Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 3

Mechanism and transmission routes of COVID-19

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3.1 Origin and transmission of Sars-CoV-2

Acute respiratory disease caused by novel coronavirus, SARS-CoV-2, is a β-coronavirus with a nonsegmented genome consisting of positive-sense, single-stranded RNA enclosed within the viral capsid. Coronaviruses (CoVs) are divided into four genera, such as α, β, γ and δ-CoV; α- and β-CoV cause infection in mammals, while γ- and δ- CoV may cause infection in birds. Six forms of coronaviruses have been shown to cause infections in humans, namely HCoV-229E, SARS-CoV, HCoV-OC43, HCoV-NL63 MERS-CoV, and HCoV-HKU1. Infection with HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43 are usually characterized by moderate respiratory symptoms while SARS-CoV and MERS-CoV are known to cause severe respiratory illness advancing to fatal conditions like multiple organ failure in some of the cases.[1] Genome sequencing data has revealed that SARS-CoV-2 is closely linked to bat-derived SARS-like coronavirus, bat-SL-CoVZC45, and bat-SL-CoVZXC21, with >85% similarity, but with reduced homology of 79% and 50% with SARS-CoV and MERS-CoV, respectively.[2,3] Based on these results and phylogenetic analysis, it is likely that SARS-CoV-2 originated in bats and was probably spread to humans through an (unidentified) intermediate host animal. The genome structure, the encoded structural and nonstructural proteins, and the key host of SARS-CoV-2 are illustrated in Fig. 3.1. Experimental evidences have clearly shown that SARS-CoV-2 infects humans by binding to angiotensin-converting enzyme 2 (ACE2) expressed in the respiratory tract, in a mechanism similar to that of. SARS-CoV.[4]

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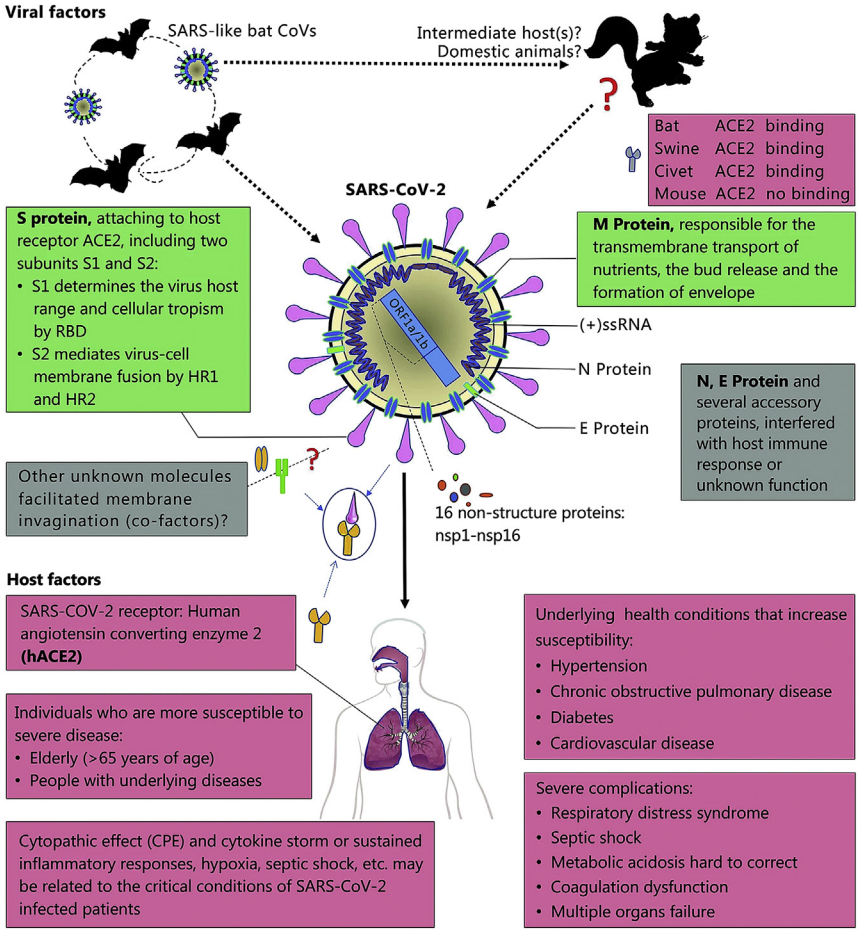

Figure 3.1 Top panel depicts the structural and genomic features of SARS-CoV-2. The genetic segment ORF 1a/b is known to code for various nonstructural proteins (nsp 1—16). The remainder genetic material codes for different structural proteins: spike glycoprotein (S), envelope (E), matrix (M), and nucleocapsid protein (N). Bottom panel represents the different host conditions that can affect the susceptibility and severity of SARS-CoV-2 infection. *(Image reproduced with kind permission from Springer Nature, New York, USA.[5])*

SARS-CoV-2 is found to exhibit higher infectivity than SARS and MERS but has less virulence in terms of morbidity and mortality. Evidences indicate that COVID-19 had a mortality rate of 3.4%, while SARS and MERS had a mortality rate of 9.6% and 35%, respectively. Human-to-human transmission of COVID-19 majorly occurs inside the members of a family and those who are closely associated (friends) with the infected person.[5]

Several studies indicated that symptomatic individuals are the primary cause of COVID-19 transmission. It majorly spreads among humans by respiratory droplets during a cough or sneezes from an infected individual.[6] Transmission of SARS-CoV and MERS-CoV among health care workers was reported to occur predominantly through the nosocomial transmission. Infection among health care staff accounted for 33%–42% of SARS cases, while it was 62%–79% during the MERS-CoV outbreak.[7] Viral transmission is believed to have occurred through direct contact with the host or interaction with the (unidentified) intermediary carrier. Moreover, it is also clear that asymptomatic individuals could also transmit the virus. It has been reported that elderly individuals represent a specific group of patients with an elevated risk of infection with swift clinical deterioration.[8] Additional experiments are required to explain the transmission pathways, the incubation time and the period of COVID-19 infectivity.

Mutations are common in the SARS-CoV-2 genome because the virus replicates and socializes in the anthropological population. They mount up at a rate of about one to two mutations per month in worldwide phylogeny. The new SARS-CoV-2 variant named VUI-202012/01 is the first "Variant Under Investigation" in December 2020 and is specified by a set of 17 changes or mutations. As a result of this ongoing process, many thousands of mutations have already occurred in the SARS-CoV-2 genome since the virus emerged in 2019.[9] Although SARS-CoV-2 shows evidence of some seasonal decline, the persistence of the pandemic may allow the accumulation of immunologically relevant mutations in the population as vaccines develop.[10,11] As mutations continue to develop, new combinations are increasingly observed. Over the last few weeks, the United Kingdom (UK) has faced a rapid increase in COVID-19 cases, especially in South East England, leading to enhanced epidemiological and virological investigations as tracked by COVID-19 genomics—UK consortium (COG-UK). Analysis of viral genome sequence data showed that a large proportion of cases belonged to a new single phylogenetic cluster. The new variant is defined by multiple spike protein mutations (deletion 69–70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, and D1118H) as well as mutations present in other genomic regions. Although it is known and expected that viruses are constantly mutating, leading to the emergence of new variants, preliminary analysis in the UK suggests that this variant is significant—more communicable than previously circulating variants, with an estimated potential to increase the reproductive number by 0.4 or more, with an estimated increased transmutability of up to 70%. This new variant emerged

at the time of the year when family and social mixing has traditionally been increased; however, at this point, there is no indication of increased severity of infection associated with the new variant.[12]

3.2 Incidence and risk factors for COVID-19 severity

The COVID-19 pandemic has become a severe burden on the global health care system due to the exponentially mounting infections and death.[13] Clinical and epidemiological data from different populations have provided vital information about the factors determining the COVID-19 susceptibility. The patients diagnosed with COVID-19, significantly older patients, often had a coexisting condition such as cardiovascular disorder, hypertension, and cardiovascular disease.[14] Emerging reports showed that older age (>65 years) and the incidence of comorbidities are significantly associated with the COVID-19 severity.[15] Some of the reported comorbidities are listed in Table 3.1. It is evident that hypertension, diabetes, and cardiovascular disease are comparatively more prevalent and represented a significant proportion of the comorbidities in COVID-19.[16–18] Chronic lung disease, chronic kidney disease, and cancer are some of the other comorbidities reported in SARS-CoV-2 infected patients.[19,20]

3.2.1 Hypertension

Hypertension is a severe condition in which the walls of the arterial blood vessels persistently experience elevated pressure. If left untreated, the results

Table 3.1 Some of the prevalent comorbidities in COVID-19.

Incidence of comorbidities	References
Hypertension (21%), Diabetes (11%), and Cardiovascular diseases (CVD)(7%)	Singh et al.[17]
Hypertension (15.8%), CVD (11.7%), Diabetes (9.4%), Cancer(1.5%), Coronary Obstructive Pulmonary Disorder (COPD) (1.4%), and Chronic Kidney Disease (CKD) (0.8%)	Sanyaolu et al.[19]
Hypertension (30%), Diabetes (19%), Cardiovascular disease (8%), COPD (3%), Cancer (1%), and CKD (1%)	Zhou et al.[20]
Hypertension (15%), Diabetes (7.4%), Coronary heart disease (2.5%), Cerebrovascular disease (1.4%), COPD (1.1%), Cancer (0.9%), and CKD (0.7%)	Guan et al.[16]
Hypertension (31.2%), CVD (14.5%), Diabetes (10.1%), Cancer (7.2%), Cerebrovascular disease (5.1%), COPD (2.9%), CKD (2.9%), and Chronic liver disease (2.9%)	Wang et al.[18]

could be deleterious, leading to ischemic heart disease or stroke.[21] Approximately 18 million global cardiovascular deaths result from hypertension.[22] Epidemiological studies show that hypertension is more common in COVID-19 patients among the other prevailing conditions viz. diabetes and cardiovascular disease. A Chinese COVID-19 study reported the prevalence of three significant comorbidities in the infected patients: hypertension (30), diabetes (19%), and coronary heart disease (8%).[20] Wu et al. reported a higher incidence of hypertension (23%) in COVID-19 patients who suffered acute respiratory distress syndrome (ARDS) compared to other comorbidities in the study such as diabetes and cardiovascular disease (CVD).[23] A large COVID-19 case-control study demonstrated a 6% case fatality rate (CFR) in patients with hypertension as compared to the total case fatality rate (2.3%) of the subjects.[24] In a subsequent Chinese population study, it was reported that 35.8% of COVID-19 patients with hypertension reached the composite endpoints (intensive care unit [ICU], mechanical ventilation, or death) as compared to the 13.7% nonhypertensive group.[16] From the above reports, a causal association between hypertension and COVID-19 is evident, but the underlying pathological mechanism remains ambiguous. Further research in the area is warranted for a better understanding of the pathophysiological role in hypertensive COVID-19 patients.

The SARS-CoV-2 is shown to primarily infect the respiratory tract of humans. The outer transmembrane spike glycoprotein of SARS-CoV-2 interacts with ACE2 expressed in the respiratory tract epithelium, thus facilitating the viral entry.[4] ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB), the contemporary drugs used in the treatment of hypertension, have been shown to elevate ACE2 expression levels in experimental models.[25] This has raised concerns on whether the treatment would increase the susceptibility to SARS-CoV-2 infection.[26,27] Due to the lack of clear evidence of the detrimental effects of ACEI and ARB in COVID-19, the American Heart Association and the European Society of Hypertension has recommended the continuation of these drugs.[28]

Interestingly, there are reports on the protective effects of ARB/ACEI in experimental studies. The potential downstream effects on the usage of ACEI and ARB are depicted in Fig. 3.2. ACEI is shown to reduce the formation of angiotensin 2, thus alleviating the proinflammatory effects. The action of ARB blocks the angiotensin 2 receptors thereby incidentally increasing the levels of angiotensins 1 to 7 and thus promoting the antiinflammatory effects.[25] When treated with ARB, mice models with avian H7N9 influenza virus-induced lung injury showed improvement.[29]

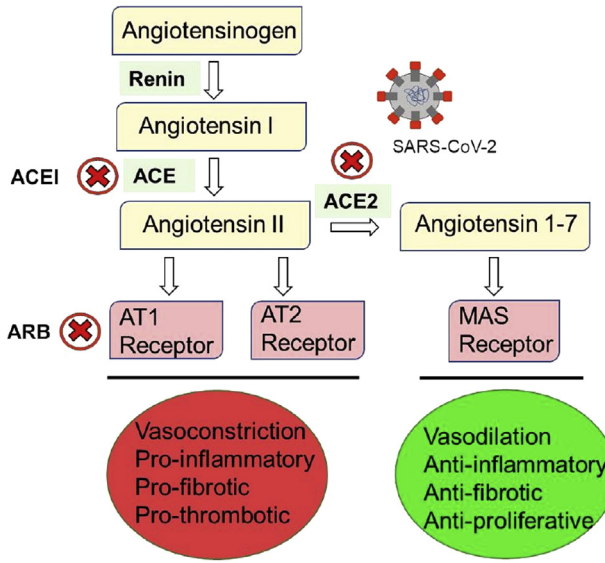

Figure 3.2 Potential effects of ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB) on the renin-angiotensin system. ACE-angiotensin-converting enzyme, ACE-2 angiotensin-converting enzyme 2, AT1/AT2-angiotensin 2 receptors.[25]

Overall, the usage of ACE inhibitors and ARBs could potentially reduce inflammation in the lungs, kidneys, and liver. These drugs can have protective effects on ARDS, myocarditis, and acute kidney injury that are frequent in severe COVID-19 cases.[30,31] Also, a recently concluded study reported that the use of ARB/ACE inhibitors in the hypertensive COVID-19 cohort demonstrated lower mortality compared to the non-ARB/ACE user group.[32] Another case-control study by Liu et al. reported that there was no significant association between the exposure to antihypertensive drugs and COVID-19 severity.[33]

3.2.2 Diabetes

COVID-19 has affected a substantial proportion of diabetic patients apart from patients with hypertension and CVD. With the current data, it is difficult to conclude whether diabetes alone contributes to the disease severity since other factors like age, obesity, and hypertension are also contributing factors. A report from the Centers for Disease Control (CDC) response team, United States[34], showed the prevalence of diabetes in 10.9% of the COVID-19 patients. In a Chinese COVID-19 study, it was reported that 22% of the nonsurvivors were diabetic as compared to the 10% diabetic survivors.[35] In another study, the

authors reported that 22.2% of the diabetic COVID-19 patients required ICU care in comparison to the 5.9% nondiabetic COVID-19 controls.[18] The Chinese CDC report on 44672 COVID-19 patients found that the CFR for diabetes was higher (7.3%) than that of hypertension (6%) but lower than CVD (10.5%).[36]

Diabetes is characterized by chronic hyperglycemic conditions arising from impaired insulin secretion or insulin action.[37] An earlier study on SARS has demonstrated diabetes and plasma glucose levels as independent predictors of mortality and morbidity.[38] Several micro- and macrovascular complications observed in diabetic subjects are shown to be significant predictors for the severe outcomes in different viral infections including influenza A virus subtype H1N1 and MERS-CoV.[39,40] As discussed earlier, the binding of ACE2 to spike glycoprotein of SARS-CoV-2 facilitates viral entry into the cells. Drugs that are used to treat diabetes including glucagon-like peptide-1 (GLP-1) agonists, thiazolidinediones, statins, ACEI, and ARB, are known to elevate ACE2 expression.[41–43] Interestingly, a Mendelian randomization study by Rao et al.[44] revealed that elevated ACE2 expression in the lungs was significantly associated with diabetes. The effect of metformin on diabetic COVID-19 patients remains to be studied. However, the use of metformin was shown to alleviate the adverse of diabetes in chronic obstructive pulmonary disease (COPD) patients.[45] This hypothetically suggests a protective role for metformin in diabetic COVID-19 patients since SARS-CoV-2 primarily affects the lungs, causing severe respiratory illness. Furin is a type-1, membrane-bound cellular protease that facilitates the entry of SARS-CoV-2 inside the host cells by cleaving the spike glycoprotein bound to the cellular receptor. Thus, an elevated furin level in diabetic patients could increase the susceptibility to SARS-CoV-2 infection.[46] ACE and ACE2 are two critical regulatory enzymes of the renin-angiotensin system (RAS) (Fig. 3.2). SARS-CoV-2 is known to bind to the ACE2, and this action could potentially result in the accumulation of angiotensin 2, resulting in downstream proinflammatory events. Elevated ACE/ACE2 activity is characteristic of COVID-19 patients with ARDS.[47]

Diabetic patients are known to exhibit impaired adaptive immunity. Abnormalities in T cell response, the impaired phagocytic capacity of macrophages, and delayed antigen presentation lead to chronic inflammation in diabetes.[48] The effect of MERS-CoV infection on experimental mice model with induced diabetes has revealed a significant reduction in CD4 T cell count and elevated levels of interleukin-17a (IL-17a).[49]

Similar observations of reduced CD4 and CD8 T cells (possibly due to lymphopenia) and elevated levels of proinflammatory Th17 cells and cytokines such as IL-6 were reported by Guan and colleagues.[16] Dysregulated T cell response could trigger a "cytokine storm" of proinflammatory cytokines such as tumor necrosis factor- α (TNF-α), IL-6, and interferon-γ (IFN-γ). This hyperinflammation is associated with COVID-19 severity and could lead to multiple organ failure observed in severe cases.[50] Also, diabetic patients are known to exhibit an inherently impaired innate immunity, affecting neutrophil functions such as phagocytosis and chemotaxis.[51] Thus, the synergistic effect of a dysfunctional immune system, elevated ACE2 expression, furin, and the effects of diabetic medications appears to increase the susceptibility and severity in diabetic COVID-19 patients. Diabetes management during the pandemic has become a daunting task for health care professionals (and for the patients) due to the limited information available. Constant glucose monitoring, personalized treatment strategies for diabetic COVID-19 patients, and careful monitoring of drug effects are some of the advocated measures for diabetes management.[52]

3.2.3 Cardiovascular disease

CVDs are considered the foremost contributor to global death than any other disease.[53] The incidence of CVD in COVID-19 is preceded by hypertension and diabetes (Table 3.1). Evidence shows that 7%–19% of COVID-19 patients presented with a history of preexisting cardiovascular complications.[16,20] CVD was found to be the second most prevalent comorbidity, next only to hypertension in some of the reports.[18,19] CDC data from the United States shows that 29% of COVID-19 patients with preexisting CVD required ICU admissions, which were concordant with the Wuhan-based Chinese report of 25% ICU admission.[18,34] Wu and McGoogan[36] reported a 10.5% CFR for CVD in COVID-19 patients compared to 7.3% for diabetes and 6% for hypertension. Shi et al.[54] reported that the risk of in-hospital mortality in COVID-19 patients was associated with the presence of cardiovascular comorbidity. COVID-19 patients are shown to experience multiple cardiac complications. Some of the probable mechanisms leading to cardiac complications and also contributing risk factors are illustrated in Fig. 3.3.

COVID-19 infection is shown to proceed in three phases.[55] The initial phase is marked by the viral entry and proliferation inside the lung cells.

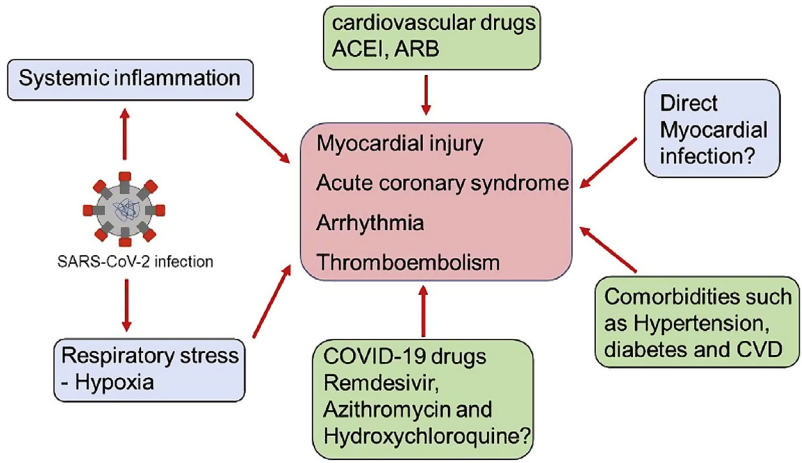

Figure 3.3 Potential mechanisms and risk factors contributing to cardiovascular damage in COVID-19 patients.[59,61,64,65]

Damage during the early phase is evident mainly in the respiratory and gastrointestinal tract with biomarkers such as elevated levels of lactate dehydrogenase (LDH), ferritin, high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and mild lymphopenia.[56] The intermediate or pulmonary phase is manifested by shortness of breath, hypoxia due to pulmonary damage, and cardiovascular stress. The tissue damage activates an inflammatory state marked by vasodilation, increased cellular permeability, and leukocyte accumulation.[55] The two significant biomarkers of the intermediate phase are the increased levels of brain natriuretic peptide (BNP) and troponin.[57] The intermediate phase is also evident from an abnormal computed tomography (CT) chest.[58] The inflammatory response of the intermediate stage gets amplified further resulting in a hyperinflammatory state. This stage is marked by a raised level of proinflammatory cytokines and cardiac biomarkers. This critical phase is evident from the fatal "cytokine storm" leading to multiple organ failure, ARDS and sepsis.[59] Xu and colleagues suggest that the heart damage observed in the COVID-19 cases was a result of a hyperactive immune system since no direct evidence of viral infiltration was found in the autopsy.[60]

Some of the patients without preexisting cardiovascular manifestations in COVID-19 are known to experience cardiac damage. Myocardial injury, acute coronary syndrome (ACS), cardiac arrhythmia, and venous thromboembolism are some of the cardiovascular manifestations reported in

SARS-CoV-2 infected individuals.[61] Myocardial injury is the one most prominent cardiovascular manifestation observed in SARS-CoV-2 infected patients. A Chinese study comprising 138 patients found elevated levels of cardiac injury-related biomarkers in COVID-19 patients. The authors observed elevated levels of high sensitivity cardiac troponin I (hs-cTnI) and echocardiographic (ECG) abnormalities in 7.2% of the patients. Also, 22% of patients with cardiac complications required ICU care.[18] Zheng and coworkers reported that 12% of the hospitalized COVID-19 patients without a history of CVD had elevated troponin levels and cardiac damage.[62] Another Chinese study observed that 12% of the COVID-19 patients had experienced myocardial injury and four out of five required ICU care.[63] Zhou and colleagues found that 17% of the COVID-19 subjects in the study had experienced acute cardiac injury with a high death rate of 97% in that particular group of patients.[20] In a similar study, Shi et al. reported that 30.6% of the nonsurvivors had suffered an acute myocardial injury and that the risk of mortality can be independently predicted using biomarkers of cardiac injury.[54]

Myocardial injury is one of the significant cardiac complications experienced by SARS-CoV-2 infected patients. A combined effect of the respiratory stress from hypoxia, cardiac infection, and injury sustained from the systemic inflammatory response is suspected of causing myocardial injury.[64] There is evidence of macrophage infiltration and a low-level of $CD4^+$ T cells potentially leading to inflammation-mediated cardiomyocyte damage.[60] Cardiovascular damage could probably result from direct SARS-CoV-2 infection of the heart tissue; however, it is yet to be proved with clinical evidence. ACE2 is also known to be expressed in myocardial pericytes, cardiomyocytes, and endothelial cells.[47] In an earlier study, Oudit and colleagues[65] have demonstrated the presence of the SARS genome in 7 out of 20 infected patients. However, the specific cell type(s) within the cardiac tissues that could be infected by SARS-CoV-2 and/or cell type(s) susceptible to systemic inflammatory attack remains unclear. Also, the degree of damages to the cardiac tissue likely from a direct viral infection or the indirect toxicity from systemic inflammation remains elusive.[61]

ACS is also reported in COVID-19 patients, primarily presenting as ST-elevation myocardial infarction (STEMI).[66] Virus-induced stress or systemic inflammation could lead to plaque rupture triggering myocardial infarction or ischemia.[62,64] A New York-based study[67] reported that in 18 patients with STEMI, variability in presentation, a higher prevalence of non-obstructive disease, and higher mortality was reported. In another study

from Italy comprising 28 COVID-19 patients with STEMI, 17 patients presented with evidence of lesions in coronary angiography, demanding revascularization.[68] Activation of endothelial cells and smooth muscle cells, macrophage, expression of tissue factors in the plaque and platelet activation are factors known to trigger ACS.[55] Plaque rupture, coronary spasm, or microthrombi from systemic inflammation are some of the potential mechanisms of ACS in COVID-19.[67]

Cardiomyopathy is the characteristic thickening of heart muscles, making it difficult to pump blood to the parts of the body. Cardiomyopathy can lead to heart failure, blood clots, and cardiac arrest.[69] Zhou et al.[20] reported that heart failure was prominent in nonsurvivors (52%) of the COVID-19 study as compared to the survivors (12%). Heart failure could result from the exacerbation of preexisting conditions such as coronary artery disease or any other undiagnosed cardiac manifestation.[61] Chen et al.[70] reported that 50% of the deceased patients (due to heart failure) had a history of preexisting hypertension or CVD. Inflammatory and respiratory stress can lead to the exacerbation of preexisting cardiac disease or even lead to the onset of new cardiomyopathy.[57] ACS and myocardial injury can induce contractile dysfunction resulting in heart failure. The reduced diastolic function in older patients might trigger heart failure with preserved ejection fraction. Preserved ejection fraction caused by high fever, excessive hydration, and renal dysfunction could lead to acute heart failure.[61,66] Also, acute response to viral infection by the host immune system could also lead to stress-induced cardiomyopathy or systemic inflammation-mediated myocardial dysfunction.[64]

Cardiac arrhythmia is also reported in a group of COVID-19 patients. A Chinese study comprising 138 patients reported that cardiac arrhythmia was observed in 17% of the total subjects and a higher prevalence of 44% in the patients in ICU care.[18] Also, subsequent Wuhan-based COVID-19 study[71] observed that elevated levels of troponin T were associated with ventricular tachycardia/ventricular fibrillation, whereas a similar observation was not noted with normal troponin levels. Arrhythmia can be triggered by hypoxia, fever, electrolyte imbalance, antibiotics, and antiviral drugs.[61]

Abnormalities of the coagulation cascade and elevated thromboembolic events are also reported in COVID-19 patients.[57] Elevated D-dimer is indicative of deep-vein thrombosis, pulmonary embolism, and disturbed intravascular coagulation. Guan et al.[16] reported elevated levels of D-dimer, platelet abnormalities, and mildly extended prothrombin time in SARS-CoV-2 infected patients. The prevalence of hypercoagulation is evident

from the increased thromboembolic events. An autopsy report by Wichmann et al.[72] showed deep-vein thrombosis in 7 out of 12 deceased COVID-19 patients while pulmonary embolism was observed in 4 out of 12 patients. The mechanism of these abnormalities remains unclear. However, the inflammation and endothelial damage along with preexisting comorbidities might increase the risk of coagulation abnormalities.[61]

3.2.4 Chronic obstructive pulmonary disease

COPD is a chronic illness of the respiratory system caused by the obstruction of normal airflow through the lungs due to alveolar damage and inflammation.[73] The prevalence of COPD in COVID-19 (1%–3%) is lower than hypertension or diabetes (Table 3.1). However, some of the reports suggest that COPD patients are more susceptible to COVID-19. A variable prevalence of COPD is reported in the hospitalized ICU patients from different regions. Reports from China reported a COPD incidence rate of 0%–10% whereas reports from New York reported an incidence rate of 2.4%–14%.[74] A recent meta-analysis study[75] showed that COPD is significantly associated with COVID-19 severity, with the COPD patients displaying a fivefold increased risk of severe infection (OR: 5.69, 95%; CI: 2.49–13.00). A Chinese nationwide study[76] found that COPD was significantly higher in severe COVID-19 cases (62.5%) compared to nonsevere cases (15.3%). Also, the authors reported that COPD was more prevalent in nonsurvivors (25%) of COVID-19 when compared to the survivors (2.8%).

Cigarette smoking is one of the proven risk factors of COPD. A case-control study by Guan et al.[16] reported a higher COVID-19 related death rate in smokers in comparison to nonsmokers (12.7% versus 4.7%). SARS-CoV-2 is known to enter the respiratory tract through the binding of spike glycoprotein to the ACE2 receptors expressed in the lung epithelial.[77] One of the predisposing factors of COPD for COVID-19 is the elevated levels of ACE2 expression observed in the COPD patients.[78] Tobacco smoking and nicotine exposure are also shown to elevate ACE2 expression in the lungs.[79] The intrinsic immune impairment in COPD could also lead to increased susceptibility to SARS-CoV-2 infection. COPD patients are known to exhibit impaired innate and adaptive immune responses to pathogens.[80] Impaired phagocytic capacity of alveolar macrophages, T cell dysfunction, the release of proinflammatory cytokines, and impaired interferon-β (IFN-β) signaling are some of the potential factors contributing to the severity in COPD patients.[81,82]

Corticosteroids are frequently used in the treatment of COPD. The use of these drugs in SARS and MERS has demonstrated unfavorable effects such as delay in viral clearance, increased mortality, and onset of psychosis.[83,84] Reports on the effect of corticosteroids on COVID-19 are limited. A recent UK-based drug trial found that the use of Dexamethasone reduced the mortality in COVID-19.[85] However, further research on larger cohorts in the different populations is necessary to determine the beneficial/detrimental outcome of Dexamethasone and similar corticosteroid drugs on COVID-19.

3.2.5 Renal diseases

Different reports indicate a lower incidence (0.7%–2.9%) of chronic kidney disease (CKD) in COVD-19.[16,18,23] Although less prevalent (Table 3.1), CKD is shown to be significantly associated with COVID severity. A systematic meta-analysis[86] revealed a strong association of COVID-19 severity in patients with CKD (OR: 3.03, 95%; CI: 1.0–8.4).

SARS-CoV-2 induced acute kidney injury (AKI) is also reported as a subset of COVID-19 patients. A case-control study by Cheng and colleagues[87] reported the biomarkers of renal abnormalities such as proteinuria (43.9%) and hematuria (26.7%) in the COVID-19 subjects. The authors also reported elevated levels of creatinine (14.4%), blood urea nitrogen (13.1%), and a glomerular filtration rate below 60 mL/min/1.73 m^2 in 13.1% in the COVID-19 subjects. In a separate COVID-19 study, it was reported that the prevalence of AKI among nonsurvivors (37.5%) was higher than that of the survivors (15%).[35] The two probable pathological mechanisms contributing to AKI are (1) direct renal damage induced by SARS-CoV-2 infection and/or (2) the systemic inflammation resulting from an activated immune system targeting the kidney. As discussed in the previous sections, organs expressing ACE2 could become the potential targets of SARS-CoV-2. ACE2 is also known to be expressed in the kidney and thus could result in kidney damage from virus-induced cytotropic effects.[88] The detection of SARS-CoV-2 nucleocapsid protein in histology samples and the observation of virus-like particles in the electron microscopy of renal structures indicates the direct vulnerability of the kidney to SARS-CoV-2 infection.[89] However, kidney autopsy analysis from six patients showed acute tubular necrosis due to lymphocyte and macrophage infiltration.[90] The systemic hyperinflammation due to the cytokine storm could potentially target the kidney resulting in AKI.

This mechanism could be linked to the T cell abnormalities, increased proinflammatory cytokines, and lymphopenia that are frequently observed in severe COVID-19 cases.[91]

Recipients of kidney transplants are also shown to be prone to SARS-CoV-2 infection. In a group of 36 COVID-19 positive kidney transplanted recipients, the authors reported a higher mortality rate (at 3 weeks) in kidney transplant recipients (19%–28%) as compared to the mortality rate in the COVID-19 infected general population (1%–5%).[92] Use of Immunosuppressive drugs posttransplantation, comorbidity, older age, and aggravation of systemic inflammatory response to viral infection are the potential contributors to the severity in kidney transplant recipients.[93]

3.2.6 Malignancy

Patients with different types of cancer can be susceptible to COVID-19 due to the immunocompromised nature of the disease resulting from chemotherapy or treatment with immunosuppressive drugs.[94] A large case-control study by Guan and colleagues[16] reported that cancer was prevalent in 0.9% of the COVID-19 patients. Two subsequent COVID-19 studies[18,35] reported a cancer prevalence of 4% and 7.2%, respectively. The effect of cancer on COVID-19 severity was demonstrated using Cox regression analysis by Liang et al.[95] The authors reported that COVID-19 patients with cancer reached the composite endpoints more rapidly (13 days) than those without cancer (43 days) (Hazard ratio: 3·56, 95%; CI: 1·65–7·69). A multicenter COVID-19 study by Dai and colleagues[96] observed a higher frequency of severe events in lung cancer, hematologic cancer, and stage IV metastatic cancer patients, while nonmetastatic cancer patients and patients without cancer showed similar frequency of severity. Also, surgery in cancer patients was shown to increase the severity of COVID-19 compared to those who received radiation therapy. Management strategies in cancer during COVID-19 included a systematic screening of patients for COVID-19 infection, postponing chemotherapy or surgery wherever possible, implementation of robust personal protection mechanisms in and around the patients under treatment, and intensive care for older patients with comorbidities.[76,97]

3.2.7 Management of COVID-19 patients with comorbidities

The treatment of COVID-19 patients has proven to be a challenging task due to the lack of a clinically proven treatment or SARS-CoV-2 vaccine as

well as the quick spread of SARS-CoV-2 infection.[98] Given the unprecedented nature of the pandemic, researchers are evaluating the effects of SARS-CoV-2 infection in large populations and are in the process of devising efficient strategies to manage the pandemic. The preexisting comorbidities are shown to be a significant risk factor for COVID-19 morbidity and mortality.[99] The careful evaluation and categorization of comorbidities is an essential step in the management of COVID-19 patients. The clinical evidence pertaining to comorbidities among the COVID-19 patients (especially the elderly) has shown that these patients need to be precautious, and even in the event of hospitalization, require additional care.[100] Also, a different set of guidelines should be established in the hospitals for treating the patients with comorbidities especially those at high risk of severity (hypertension and CVD).[14] The treatment for the preexisting conditions should be continued without disruption until clear evidence of the effects of the particular drug(s) are demonstrated. In other cases, such as cancer and organ transplantation where the use of immunosuppressive drugs is unavoidable, additional care and precaution are mandated.[101,102] Also, care should be taken during surgery and blood transfusion to make sure the donor is uninfected.[103] Special care on personal protection of patients and health care professionals particularly in the outpatient departments (OPD) are mandatory.

3.3 SARS-CoV-2 transmission cycle

The human-to-human COVID-19 transmission occurs through either inhalation of bioaerosol or self-inoculation on the eyes and mouth from the contaminated fomites (surfaces). These two conditions are facilitated in several ways: direct contact, droplets, aerosols, fomite, fecal-oral, bloodborne, and mother-to-child. All the notorious viral diseases (tuberculosis, measles, and chickenpox), including SARS-CoV-2, are shown to spread between individuals primarily through droplets or aerosol and direct contact with infected patients.[104] More than 60% of the air samples obtained from the COVID-19 care centers and the air samples collected a few meters away from the patients produce viral loads (2.5 copies/L). The presence of the highest viral loads (19−48 copies/L) on a patient receiving oxygen nasal cannula during treatment in health care centers provides strong evidence for the airborne spread of COVID-19.[105]

3.3.1 Airborne transmission

Airborne transmission mainly falls into three categories, namely, obligate, preferential, and opportunistic. COVID-19 transmission occurs under preferential or opportunistic pathogenicity through droplets or aerosols. According to the World Health Organization (WHO) and CDC, droplets are 5−10 μm wide and aerosols are <5 μm wide, created by bronchoalveolar lavage aerosolizing procedures. Droplets and aerosols are released while sneezing, coughing, speaking, and during respiration from regular human activities. Larger droplets settle faster than they evaporate, carrying a higher viral load of the infected individual. Physical activities such as talking, coughing, and sneezing produce 3000 to 40,000 droplets lesser than 1 μm in size with 7×10^6 viral copies/ml from lungs rather than the upper respiratory tract. The average time is taken for droplet settlement to the ground ranging from 3 to 17 min with a higher transmission rate.[106] As the droplets are transmitted from the warm and moist environments of the respiratory system to the cooler and drier outside climate, they evaporate and form residual particles from the dry content of the initial droplets. These residual particles are referred to as droplet nucleus or aerosols. Such aerosols remain in the air until a few hours before they settle, bearing even less viral load (bioaerosols).[107] Droplets and aerosols generated from human expiratory activities can travel different distances at different speeds. Aerosols created during sneezing may reach up to 7−8 meters (m) horizontally with an air velocity of 50 m/s, while coughing can reach only 2 m with the same velocity. The exhaling events push the large droplets only up to 1 m horizontally at 1 m/s.[108]

The virulence capacity of aerosols depends on the viral shedding time and environmental factors, the infected patient's viral shedding is at a peak between 10- and 15-days postinfection. Aerosols generated during high viral shedding could contain active virus up to six days at 20°C and 50% relative humidity. In contrast, rapid virus inactivation occurs under 60 min, with only a 5% survival rate at 38°C and 24% relative humidity.[109] Depending on the patient's activity with the susceptible person—for example, through breathing, sneezing, and coughing—aerosols inhaled could cause infection only when it contain sufficient virus quantity. However, the viral dose of viable SARS-CoV-2 required to induce active infection in the host is not clearly understood.[110]

3.3.2 Fomite transmission

The object surfaces made up of plastic, stainless steel, copper, cardboard, aluminum, sterile latex surgical gloves, and sponges act as fomites (contaminated surfaces) when droplets and aerosols expelled from the infected individuals

meet the object surfaces. The SARS-CoV-2 virus remains viable in these fomites, ranging from a few hours to days depending on the viral load, the environmental conditions, and the nature of the surface of the object.[111] Like SARS-CoV-1, SARS-CoV-2 remains viable in aerosols for more than 3 h, with the reduction of infectious titer due to time decay. SARS-CoV-2 is more stable in aerosols settled on plastic and stainless steel than in copper and cardboard. It has the maximum viable time of up to 72 h on plastic surfaces and the lowest time on copper of fewer than 4 h. The average half-life of SARS-CoV-2 in aerosols with median projections is about 1.1 h, the most extended half-life of the virus in stainless steel and plastics is 5.6 h in stainless steel and 6.8 h in plastics.[112] The spread of viral infection in fomite mode is more likely due to self-inoculation in the mouth, nose, or eyes following contact with the contaminant. Fomite transmission has the highest possibility in health care facilities, followed by public gathering areas.[111]

3.3.3 Other modes of transmission

SARS-CoV-2 remains in the digestive tract of infected patients ranging from several days to weeks. The excreta of such patients are the primary resource for cross-contamination through fecal-oral transmission, which is facilitated by a bathroom extract ventilation system, turning it into an airborne transmission route. The fecal-oral route of COVID-19 transmission happens through 5-F paths such as fomites, fingers, flies, fluids, and fields.[104] Household transmission contributes to about 23%–33% of secondary infection rate (SIR) through primary patient care and interaction. Precautionary methods, including isolation and contact-free communication with comorbid siblings, may significantly reduce the infection rate.[113] Unpacked foods and food processing during the farm-to-table process and preservation process may contribute to the transmission of the virus.[114,115] Animal forms, such as mink, are potential sources of an animal-to-human transmission; a genome study conducted on residents and employees of the form shown to have 68% infections were caused by the mink form.[116] Zoonotic transmission of the virus occurs through pet animals (dog and cat) of household or farm animals (Pig and rabbit) and their byproducts and handling processes.[117] SARS-CoV-2 is also shown to be present in biological fluids including serum, plasma, and urine up to 17 days after the onset of symptoms. Most considerable plasma viral load of SARS-CoV-2 occurred at four to eight days after the onset of the disease and decreased shortly after viral shedding. These virus-infected specimens might contribute to the possibility of transmission of

SARS-CoV-2 via cross-contamination. However, the odds of this mode of dissemination remain very low due to low viral titer content and half-life.[118] Appropriate and adequate ventilation, particle filtration and disinfection of the air, prevention of air recirculation, and avoiding overcrowding are the engineered controls that play a significant role in controlling COVID-19 transmission. The use of engineering safeguards in public collection facilities, including health care units, markets, industries, educational institutions, libraries, food courts, parks, conference rooms, public utility areas, or public transport, in addition to the use of personal protective equipment (PPE), isolation and quarantine, social distancing, and hand hygiene is vital to lower the chances of transmission between individuals.[105]

3.4 Conclusion

Coronavirus infects people of all ages; it is difficult to establish an early diagnosis as an infected person can remain asymptomatic for a period ranging from a few days to even weeks. The virus transmission predominantly occurs when the infected patient is (unknowingly) exposed to a healthy individual(s). Based on the available scientific evidence on the nature and transmission of SARS-CoV-2 virus infection, the prevention measures and management of SARS-CoV-2 infections differ depending on the person and the environmental conditions in which they reside.

The limited data available on novel SARS-CoV-2 indicates COVID-19 patients with comorbidities accounts for the higher deteriorating outcomes compared with patients without any comorbidity. The adverse impacts of the virus may vary with different disease conditions. Prolonged inflammation and immune cell dysfunction led by SARS-CoV-2 infection is the primary cause of concern in comorbid conditions. A detailed assessment or self-reporting of comorbid conditions during the viral infection can help physicians to establish risk assessment and customize the treatment. This strategic treatment plan for each individual may significantly improve the clinical outcome and success rate.

Personal care is vital in preventing viral infection, as the majority of the infection occurs through airborne transmission. PPE use and frequent washing of hands with soap or alcohol-based sanitizers greatly reduces the infection risk. Social distance and avoidance of public gatherings should be the foremost priority in coping with the pandemic.

References

1. Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology* 2018;**23**(2):130−7.
2. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;**395**(10224):565−74.
3. Ren LL, Wang YM, Wu ZQ, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. *Chin Med J* 2020;**133**(9):1015−24.
4. Li F, Li W, Farzan M, Harrison SC. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science* 2005;**309**(5742):1864−8.
5. Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak − an update on the status. *Mil Med Res* 2020;**7**(1):11.
6. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 2020;**109**:102433.
7. Kang CK, Song KH, Choe PG, et al. Clinical and epidemiologic characteristics of spreaders of Middle East respiratory syndrome coronavirus during the 2015 outbreak in Korea. *J Kor Med Sci* 2017;**32**(5):744−9.
8. Perrotta F, Corbi G, Mazzeo G, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. *Aging Clin Exp Res* 2020;**32**(8):1599−608.
9. Wise J. Covid-19: new coronavirus variant is identified in UK. *BMJ* 2020;**371**:m4857.
10. Korber B, Fischer WM, Gnanakaran S, et al. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. *Cell* 2020;**182**(4):812−27. e819.
11. Sehra ST, Salciccioli JD, Wiebe DJ, Fundin S, Baker JF. Maximum daily temperature, precipitation, ultraviolet light, and rates of transmission of severe acute respiratory syndrome coronavirus 2 in the United States. *Clin Infect Dis* 2020;**71**(9):2482−7. An Official Publication of the Infectious Diseases Society of America.
12. European Centre for Disease Prevention and Control. *Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom*. ECDC; 2020.
13. Miller IF, Becker AD, Grenfell BT, Metcalf CJE. Disease and healthcare burden of COVID-19 in the United States. *Nat Med* 2020;**26**(8):1212−7.
14. Wang T, Du Z, Zhu F, et al. Comorbidities and multi-organ injuries in the treatment of COVID-19. *Lancet* 2020;**395**(10228):e52.
15. Oliveros E, Patel H, Kyung S, et al. Hypertension in older adults: assessment, management, and challenges. *Clin Cardiol* 2020;**43**(2):99−107.
16. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;**382**(18):1708−20.
17. Singh AK, Gupta R, Misra A. Comorbidities in COVID-19: outcomes in hypertensive cohort and controversies with renin angiotensin system blockers. *Diab Metaboli Syndr* 2020;**14**(4):283−7.
18. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;**323**(11):1061−9.
19. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its impact on patients with COVID-19. *SN Compr Clin Med* 2020:1−8.
20. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;**395**(10229):1054−62.
21. Doyle AE. Hypertension and vascular disease. *Am J Hypertens* 1991;**4**(2 Pt 2):103s−6s.

22. Egan BM, Kjeldsen SE, Grassi G, Esler M, Mancia G. The global burden of hypertension exceeds 1.4 billion people: should a systolic blood pressure target below 130 become the universal standard? *J Hypertens* 2019;**37**(6):1148–53.
23. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;**180**(7):934–43.
24. Ma LY, Chen WW, Gao RL, et al. China cardiovascular diseases report 2018: an updated summary. *J Geriatr Cardiol (JGC)* 2020;**17**(1):1–8.
25. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005;**111**(20):2605–10.
26. Fosbøl EL, Butt JH, Østergaard L, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *J Am Med Assoc* 2020;**324**(2):168–77.
27. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? *J Am Med Assoc* 2020;**323**(18):1769–70.
28. Danser AHJ, Epstein M, Batlle D. Renin-angiotensin system blockers and the COVID-19 pandemic. *Hypertension* 2020;**75**(6):1382–5.
29. Yang P, Gu H, Zhao Z, et al. Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. *Sci Rep* 2014;**4**:7027.
30. Kow CS, Hasan SS. Possible protective effect of renin-angiotensin system inhibitors in COVID-19 induced acute kidney injury. *J Am Soc Nephrol* 2020;**31**(8):1917–8.
31. Wang JJ, Edin ML, Zeldin DC, Li C, Wang DW, Chen C. Good or bad: application of RAAS inhibitors in COVID-19 patients with cardiovascular comorbidities. *Pharmacol Ther* 2020;**215**:107628.
32. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 2020;**126**(12):1671–81.
33. Liu X, Long C, Xiong Q, et al. Association of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with risk of COVID-19, inflammation level, severity, and death in patients with COVID-19: a rapid systematic review and meta-analysis. *Clin Cardiol* 2020. https://doi.org/10.1002/clc.23421.
34. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 — United States, February 12-March 28, 2020. *Morb Mortal Wkly Rep (MMWR)* 2020;**69**(13):382–6.
35. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;**8**(5):475–81.
36. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA* 2020;**323**(13):1239–42.
37. Kerner W, Brückel J. Definition, classification and diagnosis of diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2014;**122**(7):384–6. Official Journal, German Society of Endocrinology [and] German Diabetes Association.
38. Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med* 2006;**23**(6):623–8. A Journal of the British Diabetic Association.
39. Banik GR, Alqahtani AS, Booy R, Rashid H. Risk factors for severity and mortality in patients with MERS-CoV: analysis of publicly available data from Saudi Arabia. *Virol Sin* 2016;**31**(1):81–4.

40. Schoen K, Horvat N, Guerreiro NFC, de Castro I, de Giassi KS. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. *BMC Infect Dis* 2019;**19**(1):964.
41. Romaní-Pérez M, Outeiriño-Iglesias V, Moya CM, et al. Activation of the GLP-1 receptor by liraglutide increases ACE2 expression, reversing right ventricle hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. *Endocrinology* 2015;**156**(10):3559−69.
42. Tikoo K, Patel G, Kumar S, et al. Tissue specific up regulation of ACE2 in rabbit model of atherosclerosis by atorvastatin: role of epigenetic histone modifications. *Biochem Pharmacol* 2015;**93**(3):343−51.
43. Zhang W, Xu YZ, Liu B, et al. Pioglitazone upregulates angiotensin converting enzyme 2 expression in insulin-sensitive tissues in rats with high-fat diet-induced nonalcoholic steatohepatitis. *Sci World J* 2014;**2014**:603409.
44. Rao S, Lau A, So HC. Exploring diseases/traits and blood proteins causally related to expression of ACE2, the putative receptor of SARS-CoV-2: a Mendelian randomization analysis highlights tentative relevance of diabetes-related traits. *Diabetes Care* 2020;**43**(7):1416−26.
45. Ho TW, Huang CT, Tsai YJ, Lien AS, Lai F, Yu CJ. Metformin use mitigates the adverse prognostic effect of diabetes mellitus in chronic obstructive pulmonary disease. *Respir Res* 2019;**20**(1):69.
46. Fernandez C, Rysä J, Almgren P, et al. Plasma levels of the proprotein convertase furin and incidence of diabetes and mortality. *J Intern Med* 2018;**284**(4):377−87.
47. Nicin L, Abplanalp WT, Mellentin H, et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. *Eur Heart J* 2020;**41**(19):1804−6.
48. Hodgson K, Morris J, Bridson T, Govan B, Rush C, Ketheesan N. Immunological mechanisms contributing to the double burden of diabetes and intracellular bacterial infections. *Immunology* 2015;**144**(2):171−85.
49. Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. *JCI Insight* 2019;**4**(20).
50. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. *Diabetes Metab Res Rev* 2020:e33213321.
51. Huang J, Xiao Y, Xu A, Zhou Z. Neutrophils in type 1 diabetes. *J Diabetes Investig* 2016;**7**(5):652−63.
52. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: knowledge in progress. *Diabetes Res Clin Pract* 2020;**162**:108142.
53. Roth GA, Johnson C, Abajobir A, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol* 2017;**70**(1):1−25.
54. Shi S, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J* 2020;**41**(22):2070−9.
55. Akhmerov A, Marbán E. COVID-19 and the heart. *Circ Res* 2020;**126**(10):1443−55.
56. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and cardiovascular disease. *Circulation* 2020;**141**(20):1648−55.
57. Dhakal BP, Sweitzer NK, Indik JH, Acharya D, William P. SARS-CoV-2 infection and cardiovascular disease: COVID-19 heart. *Heart Lung Circ* 2020;**29**(7):973−87.
58. Bernheim A, Mei X, Huang M, et al. Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. *Radiology* 2020;**295**(3):200463.
59. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020;**20**(6):363−74.
60. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;**8**(4):420−2.

61. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol* 2020;**17**(9):543–58.
62. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020;**17**(5):259–60.
63. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**(10223):497–506.
64. Bansal M. Cardiovascular disease and COVID-19. *Diabetes Metab Syndr* 2020;**14**(3):247–50.
65. Oudit GY, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest* 2009;**39**(7):618–25.
66. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis (IJID)* 2020;**94**:91–5. Official Publication of the International Society for Infectious Diseases.
67. Bangalore S, Sharma A, Slotwiner A, et al. ST-segment elevation in patients with Covid-19 – a case series. *N Engl J Med* 2020;**382**(25):2478–80.
68. Stefanini GG, Montorfano M, Trabattoni D, et al. ST-elevation myocardial infarction in patients with COVID-19: clinical and angiographic outcomes. *Circulation* 2020;**141**(25):2113–6.
69. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies. *Circulation* 2006;**113**(14):1807–16.
70. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020;**368**:m1091.
71. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;**5**(7):811–8.
72. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Int Med* 2020;**173**(4):268–77.
73. Olloquequi J. COVID-19 Susceptibility in chronic obstructive pulmonary disease. *Eur J Clin Invest* 2020;**50**(10):e13382.
74. Leung JM, Niikura M, Yang CWT, Sin DD. COVID-19 and COPD. *Eur Respir J* 2020;**56**(2).
75. Lippi G, Henry BM. Chronic obstructive pulmonary disease is associated with severe coronavirus disease 2019 (COVID-19). *Respir Med* 2020;**167**:105941.
76. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020;**55**(5).
77. Ali A, Vijayan R. Dynamics of the ACE2–SARS-CoV-2/SARS-CoV spike protein interface reveal unique mechanisms. *Sci Rep* 2020;**10**(1):14214.
78. Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *Eur Respir J* 2020;**55**(5).
79. Cai G, Bossé Y, Xiao F, Kheradmand F, Amos CI. Tobacco smoking increases the lung gene expression of ACE2, the receptor of SARS-CoV-2. *Am J Respir Crit Care Med* 2020;**201**(12):1557–9.
80. Bhat TA, Panzica L, Kalathil SG, Thanavala Y. Immune dysfunction in patients with chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2015;**12**:S169–75. Suppl 2(Suppl 2).
81. Rovina N, Koutsoukou A, Koulouris NG. Inflammation and immune response in COPD: where do we stand? *Mediat Inflamm* 2013;**2013**:413735.
82. Singanayagam A, Glanville N, Girkin JL, et al. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. *Nat Commun* 2018;**9**(1):2229.

83. Li H, Chen C, Hu F, et al. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. *Leukemia* 2020;**34**(6):1503–11.
84. Pelgrim CE, Peterson JD, Gosker HR, et al. Psychological co-morbidities in COPD: targeting systemic inflammation, a benefit for both? *Eur J Pharmacol* 2019;**842**:99–110.
85. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19 – preliminary report. *N Engl J Med* 2020. https://doi.org/10.1056/NEJMoa2021436.
86. Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. *Int Urol Nephrol* 2020;**52**(6):1193–4.
87. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020;**97**(5):829–38.
88. Gagliardi I, Patella G, Michael A, Serra R, Provenzano M, Andreucci M. COVID-19 and the kidney: from epidemiology to clinical practice. *J Clin Med* 2020;**9**(8).
89. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020;**98**(1):219–27.
90. Diao B, Wang C, Wang R, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *medRxiv* 2020. https://doi.org/10.1101/2020.03.04.20031120.
91. Yang L, Liu S, Liu J, et al. COVID-19: immunopathogenesis and Immunotherapeutics. *Signal Transduct Target Ther* 2020;**5**(1):128.
92. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. *N Engl J Med* 2020;**382**(25):2475–7.
93. Gandolfini I, Delsante M, Fiaccadori E, et al. COVID-19 in kidney transplant recipients. *Am J Transplant* 2020;**20**(7):1941–3. Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons.
94. Indini A, Rijavec E, Ghidini M, et al. Coronavirus infection and immune system: an insight of COVID-19 in cancer patients. *Crit Rev Oncol-Hematol* 2020;**153**:103059.
95. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;**21**(3):335–7.
96. Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Canc Discov* 2020;**10**(6):783–91.
97. Gosain R, Abdou Y, Singh A, Rana N, Puzanov I, Ernstoff MS. COVID-19 and cancer: a comprehensive review. *Curr Oncol Rep* 2020;**22**(5):53.
98. Esposito S, Noviello S, Pagliano P. Update on treatment of COVID-19: ongoing studies between promising and disappointing results. *Le Infezioni in Medicina* 2020;**28**(2):198–211.
99. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging* 2020;**12**(7):6049–57.
100. Shahid Z, Kalayanamitra R, McClafferty B, et al. COVID-19 and older adults: what we know. *J Am Geriatr Soc* 2020;**68**(5):926–9.
101. Al-Shamsi HO, Alhazzani W, Alhuraiji A, et al. A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: an international collaborative group. *Oncol* 2020;**25**(6):e936–45.
102. Gupta R, Misra A. Contentious issues and evolving concepts in the clinical presentation and management of patients with COVID-19 infection with reference to use of therapeutic and other drugs used in Co-morbid diseases (Hypertension, diabetes etc). *Diabetes Metab Syndr* 2020;**14**(3):251–4.
103. Bresadola V, Biddau C, Puggioni A, et al. General surgery and COVID-19: review of practical recommendations in the first pandemic phase. *Surg Today* 2020;**50**(10):1159–67.

104. Arslan M, Xu B, Gamal El-Din M. Transmission of SARS-CoV-2 via fecal-oral and aerosols—borne routes: environmental dynamics and implications for wastewater management in underprivileged societies. *Sci Total Environ* 2020;**743**:140709.
105. Morawska L, Tang JW, Bahnfleth W, et al. How can airborne transmission of COVID-19 indoors be minimised? *Environ Int* 2020;**142**:105832.
106. Tang S, Mao Y, Jones RM, et al. Aerosol transmission of SARS-CoV-2? Evidence, prevention and control. *Environ Int* 2020;**144**:106039.
107. Bourouiba L. Turbulent gas clouds and respiratory pathogen emissions: potential implications for reducing transmission of COVID-19. *JAMA* 2020;**323**(18):1837—8.
108. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: a critical review on the unresolved dichotomy. *Environ Res* 2020;**188**:109819.
109. Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. Transmission of SARS-CoV-2: a review of viral, host, and environmental factors. *Ann Intern Med* 2020. https://doi.org/10.7326/M20-5008.
110. Dhand R, Li J. Coughs and sneezes: their role in transmission of respiratory viral infections, including SARS-CoV-2. *Am J Respir Crit Care Med* 2020;**202**(5):651—9.
111. Goldman E. Exaggerated risk of transmission of COVID-19 by fomites. *Lancet Infect Dis* 2020;**20**(8):892—3.
112. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med* 2020;**382**(16):1564—7.
113. Lewis NM, Chu VT, Ye D, et al. Household transmission of SARS-CoV-2 in the United States. *Clin Infect Dis* 2020. https://doi.org/10.1093/cid/ciaa1166.
114. Ceylan Z, Meral R, Cetinkaya T. Relevance of SARS-CoV-2 in food safety and food hygiene: potential preventive measures, suggestions and nanotechnological approaches. *VirusDisease* 2020;**31**(2):154—60.
115. Han J, Zhang X, He S, Jia P. Can the coronavirus disease be transmitted from food? A review of evidence, risks, policies and knowledge gaps. *Environ Chem Lett* 2020:1—12.
116. Oude Munnink BB, Sikkema RS, Nieuwenhuijse DF, et al. Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans. *Science* 2021;**371**(6525):172—7.
117. Yekta R, Vahid-Dastjerdi L, Norouzbeigi S, Mortazavian AM. Food products as potential carriers of SARS-CoV-2. *Food Contr* 2020:107754.
118. Kim JM, Kim HM, Lee EJ, et al. Detection and isolation of SARS-CoV-2 in serum, urine, and stool specimens of COVID-19 patients from the Republic of Korea. *Osong Public Health Res Perspect* 2020;**11**(3):112—7.