adaptive response, lymphopenia and over-expression of inflammatory cytokines namely, IL- 2R, IL-6, IL-7, IL-8, IL-17, IL-10, IFN-ɣ, MCP-1, MIP-1A and TNF-α, chemokines IP10. This condition is known as a cytokine storm, and it causes severe outcomes in the patients ranging from ARDS, pneumonia to multiple organ dysfunction and mortality. The virus also causes a downregulation of ACE2 in the infected cells. ACE2 is the enzyme that converts angiotensin II to ang 1-7 keeping the homeostasis of ACE2/Ang1-7 axis, which is anti-inflammatory and proliferative, and ACE1/ angiotensin II, which is pro-inflammatory and apoptotic that further pushing the body towards tissue necrosis and dysfunction. Until this date, the virus has been medically managed through drug repurposing and symptom alleviation with non-specific antivirals, antibiotics, analgesics, immunosuppressive drugs and vitamins. The variability in patient symptoms called for classification of the disease into mild, moderate and severe depending on multiple aspects. Viral load being the predominant cause followed by factors in the patient history record. Age being the most predominant and prevalent factor, where the higher percentage of severe outcomes belongs to older patients who tend to have weakened immune system and underlying comorbidities. In this review, we collected data from studies with specific criteria as mentioned in the methods section, displaying a total of 5138 patient clinical features (Supplementary Table I). The review emphasizes the level of severity relevant to age, comorbidities, pregnancy and smoking. In agreement with previous meta-analysis studies, the highest percentage in the severe group belonged to patients with hypertension, followed by diabetes, CVD and liver dysfunction. Data on autoimmune diseases, pregnancy and smoking factors were very limited. The cause of the high percentage of severity can be linked to exacerbation of symptoms of underlying chronic disease either due to ACE2 downregulation or the acute inflammatory response. Whether the infection was mild or severe, early diagnosis, prognosis and personalized treatment greatly affects the outcome for the patient. Also monitoring the side effects of the drugs given in terms of hepatotoxicity and inflammation is essential to avoid complications.

AUTHORS' CONTRIBUTIONS
FN performed literature review, wrote and edited the manuscript; AE performed literature review and co-wrote the manuscript; STZ designed, edited and directed the study.

CONSENT FOR PUBLICATION
Not applicable.

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Not applicable.

DATA AVAILABILITY STATEMENT
All data sets, on which the conclusions of the manuscript rely, are presented in the main paper and the supplementary Table.

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SUPPORTING INFORMATION

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