COVID-19 and the cardiovascular system - implications for risk assessment, diagnosis and treatment options.

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Abstract

The novel coronavirus disease (COVID-19) outbreak, caused by SARS-CoV-2, represents the greatest medical challenge in decades. We provide a comprehensive review of clinical course of COVID-19, its co-morbidities, and mechanistic considerations for future therapies. While COVID-19 primarily affects lungs causing interstitial pneumonitis and severe acute respiratory distress syndrome (ARDS), it also affects multiple organs, particularly the cardiovascular system. Risk of severe infection and mortality increase with the advancing age and male sex. Mortality is increased by co-morbidities: cardiovascular disease, hypertension, diabetes, chronic pulmonary disease, and cancer. The most common complications include arrhythmia (atrial fibrillation, ventricular tachyarrhythmia and ventricular fibrillation), cardiac injury (elevated highly sensitive troponin I - hsCTnI - and CK levels), fulminant myocarditis, heart failure, pulmonary embolism, and disseminated intravascular coagulation (DIC). Mechanistically, SARS-CoV-2, following proteolytic cleavage of its S protein by a serine protease, binds to the trans-membrane angiotensin converting enzyme 2 (ACE2) - a homolog of ACE - to enter type II pneumocytes, macrophages, perivascular pericytes, and cardiomyocytes. This may lead to myocardial dysfunction and damage, endothelial dysfunction, microvascular dysfunction, plaque instability, and myocardial infarction (MI). While ACE2 is essential for viral invasion, there is no evidence that ACE inhibitors or angiotensin receptor blockers (ARBs) worsen prognosis. Hence, patients should not discontinue their use. Moreover, renin-angiotensin-aldosterone system (RAAS) inhibitors might be beneficial in COVID-19. Initial immune and inflammatory responses induce severe cytokine storm (IL-6, IL-7, IL-22, IL-17 etc.) during rapid progression phase of COVID-19. Early evaluation and continued monitoring of cardiac damage (cTnI, NT-ProBNP) and coagulation (D-dimer) after hospitalization, may identify patients with cardiac injury and predict COVID-19 complications. Preventive measures (social distancing, social isolation) also increase cardiovascular risk. Cardiovascular considerations of therapies currently used, including remdesivir, chloroquine, hydroxychloroquine, tocilizumab, ribavirin, interferons and lopinavir/ritonavir as well as experimental therapies, such as human recombinant ACE2 (rhACE2) are discussed.

Introduction

The novel coronavirus COVID-19 outbreak, first reported on December 8, 2019 in Hubei province in China, was designated as a pandemic by the World Health Organization (WHO) on 11th March 2020. This disease, recognized as an infection with a new betacoronavirus by Dr. Zhang Jixian from Hubei Provincial Hospital of Integrated Chinese and Western Medicine, has been spreading exponentially in almost all countries around the world. The epicenter shifted from China to Europe in February/March 2020 and then to the United States in March/April 2020. Current data presenting information on international case numbers and case-fatality is provided by the John Hopkins University Coronavirus Resource Center-https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6 [1,2]. There are several other web-based resources that provide informative graphics on the spread of the disease and the outcomes. The pandemic of COVID-19 has multiple medical, psychological and socio-economic consequences. COVID-19 represents probably the greatest threat that societies face in the 21st century. Therefore, understanding its pathophysiology, clinical implications, and development of novel preventive and therapeutic strategies are of primary importance.

Based on reviewing the available data in the public databases, the risk of infection and mortality increase with the advancing age and shows sexual dimorphism. Male elderly individuals are at the highest risk of infection as well as death.

Despite the tropism for lungs where it causes interstitial pneumonitis, in the most severe cases, multi-organ failure develops. The cardiovascular (CV) system appears to have complex interactions with COVID-19. Published reports, medRxiv, bioRxiv and personal communications and experience of co-authors detail evidence of myocardial injury in 20-40% of hospitalized cases manifesting as cardiac chest pain, fulminant heart failure, cardiac arrhythmias, and cardiac death. Indeed, symptoms of cardiac chest pain and palpitations are the presenting features in some patients [3,4-6]

While COVID-19 is non-discriminatory involving both healthy and those with co-morbid conditions, approximately half of those admitted to hospitals in Hunan province with COVID-19 had known comorbidities. The number of patients with co-morbid conditions increased to about two thirds in those requiring Intensive Care Unit (ICU) admission or those that did not survive. Patients with pre-existing CV conditions (hypertension in particular) had the highest morbidity (10.5%) following infection[7],[8]. Non-CV comorbidities, including diabetes, lung diseases and obesity, the latter identified in current Italian and Dutch cohorts, are also major predictors of poor clinical outcomes. These aspects emphasize the importance of the need for multi-disciplinary assessment and treatment, including cardiovascular evaluation and therapy, during the course of COVID-19 to reduce mortality. In the current rapid review, we summarize the state-of-the-art knowledge available currently, regarding COVID-19 focusing on key mechanistic and clinical aspects.

Properties of SARS-CoV-2

Coronaviruses are single stranded positive sense RNA viruses of between 26 and 32 kilobases in length within the family *Coronaviridae*. There are four genera in the subfamily *Orthocoronavirinae*, including the alpha, beta, gamma and deltacoronaviruses. Of these, alpha and betacoronaviruses infect mammals while the gamma and deltacoronaviruses infect birds. There are seven coronaviruses that infect humans; the alphacoronaviruses HCoV-NL63 and 229E, which tend to cause a mild illness in adults; the betacoronaviruses MERS, SARS, which cause a severe respiratory illness; and OC43 and HKU1, which are associated with a mild illness. An example electron microscopy of betacoronavirus is shown in Figure 1. COVID-19 is caused by a novel betacoronavirus, probably originating from bats following gain-of-function mutations within the receptor-binding domain (RBD) and the acquisition of a furin-protease cleavage site. It has been named by the WHO as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[9].

Coronavirus receptor binding occurs via the spike protein (encoded by the structural S gene) which has 2 subunits. Subunit S1 mediates binding and a trimeric S2 stalk mediates fusion to the infected cell. The S1 subunit is divided into two domains, the N-terminal domain (S1-NTD) and the C-terminal domain (S1-CTD). These regions mediate binding to a variety of cellular receptors containing carbohydrate or protein at their binding domains. SARS-CoV and SARS-CoV-2 (and the alphacoronavirus HCoV-NL63) all bind via the S1-CTD to the angiotensin converting enzyme 2 (ACE2) receptor (Figure 2)[9]. SARS-CoV-2 has a higher affinity for binding to ACE2 than SARS-CoV and binding involves a larger number of interaction sites[10, 11]. A pre-requisite for binding of SARS-CoV-2 to ACE2 is cleavage of the S protein of the virus by the transmembrane serine protease TMPRSS2[12] (Figure 2). Replication occurs via the RNA-dependent RNA polymerase and involves discontinuous transcription of subgenomic mRNAs that encode six major open reading frames common to all coronaviruses and multiple accessory proteins.

Importantly, SARS-CoV-2 transmission occurs at a higher basic reproduction rate (R_0=2-2.5) than SARS-CoV that caused an outbreak of severe respiratory infection in 2003 or than influenza[13]. It is associated with higher viral loads in infected people (up to a billion RNA copies per ml of sputum) and long-term resistance on contaminated surfaces. SARS-CoV-2 is more stable on plastic and stainless steel than on copper and cardboard, and viable virus may be detected up to 72 hours after application to these surfaces[14]. Patients with severe COVID-19 tend to have a high viral load and a long virus-shedding period. This finding suggests that the viral load of SARS-CoV-2 might be a useful marker for assessing disease severity and prognosis[15]. At the same time, SARS-CoV-2, pronounced nucleic acid shedding of SARS-CoV-2 was observed for 7 days in mild cases [15].

To better appreciate the links between cardiovascular disease and COVID-19, it is important to understand the underlying pathobiology of coronavirus infection. SARS-CoV-2 binds to the trans-membrane ACE2 protein (a homolog of ACE) to enter type II alveolar epithelial cells, macrophages and other cell types[12] (Figure 2). The process requires priming of viral S protein by cellular serine protease TMPRSS2[12]. Thus, infection with SARS-CoV-2 requires co-expression of ACE2 and TMPRSS2 in the same cell type, as proteolytic cleavage of viral S protein is essential for binding of the virus to ACE2. Exploitation of ACE2 by coronavirus is important in predicting potential pathology as ACE2 is particularly highly expressed in pericytes, in addition to type II alveolar epithelial cells, according to the single cell human heart atlas[16]. High expression of ACE2 in pericytes could lead to development of microvascular dysfunction[17], explaining greater propensity for acute coronary syndromes[5]. Moreover, ACE2 expression is upregulated in failing human hearts, suggesting a plausible explanation for a higher infectivity of virus and a higher mortality in patients with heart failure. [18] Moreover, cellular entry of coronaviruses through ACE2 has implications for vascular instability and hypotension as well as increased mortality of infected patients who have pre-existing hypertension, albeit the latter association is confounded by the older age of patients with co-morbidities. In addition to pathogenicity and transmissibility of the virus, these findings also have therapeutic implications, as inhibition of the cellular serine protease TMPRSS2 and sera containing blocking antibodies against ACE2, have the potential to block viral entry and hence, prevent or attenuate COVID-19 (Figure 2). In a murine model, TMPRSS2 inhibition blocked viral entry and attenuated severity of coronavirus infection with improved survival[19, 20]. Two clinical trials haves been started to test efficacy of inhibition of TMPRSS2 by Camostat Mesilate for the treatment of patients with COVID-2 (NCT04321096 and NCT04338906).

Methodological considerations of current clinical data on COVID-19

Our understanding of COVID-19 pathomechanisms, natural clinical history, and possible therapies are evolving continuously. While in this review we have collated contemporary literature regarding this pandemic to enable a comprehensive overview, numerous methodological considerations need to be taken into account regarding study design and data collection. The sources used to generate this review are original articles published in PubMed or posted on medRxiv, bioRxiv or ChinaXiv or listed in clinical trial databases (ClinicalTrial.gov and EudraCT). In addition, public databases such as World Health organization, Center for Disease Control, and Johns Hopkins Coronavirus Resource Center were utilized.

The early studies in a pandemic might suffer from inclusion bias. Baseline demographics and premorbid status of study populations are expected to reflect the characteristics of individuals who were exposed to the disease early in the outbreak. In addition, availability and access to diagnostic testing as well as a high threshold for diagnostic testing or hospital treatment or suitability for ICU admission, because of finite resources, are expected to affect characteristics of the study populations and the clinical outcomes of the disease. For example, a large number of health care workers and inpatients were exposed to COVID-19 in the hospital in the early rather than later phase in the pandemic in China[21]. The demographics of patients in the early studies from China were different from those reported later in the largest aggregate study of COVID-19 patients by Guan et al. in China[22] (Table 1). Data on cardiac involvement are unfortunately not extensively presented in the study of Guan et al.[22]

The National Health Commission of the People Republic of China (PRC) guidance[23] recommends the use of traditional Chinese medicine alongside with what is considered more conventional interventions. The published reports do not provide details of the traditional treatment regimens in patients with COVID-19. Therefore, differences in the choices of therapy were made and any positive/negative impacts of such interventions which may have influenced outcomes, might have introduced additional bias.

Finally, it is also difficult to assess the true prevalence, occurrence, mortality and spectrum of the clinical course of disease because, since a proportion of inoculated individuals might be asymptomatic and therefore, never tested. Some in silico modelling of the infection expansion as well as in initial reports from Iceland and Italy suggest that an asymptomatic group, perhaps as high as 50% of the infected individuals (DeCODE Genetics, Iceland), likely exists. This finding has considerable implications in estimating the prevalence and preventing spread of the disease. Likewise, some reports show that up to 80% of infected individuals have mild symptoms and in theory represent a group that might not seek medical care – they might not therefore, be tested nor contribute to prevalence and case fatality rate (CFR) estimates. Secondly, practically all countries experience shortage of the testing kits and therefore, limiting the testing only to selected groups of individuals. Moreover, some deaths caused by SARS-CoV-2 were not attributed to COVID-19, due to the lag time when severe complications tend to develop even up to 2-3 weeks following the initial infection[8].

Clinical course of COVID 19

The incubation period between contact and the first set of symptoms is typically 1-14 days (but up to 24 days in individual cases)[23]. The median time between registered exposure and first symptoms is 5.1 days with a mean of 6.1 days[24]. Duration of viral nucleic acid shedding ranges between 8 and 34 days (median -20 days) after the initial symptoms (Figure 3).

The main clinical symptoms develop within 11.5 days (95% CI, 8.2 to 15.6 days) and include fever, dry cough, fatigue, ageusia, anosmia and headache[24]. Other non-specific symptoms have also been reported, which included nasal congestion, rhinorrhea, sore throat, myalgia, poor appetite and diarrhea[21]. Fever and cough typically appear concomitantly, followed by shortness of breath and severe fatigue, which appear around day 6-7[6] and that are associated with development of severe bilateral (and occasional unilateral) pneumonia (Figure 4).
The most common radiologic findings include multiple patchy shadows and interstitial changes in moderate disease, with consolidation, a ground glass appearance in 56.4% of cases[22], and very occasional pleural effusions in severe cases[23]. In such severe cases, pneumomediastinum and pneumothorax have been described[25, 26].

Pathological investigations of the lungs of deceased individuals indicate blockade of bronchi and bronchioles with large amounts of mucus plugs and bronchial epithelial cell damage[23]. Lymphocyte and mononuclear cell infiltrates are present in alveolar septal spaces. Fibrinous exudate and high hyaline membranes fill alveolar cavities. Polynuclear giant cells are prominent. There is marked proliferation of Type II alveolar epithelial cells. Such severe manifestations appear only in a fraction of patients. A recent study of COVID-19 cases in China reported through 28th Jan 2020 indicated that severe illness may occur in 16% of cases[22], leading to an overall mortality rate estimated at 1.4% of the total reported cases[22] to 4.61% in the World Health Organization reports (accessed on 28th March 2020). In some geographical regions, due to unexplained reasons, mortality may be higher, (current estimates 11.9% in Italy, 9.0% in Spain and 7.9% in the UK according to JHU Coronavirus Resource Center, accessed on April 2nd, 2020 [2]). It is important to note, however, that great care must be taken, when calculating fatality rates based on currently available data, as these can be overestimated in relation to insufficient testing in the community or under-estimated, due to long lag-time between test positivity and death or the fact that there are large differences in attributing COVID-related mortality ("dying with" versus "dying from" as well as differences in performing post-mortem testing). Limitations of health care systems, abruptly overwhelmed by a surge of patients needing mechanical invasive ventilation, have also been considered a potential source of the differences. Finally, these differences may result from population structure, as Italian patients have been older than average age reported in the Chinese patients.

The typical clinical course of disease is summarized in Figure 3. The heterogeneity of responses between individual patients is striking. This indicates, that it is unlikely that COVID-19 can be considered, from the point of view of a single disease phenotype. Rather, it seems most likely that host characteristics, which at the moment remains unknown, promotes progression of the disease in more or less severe presentation e.g. mild ,severe multi organ failure, cytokine release storm.

While clinical symptoms of the disease are predominantly respiratory and associated with severe pneumonia, both direct and indirect involvement of other organs is common, with the cardiovascular system being particularly affected. Moreover, pre-existing conditions, largely linked to cardiovascular disease increase risk of severe outcomes of the infection.

Cardiovascular risk factors associated to the worse outcome of COVID-19

A number of key co-morbidities are associated with worse clinical outcomes in patients with COVID-19 (Table 1). Association with age seems to dominate this relationship[22] and may affect the actual importance of other factors reported in the univariate analyses. Older patients (mean age: 63 years old; [range: 53-71]) are more likely to experience the composite endpoint of ICU admission, mechanical ventilation, or death compared to younger patients (mean age: 46 years old [range: 35-57])[22] (Table 1). Males seem to be more susceptible to COVID-19 related complications, representing between 50-82% of the hospitalized patients in the four publications that report this data (Table 1) and most recent report from Italy[27].

Table 1 summarizes key comorbidities identified by the major studies from China showing that presence of pre-existing morbidities increase the severity of hospital-treated COVID-19. Notably, there is a large heterogeneity of reporting with some studies comparing death with survival while others comparing ICU with non-ICU cases (Table 1). However, regardless of the approach, pre-existing cardiovascular conditions seem to be particularly important predictors of COVID-19 severity.

The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team recently analyzed all COVID-19 cases reported to the China's Infectious Disease Information System through February 11, 2020[7]. The investigators found that the fatality rate for patients with no comorbidities was approximately 0.9%, whereas the case fatality rate was much higher for patients with comorbidities. This included mortality of 10.5% for patients with cardiovascular disease, 7.3% for those with diabetes, 6% for subjects with hypertension, 6.3% for chronic respiratory disease, and 6.0% for cancer[28-30]. It was as high as 14.8% for patients ≥ 80 years of age[7, 30]. It is interesting that in Italian and Dutch cohorts there are reports of higher severity in younger obese individuals as well. Severe cases accounted for 13.8%, and critical cases accounted for 4.7% of all cases. Of significance, cardiovascular disease (CVD) occurrence affects mortality rate to a larger extent than presence of pre-existing chronic obstructive pulmonary disease (COPD), which had not been the case in SARS[7].

These observations are confirmed by a recent meta-analysis, based largely on these studies and an additional 44,672 patient data set reported by China CDC[28]. In this large cohort, cardiovascular disease was reported in 4.2% of the total population and in 22.7% of those who died[28]. By extension, it is expected that comorbidities are associated with higher rates of hospitalization in patients with COVID-19, but any effects that comorbidities may have on susceptibility to infection remain conjectural: accordingly, published frequencies of these comorbidities in China are included in Table 1. Surprisingly, a history of smoking and of chronic pulmonary disease appear to be far less powerful determinants of severity in hospitalized patients than is the history of cardiovascular diseases. Curiously, the prevalence of smoking in hospitalized COVID-19 patients appears far lower than might be expected from assumed population prevalence and primary respiratory infection

COVID-19 and hypertension

It is not clear if hypertension is a risk factor for susceptibility to SARS-CoV-2 infection – the available data show prevalence rates of 15%-40%, largely in line with the rates of high blood pressure in the general population (approximately 30%)[22, 31]. At a first glance, hypertension is more prevalent in subjects with more severe course of the disease. In a recent analysis from China[22], it was present in 13.4 % of subjects with non-severe disease and in 23.7% of subjects with severe disease. This study also included a composite outcome, which was also associated with a higher prevalence of hypertension in those with a poor composite outcome (35.8 vs 13.7%). In the cohort of 44,672 patients reported by China CDC[28], hypertension prevalence was reported as 12.8% in the whole group of patients and 39.7% in patients who eventually died[28]. Hypertension was reported to increase odds ratio for death by 3.05 (1.57–5.92)[32] in patients with COVID-19. These associations may however be largely confounded by the higher prevalence of hypertension in older people, as older individuals have significantly worse outcomes, more severe course of the disease, and a higher mortality rate than the younger patients[22]. Thus, in summary, while hypertension does appear to be associated with more severe disease, a higher risk of acute respiratory disease syndrome, and increased mortality in unadjusted analyses, there is no strong evidence to indicate increased susceptibility of patients with hypertension to COVID-2, when the association is adjusted for other risk factors[33].

The mechanisms of this possible relationship and their clinical relevance has been reviewed in a recent statement of the European Society of Hypertension.[33] The putative relationship between hypertension and COVID-19 may relate to the role of ACE2. ACE2 is a key element in the renin angiotensin aldosterone system (RAAS), which is critically involved in the pathophysiology of hypertension[34]. Experimental studies demonstrated that inhibition of the RAAS with ACE inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs) may result in a compensatory increase in tissue levels of ACE2[35], leading to suggestions that these drugs may be detrimental in patients exposed to SARS-CoV-2.[36] It is however important to emphasize that there is no clear evidence that ACEI or ARBs lead to up-regulation of ACE2 in human tissues[36]. Thus, currently there is no justification for stopping ACE-Is or ARBs in patients at risk of COVID-19[33]. This has now been endorsed officially by many learned

Societies, including European Society of Hypertension, International Society of Hypertension and European Society of Cardiology[33]. It also appears that in experimental models some RAAS blockers may exert a potentially protective influence[37]. Indeed, while Ang II promoted the internalization and intracellular degradation of ACE2, losartan reduced this effect, suggesting that ARBs may offer protection against viral entry into cells[36]. The recent integrative antiviral drug repurposing analysis implicated another ARB – irbesartan – as a potential repurposable medication for COVID-19[10] . In fact, the known effect of ARBs on potassium metabolism may be seen as clinically advantageous in patients infected by COVID-19 given that hypokalemia was reported as a fairly common manifestation of COVID-19 (possibly through increased kaliuresis rather than gastrointestinal loss)[38]. Hypokalemia in COVID-19 patients is difficult to manage, correlates with the severity of the disease, and is has been suggested to be driven by activation of the RAAS system[38]. ACE-Is or ARBs might offer some protection in this setting. It also needs to be emphasized that hypokalemia has not been reported in other studies. For example in patient characterization by Guan et al.[22] median value of potassium level reported was is 3.8 mmol/L with lower margin of IQR is 3.5 mmol/L. Nevertheless, antihypertensive medications known to increase serum levels of potassium (including carvedilol and eplerenone) were implicated as potential drug repurposing opportunities for patients with COVID-19 infection[10]. Moreover, observations from intensive care units in Italy suggest that hypocalcemia is a common metabolic abnormality in patients infected by COVID-19, that could be linked due to reduced albumin levels, which are commonly seen and/or Ca^{++} consumption through excessive activation of coagulation cascade.

Another mechanism linking hypertension and COVID-19 is the immune system, which is dysregulated in hypertension and SARS-CoV-2 infection [39, 40]. Poor control of blood pressure may contribute to further dysregulation of the immune system. For example, it has been shown that hypertension, in humans, is associated with circulating lymphocyte counts[41] and CD8+ T cell dysfunction is observed in patients with hypertension[42]. Such immunosenescent CD8+ T cells are unable to efficiently combat viral infections and contribute to pathological overproduction of cytokines – a situation providing possible link to COVID-19. One may also postulate that ACE-Is or ARBs by providing a better control to blood pressure may restore, at least partially, dysregulated immune system in hypertension.

Overall it is essential to ensure that blood pressure control in hypertensive patients during viral infections is optimized, unnecessary and uncontrolled changes to therapy are discouraged, and hypertensive patients should be carefully monitored for cardiovascular and other complications during COVID-19 infection.

Cardiovascular Manifestations of COVID-19

Severe COVID-19 is associated with rapidly progressing systemic inflammation, pro-inflammatory cytokine storm, and sepsis, leading to multi organ failure, and death (Figure 5). Selected evidence and manifestations of cardiovascular injury in COVID-19 patients are summarized in Table 2. Importantly, there is a delay between initiation of symptoms and myocardial damaged in studies reported so far (Table 3)

COVID-19 and cardiac arrhythmia

Viral infections are associated with metabolic dysfunction, myocardial inflammation, and activation of the sympathetic nervous system, all of which predispose to cardiac arrhythmia. In a recent report on 138 hospitalized COVID-19 patients[21], 16.7% of patients developed arrhythmias, which ranked only second among serious complications after acute respiratory distress syndrome (ARDS). Arrhythmia was observed in 7% of patients who did not require ICU treatment and in 44% of subjects who were admitted to ICU[18]. Further details of these manifestations remain elusive but included atrial fibrillation, conduction block, ventricular tachycardia and ventricular fibrillation. These arrhythmias are also observed in viral myocarditis. Interestingly the report of the National Health Commission of China estimates that during the initial outbreak, some patients reported primarily cardiovascular symptoms, such as palpitations and chest tightness, rather than respiratory symptoms [43]

COVID-19 and myocardial injury and heart failure

Most reports indicate that almost all hospitalized COVID-19 patients show elevated serum creatine kinase (CK) and lactate dehydrogenase (LDH) levels[6, 43, 44]. In addition, a number of studies indicate that cardiac complications, including fulminant myocarditis, are potential outcomes of SARS-CoV-2 infection. Heart failure has been reported as an outcome in 23% of COVID subjects in a recent report from in hospital Chinese subjects. Approximately 52% of non-survivors had heart failure as opposed to 12% of survivors.[32] Evidence of myocardial injury, such as an increase in high-sensitivity cardiac troponin I (cTnI) levels (>28 pg/ml) was detected in 5 of the first 41 patients diagnosed with COVID-19 in Wuhan [6, 43, 44]. More recent reports indicate that 7.2% [21] to 17% [32] of hospitalized COVID-19 patients sustain acute myocardial injury. This may be in the form of acute myocarditis (see below) or injury secondary to an oxygen supply/demand mismatch (type 2 myocardial infarction).

In an analysis of 68 fatal cases in Wuhan, 36 patients (53%) died of respiratory failure, five (7%) patients with myocardial damage died from circulatory failure, and 22 patients (33%) died from both[3]. Similarly, analysis of 120 COVID-19 patients reported elevated levels of N-terminal pro B-type natriuretic peptide (NT-ProBNP) in 27.5% of the cases, and cTnI in 10% of deceased patients, respectively, indicating that the effects of cardiovascular injury on systemic stability may be important and should not be ignored. In another report of 138 inpatients with COVID-19 in Wuhan, the levels of biomarkers of myocardial injury were significantly higher in patients treated in the ICU as compared to those not requiring ICU care (median CK-MB level 18 U/l versus 14 U/l, $P < 0.001$; hs-cTnI level 11.0 pg/ml versus 5.1 pg/ml, $P = 0.004$). [21] . In a study of 191 patients [32] cTnI levels were strongly associated with increased mortality in the univariate analysis, but the association was not tested in a multivariate model. Similar associations between cTnI elevation and disease severity are shown when analyzing cohorts on the basis of the need for ICU care [6, 21]. Thus patient monitoring should include a number of laboratory tests summarized in Table 4, based on current experience and studies.

Mechanisms underlying myocardial injury remain unknown and it is unclear whether they reflect systemic/local and/or ischaemic/inflammatory process. It is still not known whether acute injury is a primary infective phenomenon or secondary to lung disease. Associations between cTnI elevation and pre-existing cardiovascular conditions (and other pre-COVID features) have not yet been examined to detect evidence of causality, and no detailed analyses of patients with cardiovascular complications of COVID-19 have been published to date. As elevated cTnI level is associated with poorer outcomes in other (non-COVID) systemic illnesses [45]– the reported association could simply reflect the severity of systemic illness (e.g. hypoxia, hypotension) rather than indicating a specific cardiac pathology. In this context, a 'cytokine storm' triggered by immunologic dysregulation[43] may be a key mediator. Plasma IL-6 concentrations are elevated in COVID-19 patients with cardiac injury[46], and abnormalities in a variety of cytokines are prominent in patients with severe COVID-19 disease.

Cardiac-specific mechanisms may also be important. Since ACE2 is expressed in the cardiovascular system[47], direct cardiomyocyte infection by SARS-CoV-2 may be a possibility, as discussed below. Moreover, therapies used in treatment of severe multiorgan dysfunction in COVID-19 patient as well as antiviral drugs may exhibit cardiac toxicity.

Attempts to treatment COVID-19 cardiac injury have included the use of steroids, i.v. immunoglobins, hydroxychloroquine, and other antivirals, and active mechanical life-support[46]. While it remains uncertain if these or other therapies successfully limit myocardial injury, the detection of cardiac damage in hospitalized COVID-19 patients may help identify a subset of patients at greater risk of COVID-19 complications.

COVID-19 and myocarditis

Cardiac injury and acute myocarditis are well-recognised complications in of acute viral infections. Myocyte necrosis and mononuclear cell infiltrates are reported in cardiac muscle autopsy specimens in a recent report of the National Health Commission of the People's Republic of China[23]. This finding, along with case reports[46],[48] of fulminant myocarditis, suggests that myocarditis may be an important cause of the acute cardiac injury in COVID-19 patients. However, the prevalence, clinical importance and mechanism(s) of myocardial inflammation in COVID-19 disease remain unclear [6], [49].

Clinically, COVID-19 myocarditis may manifest only as mild chest discomfort and palpitations which may be impossible to distinguish from other causes in most patients. In some, however, myocarditis results in fulminant disease (Figure 6). Transient ECG changes are common and may help detect the presence and severity of myocardial injury. Myocarditis may progress to conduction block, tachy-arrhythmias and left ventricular function impairment.

In other clinical settings, myocarditis is often suspected when cardiac injury is detected in the absence of an acute coronary syndrome. The diagnosis can often be confirmed if cardiac MRI detects typical acute myocardial injury signals[50]. Endomyocardial biopsy (EMB), long considered the Gold-Standard diagnostic test, can directly demonstrate myocyte necrosis and mononuclear cell infiltrates[51]. EMB will detect evidence of a viral cause in some cases though in others an immunologically autoimmune-mediated cause of the myocarditis is suspected [51]. Biopsy studies of patients with acute myocarditis in Europe indicate that viral etiology ranges between 37.8% and 77.4% [52, 53]. In COVID-19 this evidence is at the moment sparse and based on individual case series emphasizing the need for systematic assessment. While several reports emphasize that fulminant myocarditis may be an important clinical presentation of the disease [46 48], the real prevalence of this complication remains unclear. Cardiac MRI and EMBs as diagnostic tools are likely inappropriate during the current COVID-19 pandemic and associated healthcare crisis but should be considered in the future (Table 5).

Animal models of viral myocarditis suggest discrete pathological phases that begin with viral-mediated myocyte lysis [54]. This cardiac injury leads to activation of the innate immune response with release of proinflammatory cytokines[54]. Proteins released through cell lysis might display epitopes similar to the viral antigens and be presented via the major histocompatibility complex (MHC). Myosin heavy chain, a cardiac sarcomere protein appears to be a prime example of 'molecular mimicry' [55]. At this stage, endomyocardial biopsies may show inflammatory changes but no detectable viral particles because of clearance of the virus by the innate immune response. An acquired immune response is the predomint feature evidenced by activation of antibodies and T lymphocytes. CD4+ Th cells and cytotoxic CD8+ T cells mediate their responses through activation of the inflammatory cascade and cytolysis (Th1 – interferon gamma, Th2 - e.g. IL-4, Th17 - – IL-17 and Th22 – IL-22). Macrophages migrate to the site of injury[54]. In the final stage, there is either recovery or low levels of chronic inflammation with concomitant development of left ventricular dysfunction[54].

Interestingly, myocarditis appears in COVID-19 patients after a prolonged period (up to 10-15 days) after the onset of symptoms (Table 3). Moreover, investigators in China point to a lack of viral particle identification on EMB (oral communication). Given these observations and the experimental context above, a question central to potential therapeutic options is the extent to which myocardial injury results from viral replication (cytopathic), is immune-mediated, or is due to other mechanisms. Given that acute myocardial injury is said to begin 2 weeks after the onset of symptomatic COVID-19 [32], adaptive T-cell mediated immunity, or dysregulated innate effector pathways are likely to play a pivotal in the development of myocardial inflammation. In this context, it is notable that an increase of highly proinflammatory CCR6+ Th17 in CD4+ T cells, prominent inflammatory mediators of myocarditis[56], has been reported in severe cases.

Together, the data suggest that a delay in myocardial inflammation is consistent with at least two pathogenic mechanisms: firstly, that the 'cytokine storm' unleashes a sub-clinical autoimmune myocarditis, and secondly that myocardial damage and/or molecular mimicry initiate a de-novo autoimmune reaction.

Targeted therapeutic options remain elusive; as is the case for myocarditis in other settings, a management strategy that uses a broad range of supportive therapies remains key. A case report recently described effectiveness of the early application of steroids and i.v. immunoglobins, neuraminidase inhibitors, and active mechanical life-support[46].

COVID-19 and ischemic heart disease

While little is known regarding the effects of COVID-19 on acute coronary syndrome (ACS), several pathways associated with viral diseases may contribute to destabilize plaques in COVID-19 patients [57]. Heart failure patients are at increased risk of acute events or exacerbation; viral illness can potentially destabilize atherosclerotic plaques through systemic inflammatory responses [58], cytokine storm, as well as specific changes of immune cell polarization towards more unstable phenotypes. All of these have been observed in COVID-19. In the case of SARS and MERS, acute MI [59, 60] myocardial infarction (MI) has been reported in 2 out of the 5 deaths in early reports [61].

It is important to consider that type 2 MI is the most common subtype in viral conditions, thus the usefulness of invasive management with a view toward coronary revascularization (especially in Type 2 MI) is limited. The decision for invasive vs. non-invasive management of a patients with an ACS and COVID-19 illness should be carefully considered. Moreover, a recent single cell atlas of human heart indicated that pericytes express particularly high levels of ACE-2 in the heart[47]. One of the implications of this finding is possible local microvascular inflammation during SARS-CoV-2 infection of the pericytes leading to severe microvascular dysfunction, contributing to Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA). This could explain recent reports of clinical course of cases of myocardial infarction during COVID-19. In addition, cytokine storm can contribute to development of endothelial dysfunction through well characterized mechanisms [62-65].

COVID-19 and coagulation abnormalities

Features of disseminated intravascular coagulation (DIC) and pulmonary embolism, characterized by increased D-dimer levels and fibrin degradation products, are highly prevalent in COVID-19. DIC has been observed in 71.4% of non-survivors[66]. Massive pulmonary embolism have been reported [67]. This might not be surprising given the critical condition of these subjects, although early appearance of DIC features is often evident. Notably experience from China indicates that D-dimer increase is highly predictive of adverse outcomes in COVID-19. In a retrospective cohort study, elevated D-dimer levels (>1g/L) were strongly associated with in-hospital mortality and this relationship was maintained in multivariate analysis (OR:18.4 95% C.I. 2.6-128.6; p=0.003)[32]. Moreover, Chinese and Italian experience emphasizes that more discrete changes in D-dimer levels are observed earlier in the course of disease preceding rapid progression stage.

COVID-19, inflammation and cytokine release storm

After the lungs, immune organs are the second most affected system by COVID-19. Pathological investigations in COVID-19 victims[23] have demonstrated splenic atrophy, with a very significant reduction in the number of lymphocytes and neutrophils as well as necrosis and hemorrhages. Similarly, lymphocytes are depleted in lymph nodes with decreased the numbers of both CD4+ and CD8+ cells are decreased [23]. This corresponds to lymphopenia in peripheral blood observed in severe cases. Interestingly, an increase in systemic IL-2, IL-6, IL-7, granulocyte colony-stimulating factor, C-X-C motif chemokine 10 (CXCL10), chemokine (C-C motif) ligand 2 (CCL2) and tumor necrosis factor-α has been observed in subjects with COVID-19 [6], which corresponds to the characteristics of a cytokine release syndrome (CRS) [16, 68, 69]. CRS development in COVID-19 is associated with COVID-19 severity. CRS has been characterized as a complication of immune targeted therapies in oncology, in particular in relation to severe chimeric antigen receptor (CAR) T-cell-induced CRS [70]. It is also reminiscent of the cytokine profile noted in Haemophagocytic lymphohistiocytosis (HLH) syndromes[71]. Resemblance to the latter brought considerations that COVID-19 may be a cause of secondary HLH with cytopenias, significant haemophagocytosis in bone marrow, and low fibrinogen concentration. Clinical classifications have been introduced to aid recognition of secondary HHL [71]. FACS analyses of COVID-19 active cases have also shown hyperactivated T lymphocytes with large fractions of HLA-DR+ and CD38+ CD8+/CD4+ T cells and CCR6+ TH17 CD4+ cells. High concentrations of cytotoxic granules in cytotoxic T (CD8) cells have been observed. Thus, uncontrolled overactivation of T cells may account for, in part, the severe immune injury[16], in similarity to atherosclerosis and other cardiovascular conditions[72, 73]. These aspects should also be considered in the light of sexual dimorphism related to susceptibility to cardiovascular inflammation [74-76]

High serum IL-6 levels are a common feature in CRS patients. Indeed, in a recent retrospective multicenter analysis of 150 patients from Wuhan, circulating IL-6 levels were a clinical predictor of mortality in COVID-19[3]. IL-6 is an important biomarker and possible target for cardiovascular morbidity and mortality linked to atherosclerosis [77-79]. This is important as therapeutic targeting of the IL-6 receptor (IL-6R) with tocilizumab is used in preventing and treating CRS caused by cancer therapies and HLH [70]. Tocilizumab is approved in more than 100 countries for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) [80], Castleman's diseases and giant cell or Takayasu arteritis [81]. Other IL-6R targeting agents e.g. sariulumab are similarly potentially of use. Therefore its possible use in COVID-19 may be attractive to tackle CRS. However, when considering immunomodulation, one has to bear in mind that the primary problem is an infectious disease rather than the complications of cancer therapy. Therefore, its potentially utility must be carefully considered.

During the initial outbreak in China the use of tocilizumab to stop severe CRS-associated organ failure and death in COVID-19 patients was attempted[71]. Twenty one severe COVID-19 cases were treated with tocilizumab in an initial pilot trial. Nineteen of them were discharged from the hospital within two weeks, as reported by China's National Health Commission. The drug has now been approved in China to treat patients developing severe complications from COVID-19 and showing elevated plasma levels of IL-6[82]. Chinese researchers have now registered several clinical trials for tocilizumab, expected to enroll patients with COVID-19 very soon. A partial list includes: ‘A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19)’ (ChiCTR2000029765); ‘Tocilizumab vs CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 (TACOS)’ (ClinicalTrials.gov Identifier: NCT04306705); and ‘Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019’ (ClinicalTrials.gov Identifier: NCT04310228).

Similarly, case reports originating from Italy, show that in a case series of six patients treated with tocilizumab in Naples, three have showedn signs of improvement. This has prompted several studies evaluating the role of IL-6 antagonism by monoclonal antibodies in COVID-19. For example, Italian Medicines Agency (AIFA) approved the clinical study ‘Tocilizumab in COVID-19 Pneumonia (TOCIVID-19)’ (ClinicalTrials.gov Identifier: NCT04317092). This multicenter, single-arm, open-label, phase 2 study will assess mortality at one month in 330 patients affected by COVID-19 pneumonia. The inclusion criteria comprises patients showing signs of respiratory distress syndrome or were subject to tracheal intubation in the preceding 24 hours. The study iswill be led by the Instituto Nazionale Tumori IRCCS - Fondazione Pascale in Naples. Similarly, 30 participants will be enrolled in the Marche region, in the interventional clinical trial ‘Tocilizumab (RoActemra) as Early Treatment of Patients Affected by SARS-CoV2 Infection With Severe Multifocal Interstitial Pneumonia’ (ClinicalTrials.gov Identifier: NCT04315480). In the US, the ‘Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19’ (ClinicalTrials.gov Identifier: NCT04315298), has just started aiming to recruit 400 patients, and will be shortly followed by the ‘Tocilizumab to Prevent Clinical Decompensation in Hospitalized, Non-critically Ill Patients With COVID-19 Pneumonitis (COVIDOSE)’ (NCT04331795) trial, which is expected to start very soon. Finally, most recently registered, trial recruiting 330 patients - A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA) (ClinicalTrials.gov Identifier: NCT04320615) is being initiated. Similar trials have been registered in France, Belgium and Denmark. It should be noted, however, that there are currently no published clinical trial data on IL-6 targeting safety or efficacy against the virus. Moreover, tocilizumab has not received approval from China's National Medical Product Administration to be sold for COVID-19 treatment.

The cytokine storm and increase in IL-6 signaling observed in some COVID-19 patients could have profound cardiovascular consequences causing tachycardia, hypotension and left ventricular dysfunction. CRS-related cardiotoxicity has also been reported, mainly in the form of conduction abnormalities, atrial fibrillation, and elevation in B-type natriuretic peptide and cardiac cTnIs [83].

In COVID-19 patients, medium-to-long term cardiovascular consequences may be caused by increased IL-6 signaling. Experimental evidence supports an atherogenic role for IL-6 and CRS related cytokines [59, 60, 84-86], as well as its effects on cardiac fibrosis and failure [87]. The cytokine increases adhesion molecule expression in human endothelial cells *in vitro* [88]; at the same time, stimulation of human macrophages with oxidized low-density lipoproteins (oxLDL) lead to increased release of IL-6 [89]. In experimental atherosclerosis, IL-6 mRNA is detectable in the aorta of hyperlipidaemic mice [90], and administration of recombinant IL-6 increased plaque formation [91]. Similarly, reduced pathology has been observed in $LDLr^{-/-}$ mice treated with a fusion protein of the IL-6 trans-signaling inhibitor soluble glycoprotein 130 (sgp130) [92]. Plasma IL-6 levels also have been associated with development and progression of abdominal

aortic aneurysm [93], IL-6 has been shown to influence lipid homeostasis in mice [94]. IL-6 trans-signaling contributes to experimental cardiac fibrosis[87]; while the upregulation of membrane-bound IL-6R causes vascular remodeling in pulmonary arterial hypertension [95].
Genetic variants leading to the increased circulating level of IL-6R, and therefore reduced IL-6 cell signaling, have been shown to protect against coronary heart disease (CHD)[96, 97]. Similarly, IL-6 trans-signaling is associated with increased CV risk[77, 98]. IL-6 is routinely used as an inflammatory biomarker in CVD. The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) trial, demonstrated a stronger effect of IL-1β inhibition, in the reducing secondary cardiovascular events in patients with higher circulating levels of IL-6 and C-Reactive Protein (CRP), indicative of residual inflammatory risk[98]. Whether the observed cytokine storm and IL-6 increase in COVID-19 patients are transient or sustained remains unknown. Accordingly, monitoring inflammatory biomarkers in these patients in the medium-to-long term is of major importance. Similarly, CV risk should be closely evaluated during the acute phase response and in the following years.

There are however likely to be a range of additional cytokine moieties that will emerge to have pathways specific contributions in the severe spectrum of COVID-19 syndrome. These include pathways driven by GM-CSF, TNFalpha, IL-17, IL-18 and IFN-gamma. Moreover, the imminent prospect of single cell and other immunologic analyses will offer a more systematic insight into the immune dysregulation syndrome(s) that are emerging and especially the disease trajectory – in essence which pathways are directing COVID related CRS and which are simply adding to the inflammatory tissue damage burden upon which the other co-morbidities are operating. Thus, we propose a useful way of thinking about this would be that inflammatory burden might be considered as direct effector (.e. CRS-type), or secondary amplificatory in terms of the contribution that pathways make to pathogenesis and clinical outcome.

Lessons from SARS-CoV infection

In 2002 a novel coronavirus, SARS-CoV emerged from China, crossing from bats to humans, eventually leading to over 8,000 cases and the death of more than 700 people. SARS utilized ACE2 for cell attachment and infection through the viral envelope spike (S) protein [99] and a subsequent interaction with a cellular protease, TMPRSS2, which primes S protein for cell entry [100]. The closely related SARS-CoV-2, also thought to have originated in bats [9], encodes a S protein with approximately 76% amino acid similarity to SARS-CoV and importantly SARS-CoV-2, as already discussed, has also recently been demonstrated to uses the same cellular entry pathway via ACE2 and TMPRSS2 [12], as discussed above. Both these novel coronaviruses are in contrast to another recently emergent coronavirus, middle east respiratory syndrome (MERS) virus, which crossed from the dromedary camel to humans and also caused acute respiratory failure, although utilizing a different cell entry mechanism via the receptor dipeptidyl peptidase 4 (DPP4) [101]. Overall, this highlights the potential divergence of respiratory coronavirus infections in humans, but emphasizes the close relationship between SARS-CoV and SARS-CoV-2. So, what can we learn from knowledge of SARS-CoV and associated cardiovascular risk to help in the current battle against COVID-19?

During human SARS-CoV infection of the murine lung, ACE2 is utilized and subsequently almost completely lost at the protein level [102]. Importantly, delivery of the viral S protein alone, also led to downregulation of ACE2 and decreased lung function in normal mice, and worsened lung pathology in an acid challenge model of acute lung failure. Furthermore, disease pathology was reduced in the presence of the angiotensin receptor blocker losartan. Intriguingly, in acute lung disease triggered by acid respiration or sepsis, ACE2 has also been shown to be directly protective, acting in partnership with the angiotensin type 2 receptor (AT_2R) and administration of recombinant ACE2 in this model is protective [103]. Takening together the evidence from multiple experimental studies beneficial effects of ACE-Is or ARBs and also ACE2 supplementation in various animal models of lung injury or SARS have been shown and supported the concept that loss of ACE2 expression promotes the disease in lung injury models (reviewed in Kreutz et al. 2020[25]). ACE2 is also directly regulated by cytokines [104]. Decreased ACE2 levels could be a direct consequence of viral infection and/or the subsequent to inflammatory and immune responses that occur in the infected lung. Interestingly, ACE2 is also reported to be detectable in macrophages [105] and its knockout in leukocytes promotes adipose inflammation [106], highlighting a role for ACE2 in the inflammatory response. Patients suffering from SARS have overwhelming immune and inflammatory responses and high mortality rates from acute respiratory failure, and furthermore there are also associated cardiac sequelae. For example, SARS patients also suffer from systolic and diastolic dysfunction and arrythmias, leading to sudden death [107] [108]. In murine models, intranasal administration of human SARS-CoV results in ACE2-mediated infection of the myocardium [109]. These observations support a role for SARS-CoV in direct myocardial infection and a possible causative role in cardiac disease subsequent to respiratory infection. In the murine heart, ACE2 was also almost completely downregulated at the protein level following infection. Moreover, in autopsied cardiac tissue from SARS patients with SARS-CoV positive lung infection, viral RNA was detected in the heart, combined with decreased cardiac ACE2 protein levels and elevated cardiac macrophage infiltration. Downregulation of ACE2 without compensatory effects on ACE may lead to the RAS being tipped towards the detrimental ACE-AngII-AT_1R axis and away from the protective ACE2-Ang-(1-7)-Mas axis.

ACE2 is also upregulated after myocardial infarctionMI in rodents and humans in macrophages, endothelial cells, smooth muscle cells[110, 111] and cardiomyocytes[112] and may play a role in restoring RAS homeostasis in the heart post-MI. In fact, viral vector-mediated overexpression of ACE2 in rodents also protects the heart from adverse cardiac remodeling and dysfunction post-MI[113]. Overall, these findings highlight that ACE2 has a key protective function in both the lung and the heart. Therefore, SARS-CoV infection-mediated downregulation of ACE2, either as a direct mechanistic consequence of viral infection, and/or as a result of the subsequent inflammatory responses may lead to an imbalance in RAS signaling and consequent cardiovascular sequelae. The knowledge that systemic spread of SARS from primary lung infection to other cardiovascular tissues, including the heart, is also important. Given that ACE2 functions as a receptor for virus entry into the cell, downregulation of ACE2 upon infectioin with SARS-CoV is expected to prevent further viral entry, serving as a negative regulatory mechanism. Clearly additional investigations are needed to increase our understanding of the pathological mechanisms of acute disease and potential increased cardiovascular risk in COVID-19 patients.

Therapeutic options for COVID-19

Managing COVID-19 is challenging as there are no specific treatments for the SARS-CoV-2 virus. Obtaining high-quality randomized clinical trial data during an outbreak is difficult. Research and clinical efforts focus in parallel on development of new drugs against coronavirus as well as repurposing already approved drugs for the treatment of the disease. ClinicalTrials.gov site lists over 300 studies that are testing various interventions in COVID-19 patients. This emphasis on trials as opposed to compassionate use and case reports is a major lesson from prior pandemics and it is good to see the community moving so robustly in this direction.

In the meanwhile, public health measures rely mostly on social measures intended to prevent viral/disease spread, in order to avoid massive surge of patients with healthcare facilities overload, and on supportive treatment for the patients, which can be considered the mainstay of management. Available treatments once clinically evident can be classified as supportive, immune-suppressive, antiretroviral, and potential novel therapies. Supportive treatment should be the mainstay of management coordinated by the relevant specialist - multidisciplinary team. The approaches have been provided by numerous scientific and clinical societies during the early stages of the European outbreak and are continuously being updated. This includes a concise but comprehensive guidelines of the *Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva*[114]

When disease progresses to severe phenotype, supportive treatment includes use of oxygen therapy if SpO2 is less than 92% on room air[23] as well as hemodynamic support. Ealry intubation and invasive mechanical ventilation are essential in those with progressive symptoms and increasing oxygen requirement. High flow nasal cannulae and non-invasive positive pressure ventilation (NIPPV) may play a role in some patients especially where resources for mechanical ventilation are likely to be stretched. A lung protective ventilation strategy is recommended by the WHO. Conservative use of intravenous fluids aiming to maintain tissue perfusion but a negative fluid balance in order to aids lung recovery[23]. Extracorporeal membrane oxygenation (ECMO) may be required in severe cases as per standard indications but should be considered early (veno-venous mode and could be initiated prior to intubation).

As cardiac damage is highly prevalent, heart failure therapies should be initiated where appropriate. Similarly, broad spectrum antibiotics/antifungal treatments and treatment of arrhythmias are needed. Finally, due to the growing evidence of DIC as a cause of organ injury anticoagulation should be considered [23].

Approximately, 75% of patients in the early Chinese cohort received antiviral therapy[6, 32, 43, 115]. The Italian recommendation is to commence treatment with antiviral therapy when COVID-19 is confirmed in patients with mild symptoms but not in a high mortality risk category or moderate/severe signs of infection. Numerous anti-viral therapies have been used to try and limit viral replication. These include protease inhibitors such as Liponovir/ritonavir (used for the treatment of HIV). However, a recent rapid randomized non-placebo controlled trial including 100 patients in each arm, showed no difference in the outcome[116]. Remdesivir is a nucleotide analogue and polymerase inhibitor that was previously used for the experimental treatment of Ebola in a large phase III study[117]. While it had an acceptable safety profile, the remdesivir (GS-5734) arm was halted due to a higher antiviral efficacy of monoclonal antibodies in the trial. Finally chloroquine or hydroxychloroquine have been suggested as having antiviral activity against many RNA viruses including SARS and SARS-CoV-2, through increase of the endosomal pH and interference in the glycosylation process[118]. However, it has never been shown conclusively to have antiviral effect in vivo. In alphavirus infection, while demonstrating antiviral effect in vitro, it is not associated with clinical effects in a randomized clinical trial and may even be associated with prolonged viremia in vivo[119]. While these observations cannot be directly translated to COVID-19, Large phase III trials are underway with hydroxychloroquine, that will inform about possible therapeutic value of this approach. This includes recently initiated "Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial)" (NCT04318015).

As the cytokine storm appears to be a key pathogenetic process in patients exhibiting rapid deterioration of patients, immune suppression and immune modulation approaches have been tried. This includes glucocorticoids, which are recommended by guidelines in Chinese, but not in Italian guidelines. Patients with evidence of lung fibrosis or severe cardiac involvement in ICU may benefit from this approach. Methylprednisolone was used in combination with i.v. immunoglobulins in the treatment of subjects with fulminant myocarditis[118].

Immunomodulatory therapies used include monoclonal antibodies against IL-6R, discussed above. Interferon beta, registered for treatment of multiple sclerosis, enhances suppressor T cell activity, reducing proinflammatory cytokine production. It may be also helpful in patients with myocarditis who develop left ventricular systolic dysfunction, but current experience is limited to enteroviruses[120]. It is also being tried as an inhaled preparation. Finally, 27% of patients in the early Chinese cohort received intravenous immunoglobulins. This approach was based on the evidence of their beneficial effects in cases of myocarditis-induced dilated cardiomyopathy and are recommended in cases of viral myocarditis that are refractory to standard heart failure therapies[121].

A list of planned, ongoing, and completed clinical trials could be found at: https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=&cntry=&state=&city=&dist=

In addition to the many ongoing clinical trials, a new trial in Europe will investigate effects of APN01, the recombinant form of human ACE2 (hrACE2) (clinicaltrialsarena.com). HrACE2 has a dual mode of function. Firstly, it has the potential to block infection of host cells by SARS-CoV-2, and secondly it may reduce lung injury through the protective actions of endogenous ACE2. The phase II clinical trial will be conducted in Germany, Austria and Denmark.

Cardiovascular effects of potential therapies for COVID-19

The potential therapies for COVID-19 discussed above have important cardiovascular side effects and toxicities as well as co-morbid conditions that require caution or avoidance of these drugs as listed in Table 6. It should be noted that data for these side effects and toxicities come from patients that use these drugs chronically for the treatment of autoimmune diseases (chloroquine/hydroxychloroquine, Tocilizumab), hepatitis (Ribavarin, Interferon Alpha), or HIV infection (Lopinivir/Ritonivir). Thus, the effect of short-term use of these medications for patients without these underlying conditions is not clear. Remdesivir is an experimental drug used in the treatment of Ebola[117]. Thus, its cardiovascular effects and toxicities are unknown. The antimalarial drugs, chloroquine and hydroxychloroquine, have recently received considerable attention and interest for the treatment and possibly prophylaxis of COVID-19. However, the data to date in support of these drugs is weak and cardiac toxicities are considerable. A systematic review of the literature performed on patients treated with these drugs, albeit for an extended period of time (median 7 years) and with a high cumulative dose, demonstrated conduction disorders as the main side effect (85%).[122] Other adverse cardiac events included ventricular hypertrophy (22%), hypokinesia (9.4%), heart failure (26.8%), pulmonary arterial hypertension (3.9%), and valvular dysfunction (7.1%). Cardiac function normalizes in a significant number of patients (44.9%) upon withdrawal of chloroquine and hydroxychloroquine, while others continue to show irreversible damage (12.9%) or death (30.8%).[122] Thus, careful consideration should be given to the use of these drugs, particularly without stronger data for their efficacy. Of note, tocilizumab treatment has been shown to influence lipid metabolism in RA patients. Following tocilizumab, total-, LDL- and HDL-cholesterol were increased, while cardiovascular risk biomarkers such as HDL-SAA, secretory phospholipase A2 IIA, and lipoprotein(a) were significantly reduced[123]. Very recently, the ENTRACE clinical trial supported the cardiovascular safety of tocilizumab in RA patients [124]however, to date, IL-6 targeting has not been tested for secondary prevention in CVD.

Follow Up of patients with cardiovascular involvement in COVID-19

While there are currently no evidence-based recommendations, considering clinical presentation, it is reasonable to propose that patients who have had cardiac involvement initially should be seen every 1 to 3 months. Periodic evaluation, in addition to detailed history taking and physical examination, should include a 12-lead electrocardiogram and 2D/Doppler echocardiography[125] or, preferably, cardiac magnetic resonance imaging with late gadolinium enhancement. Appropriate heart failure therapy should be initiated and maintained when required, and plans put in place to optimize doses. Patients should be given standard advice regarding physical activity. Considering unknown long-term consequences of COVID-19, regular cardiovascular risk assessment should be considered in all patients who survived COVID-19.

Ethical dilemmas brought by COVID-19

COVID-19 brings unprecedented ethical problems and situations facing medical profession around the world. In the light of huge imbalance between therapeutic needs and resource availability of the unprecedented scale in our generation, Italian Society of Anesthesiology and Intensive Care (SIAARTI)[126], along with other National Societies provided an ethical statement aimed to guarantee the correct psychological framework to physicians massively exposed to the need to apply hard triage rules while facing a huge ethical dilemmas[126]. These are derived from the fact that the need for intensive care must be integrated with other elements of “clinical suitability”, thus including: the type and severity of the disease, the presence of comorbidities, the impairment of other organs and systems, and their reversibility[126]. Clinicians, neither deontologically nor by training, are not accustomed to reasoning with criteria of maxi-emergency triage, as the current exceptional situation[126].

Impact of COVID-19 on routine and emergency cardiovascular care

In preparation of the COVID-19 pandemic many healthcare providers have had to scale down outpatient services and also defer elective cardiac procedures and surgeries. This in some instances has led to the positive integration of technology and development of virtual clinics[127]. However, uptake of virtual clinics has not been universal and has also been compromised by re-deployment of the workforce to help manage the pandemic. The long-term clinical impact of scaling down outpatient activity, reduced access to diagnostics and deferral of routine procedures is likely to be significant and extend beyond the pandemic. Similarly, the perceived risk of being exposed to COVID-19 has led to a decline or a delay in presentation of acute cardiac emergencies which is likely to contribute to cardiac mortality and morbidity.

Cardiovascular implications of social distancing

COVID-19 implications are wider than the effects of the disease on individual patients. Practically all countries affected by the disease developed mitigation and containment strategies based on social distancing. Cardiovascular consequences of social distancing may be profound. Both experimental and clinical research has shown the effects of social isolation and loneliness on cognition and memory [128-132], metabolic disorders [133-136], cancer [137-139] and immune disorders [139-141]. In the context of cardiovascular diseases, the absence of positive relationships and the reduced chance of interaction with other people (social distancing) have been identified as major risk factors for cardiovascular mortality [142-151]. Recent meta-analysis including a total of 181,006 participants[152] demonstrated that the risk for ischemic heart disease and stroke increased by 29% and 32%, respectively, in lonely and socially isolated people. Similar results were reported from UK Biobank analysis [153].

The mechanisms of detrimental effects of social isolation are multiple and are related to the activation of the hypothalamic-pituitary-adrenocortical (HPA) axis [154-157], changes in the sympathetic vascular tone [148, 158, 159], elevated levels of cortisol [156, 160, 161] and a reduced responsivity of the glucocorticoid receptor [162-165]. The social distancing strategies used in COVID-19 should consider these effects and aim to mitigate them using available technological advances.

Key unanswered questions

In this comprehensive review, we aimed to highlight the current state of the art information regarding COVID-19 and cardiovascular disease (Table 7). Our understanding of cardiovascular risk and consequences of COVID-19 is developing continuously. However, there are many knowledge gaps and there many unanswered questions. Below we point out a few burning unknowns at the moment.

What are the factors, genetic or otherwise that influence inter-individual variability in susceptibility to COVID-19, its severity, or clinical outcomes? The mechanisms through which

CVD worsen the prognosis in COVID-19 are unknown. It remains to be addressed to which extend individual CVD are exacerbated by COVID-19? Does pre-existing hypertension and CVD increase infection risk and/or worsen the course of disease progression? Is the severity of CVD related to high expression levels of ACE2, the SARS-CoV-2 receptor, in heart and blood vessels? What influence, if any, do inhibitors of the RAAS have on susceptibility to COVID-19 and its clinical outcomes? What are the factors or therapies for CVD that may confer protective effects against COVID-19 and its clinical outcomes? How does preexisting CVD worsen cardiac involvement specifically? What transferable knowledge can be learned about this pathogen that would advance our understanding of cardiovascular risk for SARS-CoV-2, influenza and other virus infections in the future? Finally, probably the most important question remains, what are the determinants of heterogeneous host responses to SARS-CoV-2 infection. The answers will be found in integrated approaches by cardiovascular immunologic ID and other expertise coming together. The use of systems based on hypothesis-free in silico methodologies will be essential. This pandemic is unlike any other in arriving at the same time as humankind being in possession of remarkable molecular data science and informatic tools. This is a major test of our ability to harness such capacity in the greater good.

These questions need to be answered with highest quality science and clinical research since the current pandemic of coronavirus might not be the last.

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Table 1: Baseline demographic data and co-morbidities in selected early studies[3, 6, 18, 21, 22, 32] (n/a- not available; ICU-intensive care unit; end-point-composite end point of admission to an intensive care unit (ICU), the use of mechanical ventilation, or death[22]. These should be analysed in the context of recent European data which appeared after submission of this paper[27].

Study	Region	All patients	Severity qualification	Lower severity	High severity	p-value
Gender (M =51.3%, F=48.7% in China); n-number (% Men)						
Huang et al.	Jin Yin-Tan	41 (73%)	nonICU/ICU	28 (68%)	13 (85%)	0.24
Wang et al.	Zongnan	138 (54%)	nonICU/ICU	102 (52%)	36 (61%)	0.34
Zhou et al.	JY-T & Wuhan	191 (62%)	survive/dead	137 (59%)	54 (70%)	0.15
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	0.43
Liu et al.	Tongi + 3 others	78 (50%)	stable/deteriorate	6 (48%)	11 (64%)	0.52
Guan et al.	31 provinces/provincial municipalities	1099 (58%)	non-severe/ severe	926 (58%)	173 (58%)	n/a
Guan et al.	31 provinces/provincial municipalities	1099 (58%)	stable/end-point	1032 (58%)	67 (67%)	n/a
Age; n-number (yrs/ IQR)						
Huang et al.	Jin Yin-Tan	41 49(41-58)	nonICU/ICU	28 49(41-58)	13 49(41-61)	0.6
Wang et al.	Zongnan	138 56(42-68)	nonICU/ICU	102 51(37-62)	36 66(57-78)	<0.001
Zhou et al.	JY-T & Wuhan	191 56(46-67)	survive/dead	137 52(45-58)	54 (63-67)	<0.001
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	<0.001
Liu et al.	Tongi + 3 others	78 38(33-57)	stable/deteriorate	66 37(32-41)	11 66(51-79)	0.001
Guan et al.	31 provinces/provincial municipalities	1099 47(35-58)	non-severe/ severe	926 45(34-57)	137 52(40-65)	<0.001
Guan et al.	31 provinces/provincial municipalities	1099 47(35-58)	stable/end-point	1032 46(35-57)	67 63(53-71)	<0.001
Any Comorbidity; n-number (%)						
Huang et al.	Jin Yin-Tan	41 (32%)	nonICU/ICU	28 (29%)	13 (38%)	0.53
Wang et al.	Zongnan	138 (46%)	nonICU/ICU	102 (37%)	36 (72%)	<0.001
Zhou et al.	JY-T & Wuhan	191 (48%)	survive/dead	137 (40%)	54 (67%)	0.001
Ruan et al.	Tongji	150 (51%)	survive/dead	82 (41%)	68 (63%)	0.0069

Liu et al.	Tongi + 3 others	78 -	stable/deteriorate	66 -	11 -	-
Guan et al.	31 provinces/provincial municipalities	1099 (24%)	non-severe/ severe	926 (21%)	173 (39%)	-
Guan et al.	31 provinces/provincial municipalities	1099 (24%)	stable/CEP	1032 (21%)	57 (58%)	-
Hypertension (Prevalence 15-33% WHO data/Bundy); n-number (%)						
Huang et al.	Jin Yin-Tan	41 (15%)	nonICU/ICU	28 (14%)	13 (15%)	0.93
Wang et al.	Zongnan	138 (31%)	nonICU/ICU	102 (22%)	36 (58%)	<0.001
Zhou et al.	JY-T & Wuhan	191 (30%)	survive/dead	137 (23%)	54 (48%)	0.0008
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	-
Liu et al.	Tongi + 3 others	78 (40%)	stable/deteriorate	66 (9%)	11 (18%)	0.3
Guan et al.	31 provinces/provincial municipalities	1099 (15%)	non-severe/ severe	926 (13%)	173 (24%)	-
Guan et al.	31 provinces/provincial municipalities	109 (15%)	stable/end-point	1032 (14%)	67 (36%)	-
Diabetes Mellitus (General rate in China is 8.4-10% [Diabetes UK, WHO]); n-number (%)						
Huang et al.	Jin Yin-Tan	41 (20%)	nonICU/ICU	28 (25%)	13 (8%)	0.16
Wang et al.	Zongnan	138 (10%)	nonICU/ICU	102 (6%)	36 (22%)	0.009
Zhou et al.	JY-T & Wuhan	191 (19%)	survive/dead	137 (14%)	45 (31%)	0.005
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	-
Liu et al.	Tongi + 3 others	78 (25%)	stable/deteriorate	66 (5%)	11 (18%)	0.143
Guan et al.	31 provinces/provincial municipalities	1099 (7%)	non-severe/ severe	926 (5%)	173 (16%)	-
Guan et al.	31 provinces/provincial municipalities	1099 (7%)	stable/EP	1032 (6%)	67 (27%)	-
Renal Disease (CKD - 10.8% in China - Wang, Jinwei et al); n-number (%)						
Huang et al.	Jin Yin-Tan	41 -	nonICU/ICU	28 -	13 -	-
Wang et al.	Zongnan	138 (3%)	nonICU/ICU	102 (2%)	36 (6%)	0.28
Zhou et al.	JY-T & Wuhan	191 (1%)	survive/dead	137 (0%)	54 (4%)	0.02
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	-
Liu et al.	Tongi + 3 others	78 -	stable/deteriorate	66 -	11 -	-

Guan et al.	31 provinces/provincial municipalities	1099 (8%)	non-severe/ severe	926 (0.5%)	173 (2%)	-
Guan et al.	31 provinces/provincial municipalities	1099 (8%)	stable/end-point	1032 (0.6%)	67 (3%)	-
COPD (5.7% in 2018 - Zhu B); n-number (%)						
Huang et al.	Jin Yin-Tan	41 (2%)	nonICU/ICU	28 (0%)	13 (8%)	0.14
Wang et al.	Zongnan	138 (3%)	nonICU/ICU	102 (1%)	36 (8%)	0.54
Zhou et al.	JY-T & Wuhan	191 (3%)	survive/dead	137 (1%)	54 (7%)	0.047
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	-
Liu et al.	Tongi + 3 others	78 (10%)	stable/deteriorate	66 (1.5%)	11 (9%)	0.264
Guan et al.	31 provinces/provincial municipalities	1099 (1%)	non-severe/ severe	926 (1%)	173 (4%)	-
Guan et al.	31 provinces/provincial municipalities	1099 (1%)	stable/end-point	1032 (0.5%)	67 (10%)	-
Cardiovascular Disease / Coronary Heart Disease (estimated 20% WHO); n-number (%)						
Huang et al.	Jin Yin-Tan	41 (15%)	nonICU/ICU	28 (11%)	13 (23%)	0.32
Wang et al.	Zongnan	138 (15%)	nonICU/ICU	102 (11%)	36 (25%)	0.04
Zhou et al.	JY-T & Wuhan	191 (8%)	survive/dead	137 (1%)	54 (24%)	<0.0001
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	-
Liu et al.	Tongi + 3 others	78 -	stable/deteriorate	66 -	11 -	-
Guan et al.	31 provinces/provincial municipalities	1099 (3%)	non-severe/ severe	926 (2%)	173 (6%)	-
Guan et al.	31 provinces/provincial municipalities	1099 (3%)	stable/end-point	1032 (2%)	67 (9%)	-
Smoking (Chinese Prevalence 26.3% - WHO); n-number (%)						
Huang et al.	Jin Yin-Tan	41 (7%)	nonICU/ICU	28 (11%)	13 (0%)	0.16
Wang et al.	Zongnan	138 -	nonICU/ICU	102 -	36 -	-
Zhou et al.	JY-T & Wuhan	191 (6%)	survive/dead	137 (4%)	54 (9%)	0.21
Ruan et al.	Tongji	-	survive/dead	-	-	-
Liu et al.	Tongi + 3 others	78 (6%)	stable/deteriorate	66 (3%)	11 (27%)	0.018
Guan et al.	31 provinces/provincial municipalities	1099 (13%)	non-severe/ severe	926 (12%)	173 (17%)	-

Guan et al.	31 provinces/provincial municipalities	1099 (13%)	stable/end-point	1032 (12%)	67 (26%)	-
Malignancy (Chinese Prevalence 0.6% - WHO); n-number (%)						
Huang et al.	Jin Yin-Tan	41 (2%)	nonICU/ICU	28 (4%)	13 (0%)	0.49
Wang et al.	Zongnan	138 (7%)	nonICU/ICU	102 (6%)	36 (11%)	0.29
Zhou et al.	JY-T & Wuhan	191 (1%)	survive/dead	137 (1%)	54 (0%)	0.037
Ruan et al.	Tongji	-	survive/dead	-	-	-
Liu et al.	Tongi + 3 others	78 (5%)	stable/deteriorate	66 (10%)	11 (18%)	0.09
Guan et al.	31 provinces/provincial municipalities	1099 (1%)	non-severe/ severe	926 (1%)	173 (2%)	-
Guan et al.	31 provinces/provincial municipalities	1099 (1%)	stable/end-point	1032 (1%)	67 (1%)	-

Guan et al present data based on disease severity at the time of assessment (using American Thoracic soc guidelines for community-acquired pneumonia) and according to composite end-point status (EP: ICU admission, ventilation or death).

Table 2: Cardiac and associated outcomes in hospitalized COVID-19 disease in selected early studies[3, 6, 18, 21, 22, 32]. (ICU-intensive care unit; ARDS – acute respiratory distress syndrome; AKI – acute kidney injury; p values provided if provided in publication)

Study	Region	All patients	Severity qualification	Lower severity	High severity	p-value
Cardiac injury; n-number (%)						
Huang et al.	Jin Yin-Tan	41 (12%)	nonICU/ICU	28 (4%)	13 (31%)	0.017
Wang et al.	Zongnan	138 (7%)	nonICU/ICU	102 (2%)	36 (22%)	<0.001
Zhou et al.	JY-T & Wuhan	191 (17%)	survive/dead	137 (1%)	54 (59%)	<0.001
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	
Heart Failure;n-number (%)						
Huang et al.	Jin Yin-Tan	41 -	nonICU/ICU	28 -	13 -	-
Wang et al.	Zongnan	138 -	nonICU/ICU	102 -	36 -	-
Zhou et al.	JY-T & Wuhan	191 (23%)	survive/dead	137 (12%)	54 (52%)	<0.001
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	
Arrhytmia; n-number (%)						
Huang et al.	Jin Yin-Tan	41 -	nonICU/ICU	28 -	13 -	-
Wang et al.	Zongnan	138 (17%)	nonICU/ICU	102 (7%)	36 (44%)	<0.001
Zhou et al.	JY-T & Wuhan	191 -	survive/dead	137 -	54 -	-
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	-
Shock; n-number (%)						
Huang et al.	Jin Yin-Tan	41 (7%)	nonICU/ICU	28 (0%)	13 (23%)	0.027
Wang et al.	Zongnan	138 (9%)	nonICU/ICU	102 (1%)	36 (31%)	<0.001
Zhou et al.	JY-T & Wuhan	191 (20%)	survive/dead	137 (0%)	54 (70%)	<0.0001
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	-
ARDS; n-number (%)						
Huang et al.	Jin Yin-Tan	41 (29%)	nonICU/ICU	28 (4%)	13 (85%)	<0.001
Wang et al.	Zongnan	138 (20%)	nonICU/ICU	102 (5%)	36 (61%)	<0.001
Zhou et al.	JY-T & Wuhan	191 (31%)	survive/dead	137 (7%)	54 (93%)	<0.0001
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	-
AKI; n-number (%)						
Huang et al.	Jin Yin-Tan	41 (7%)	nonICU/ICU	28 (0%)	13 (23%)	0.027

Wang et al.	Zongnan	138 (4%)	nonICU/ICU	102 (2%)	36 (8%)	0.11
Zhou et al.	JY-T & Wuhan	191 (15%)	survive/dead	137 (1%)	54 (50%)	<0.0001
Ruan et al.	Tongji	150 -	survive/dead	82 -	68 -	-

Table 3. Delays from Illness onset to complication (adapted from Zhou et al. n=191. Survive=137, Die=54) :

	All (191)	Non-survivors (54)
Sepsis	In 59%: 9 days(7-13)	In 100%: 10 days (7-14)
ARDS	In 31%: 12 days (8-15)	In 93%: 12 days (8-15)
Acute Cardiac Injury	In 17%: 15 days (10-17)	In 59%: 14.5 days (9.5-17)
Secondary Infection	In 15%: 15 days (13-19)	In 50%: 15 days (13-19)
Acute Kidney Injury	In 15%: 15 days (13-19)	In 50%: ? days (?)

Table 4. Diagnostic tests in patients with COVID-19 and cardiovascular involvement. *-The current ACC position advises against routine measurement of troponin or BNP (ACC 18.03)

Test	Diagnostic considerations in COVID-19 patients
NT-Pro BNP/BNP*	Conflicting data on NT-ProBNP. In a MERS-CoV cohort NT-ProBNP was increased but it may be normal in COVID-19 affected patients Higher NT-ProBNP levels in the Chinese cohort are associated with a greater need for ICU care
Troponin*	High sensitivity troponin assay may be helpful for risk assessment in patients requiring ICU care and to identify individuals with silent myocardial injury.
D-dimer	Reports from initial outbreak in Wuhan show a key relationship with a requirement for ICU care and mortality.
Procalcitonin	A marker of bacterial infection, is more likely to be raised in patients who will require ICU care
Full blood count	Often shows leucopenia/lymphocytopenia Low platelets associated with adverse outcome
IL6	Where available - high concentrations associated with adverse outcome
Ferritin	A marker of poor outcome, very significant changes reported in COVID-19 patients
Cardiac CT	To be considered in uncertain cases of patients with elevated troponins with and without signs of obstructive coronary artery disease (EACVI position[166])
ECG	In MERS-CoV the 12-lead electrocardiogram generally shows diffuse T wave inversion where there is myocardial involvement - this can be dynamic. Changes in COVID-19 were also described
Echocardiography	May show global or regional myocardial systolic dysfunction with or without a pericardial effusion and vice versa.

Table 5. Proposed investigations in case of suspicion of myocarditis in COVID-19 patients

1. Detailed history and physical examination.
2. 12-lead ECG on initial visit and perdically, as needed.
3. Serum high-sensitivity troponin, NT-ProBNP (according to index of clinical suspicion)
4. Echocardiography to assess for global and regional wall motion abnormalities and function.
5. Cardiac rhythm monitoring
6. Cardiac MRI, as clinically indicated
7. Cardiac autoantibody titers may be helpful but not in the acute phase

Table 6. Potential COVID-19 Therapies and their CV Effects
References: www.medscape.com; CAD=coronary artery disease; MI=myocardial infarction

	CV Side Effects:	CV Warnings/Toxicities:	Use with Caution or Avoid in Presence of:
Antimalarials:			
Chloroquine/ Hydroxychloroquine	-QT interval prolongation -Thrombocytopenia -Anemia	-Cardiomyopathy/heart failure -Conduction disorders (bundle branch block/AV block) -Torsades de Pointes -Ventricular arrhythmias	-Cardiomyopathy -Ventricular arrhythmias -Uncorrected hypokalemia or hypomagnesemia -Bradycardia (<50 bpm) -Concomitant administration of QT prolonging agents -Hepatic disease and co-administration with other hepatotoxic drugs
Antivirals:			
Ribavarin	-Thrombocytopenia -Hemolytic anemia	-Anemia may result in worsening of CAD leading to MI	-Ischemic heart disease
Lopinivir/Ritonivir	-Hyperlipidemia -Hypertriglyceridemia	-Hepatotoxicity -QT and PR interval prolongation -Torsades de Pointes -Second and third degree AV block	-Conduction system disease -Ischemic heart disease -Cardiomyopathy or structural heart disease -Uncorrected hypokalemia or hypomagnesemia -Concomitant administration of QT or PR prolonging agents
Remdesivir	-unknown	-unknown	-unknown
Biologics:			
Tocilizumab	-Hypertension -Thrombocytopenia -Elevated liver transaminases -Hyperlipidemia	-Hepatotoxicity	-Elevated liver transaminases
Interferon alpha 2B	-Hypertension -Thrombocytopenia -Anemia -Elevated liver transaminases -Hypertriglyceridemia	-Hepatotoxicity -Thyroid dysfunction -Pericarditis -Ischemic and hemorrhagic cerebrovascular events -Arrhythmias -Myocardial ischemia/infarction -Cardiomyopathy	-Decompensated liver disease -Cardiac abnormalities

Table 7. Summary of current key considerations in COVID-19 diagnosis and treatment.

Key Take home messages:
• Cardiovascular patients are at increased risk of severe COVID-19 and its complications. Intensive preventive measures should be followed in this group in accordance with WHO and CDC guidelines. This should include wider use of telemedicine tools in day to day monitoring of the patients during the outbreak to limit their exposure. • The heterogeneity of responses between individual patients indicates, that it unlikely can be considered as a single disease phenotype. Host characteristics promotes more or less severe progression of the disease. • The most common cardiac complications include arrhythmia (AF, ventricular tachyarrhythmia and ventricular fibrillation), cardiac injury (elevated hsCTnI and CK), fulminant myocarditis, and heart failure. • Cardiac complications appear often >15 days after initiation of the fever (symptoms) • Evaluation of cardiac damage (particularly cTnI levels) immediately after hospitalization for COVID-19, as well as monitoring during the hospital stay, may help identifying a subset of patients with possible cardiac injury and thereby predict the progression of COVID-19 complications. • Some of the medications used in COVID-19 treatment may contribute to cardiac toxicity, while their effectiveness in treating COVID-19 is unconfirmed
Cardiovascular Co-Morbidities:
• Hypertension is one of the common risk-associated co-morbidities, but this association is cofounded by age. It is not clear if hypertension is an age-independent risk factors of COVID-19-associated outcomes. As a precaution, it is essential that hypertension remains well controlled • There is no evidence that ACE-Is or ARBs are associated with worse prognosis, and patients should not discontinue use of these medications. • Based on experimental evidence in other conditions particularly ARB and possibly also ACE-Is might exert potentially protective influence in the setting of COVID-19. • COVID-19 may lead to plaque instability and MI, which has a common cause of death in SARS/COVID-19 patients. However, the evidence of effectiveness of primary PCI for type-2-MI during acute viral disease is limited • ACE2 can be considered as a Cinderella of cardiovascular medicine. A molecule which has been underappreciated in cardiovascular pathology is taking central stage in understanding and potentially combating COVID-19

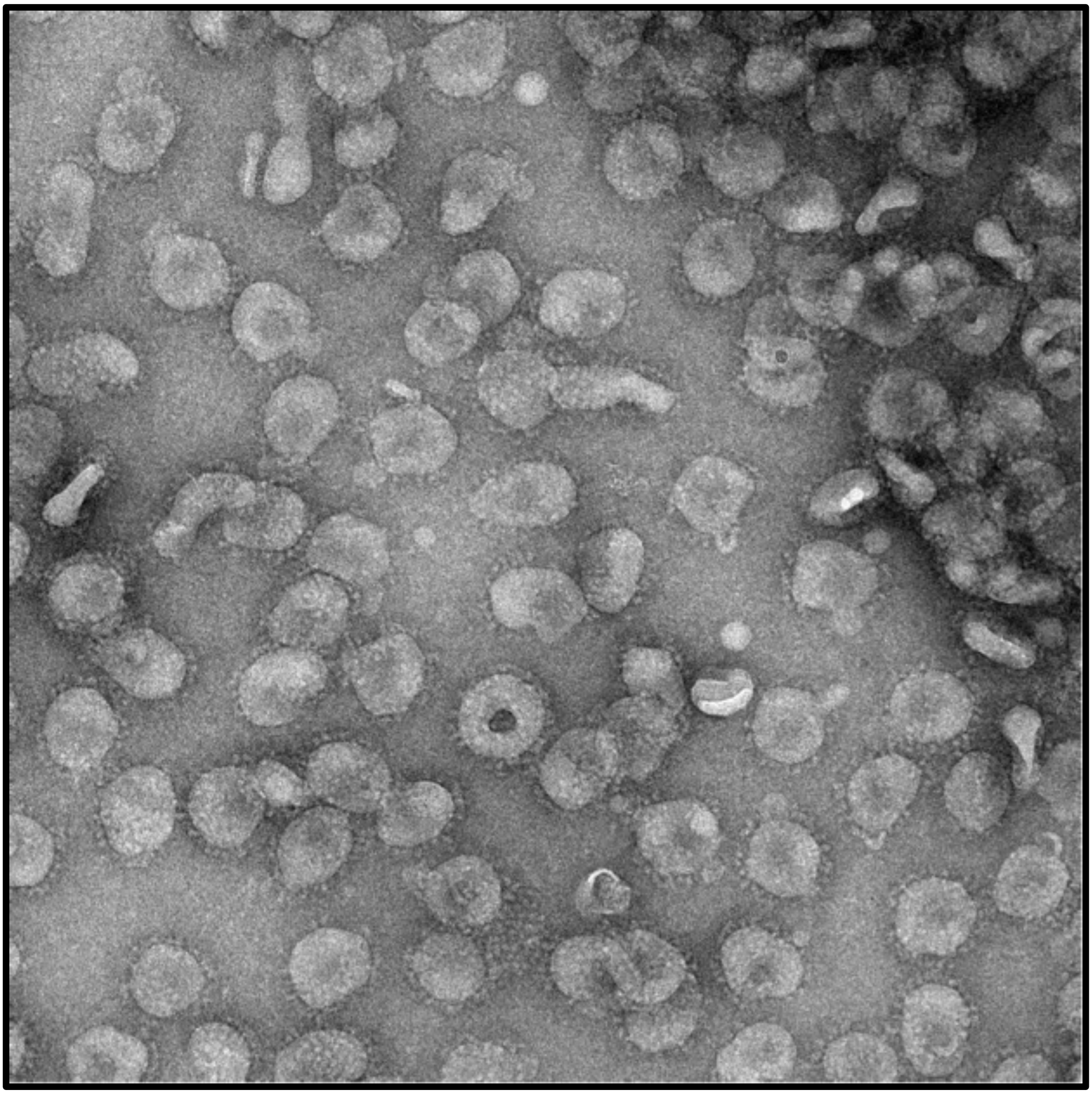

Figure 1. Characteristic structure of betacoronavirus. Negative stain electron microscopy showing a betacoronavirus particles with club-shaped surface projections surrounding the periphery of the particle, a characteristic feature of coronaviruses. The photograph depicts a murine coronavirus. Kindly provided by Prof. David Bhella, Scottish Centre for Macromolecular Imaging; MRC Centre for Virus Research; University of Glasgow.

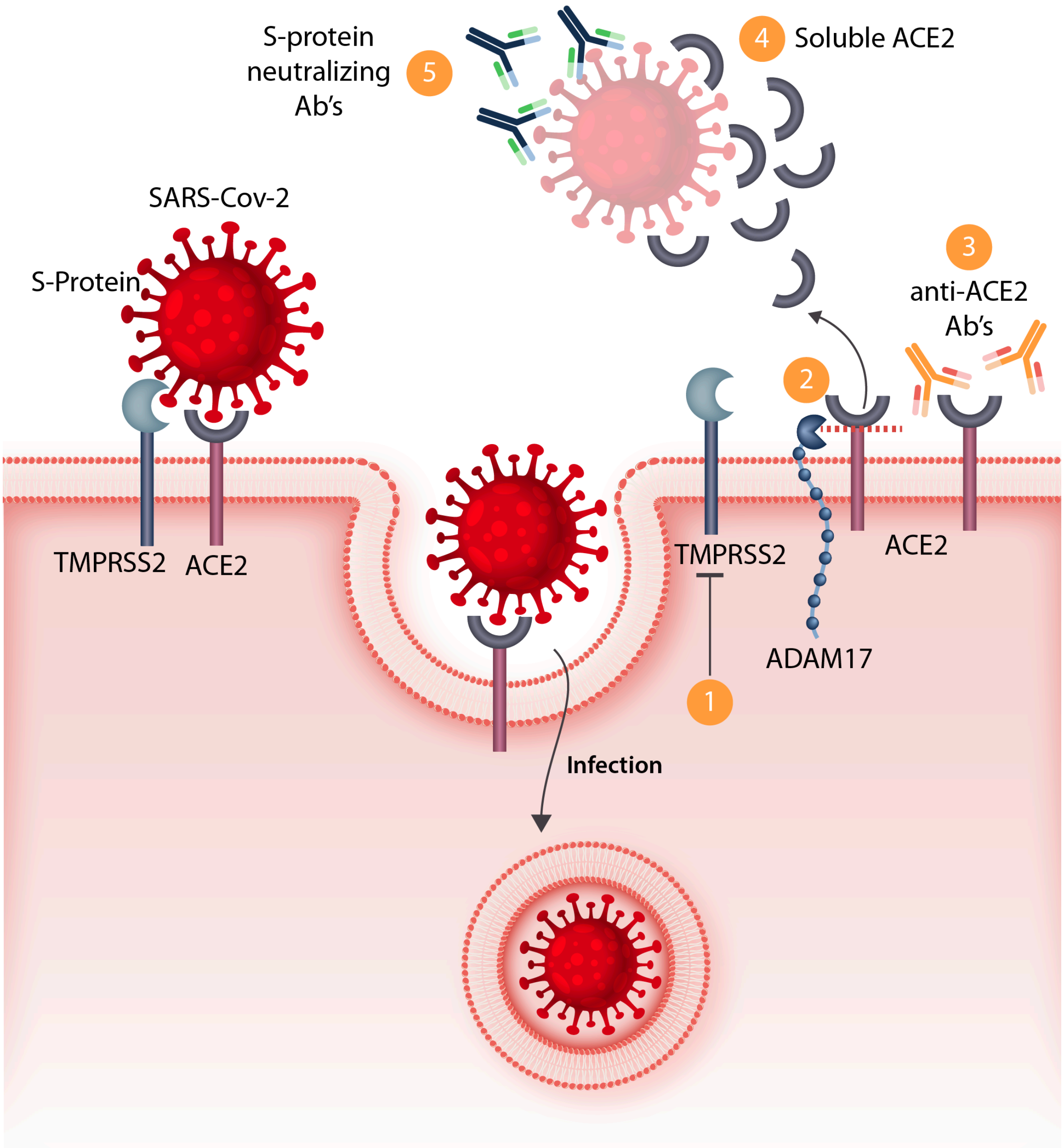

Figure 2. Basic pathobiology of SARS-CoV2 infection and possible treatment strategies – Upon the viral spike protein priming by the transmembrane protease serine 2 (TMPRSS2) SARS-CoV-2 uses the host angiotensin-converting enzyme 2 (ACE2) to enter and infect the cell. Inhibiting TMPRSS2 activity (by camostat mesylate) could be used to prevent proteolytic cleavage of the SARS-CoV-2 spike protein and protect the cell against virus-cell fusion (1). Another approach could be neutralizing the virus from entering cells and keeping it in the solution by activation of a disintegrin and metalloprotease 17 (ADMA17) which shedding the membrane-bound ACE2 and leads to releasing of the soluble extracellular domain of ACE2 (2), treatment with anti-ACE2 antibodies leading to blockage the interaction between virus and receptors (3) or administration of soluble recombinant human ACE2 protein acting as a competitive interceptor for SARS-CoV-2 (4). Alternatively, purified polyclonal antibodies targeting/neutralizing the viral spike protein may offer some protection against SARS-CoV-2 (5). Interestingly, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs), frequently used to treat hypertension, could alter ACE2 expression and intensify the SARS-CoV-2 infection.

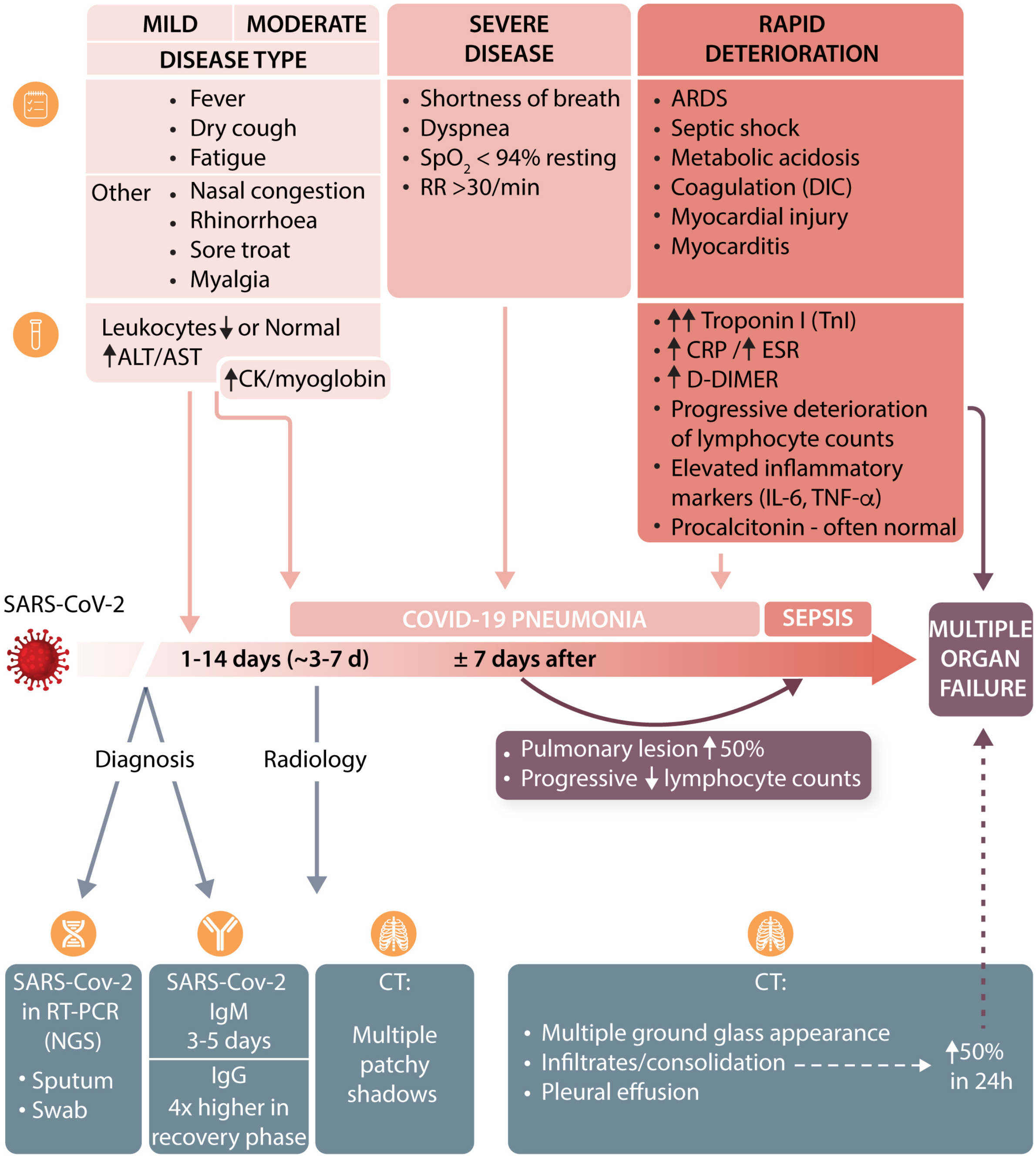

Figure 3. Key symptoms, biochemical and radiological features of the clinical course of COVID-19

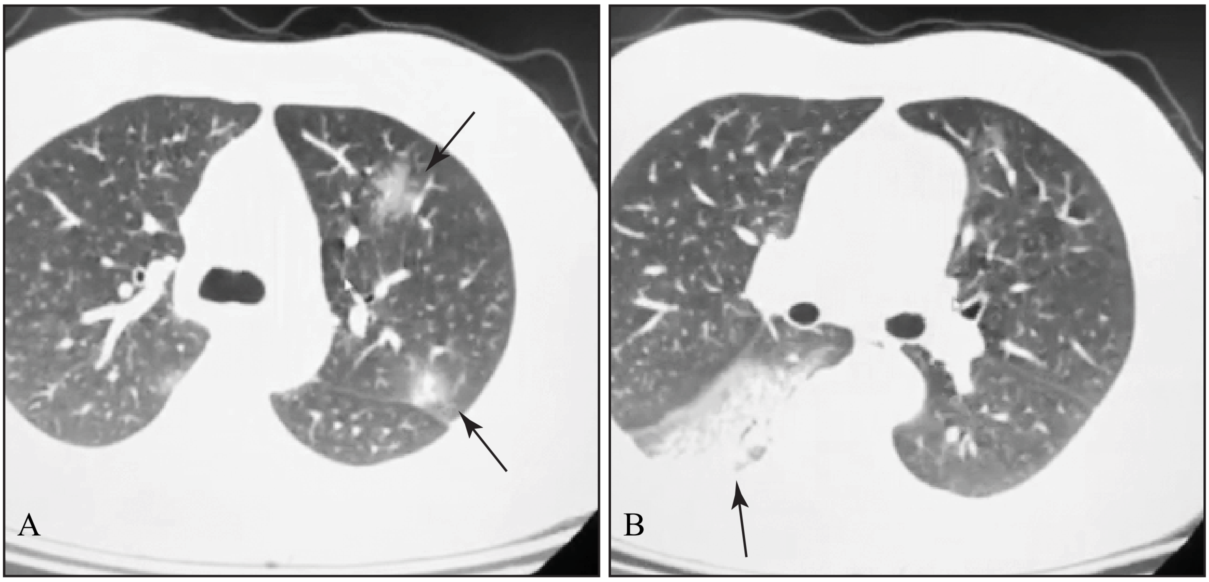

Figure 4: Multi-focal pneumonia in a patient with COVID-19. Panel A illustrates a cross sectional CT image of the lungs showing two distinct pulmonary infiltrates in left upper lobe (arrows). Panel B illustrates a large posteriorly located right lower lobe infiltrate on CT scan of the chest (arrows). Data were collected as part of retrospective study retrospective study, consent was waived and collection of these data was approved by local ethics committee of Wuchan, China. Kindly provided by Prof. Dao Wen Wang.

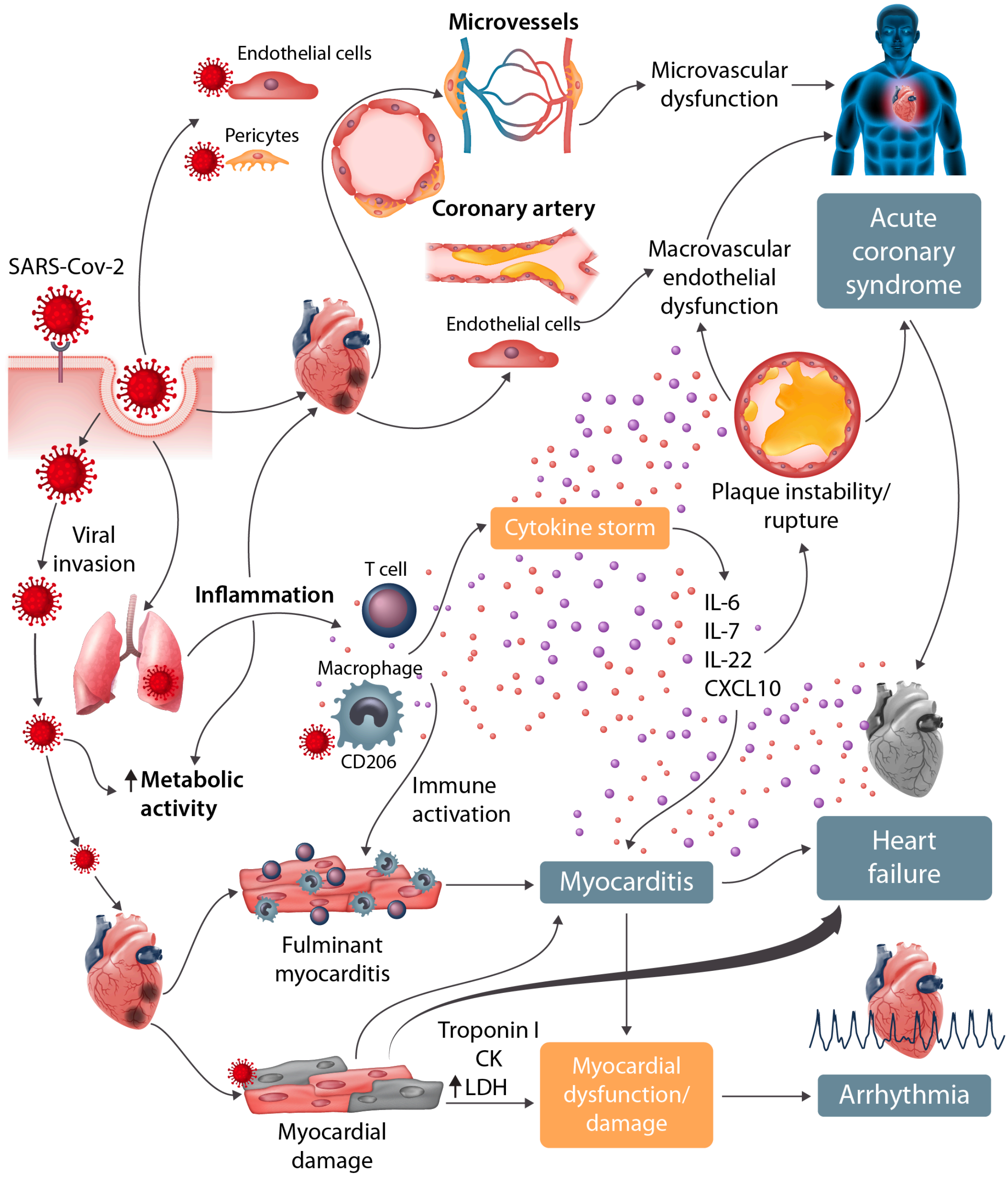

Figure 5. Cardiovascular involvement in COVID-19 – key manifestations and hypothetical mechanisms. SARS-CoV-2 anchors on trans-membrane ACE2 to enter the host cells including type-2 pneumocytes, macrophages, endothelial cells, pericytes and cardiac myocytes leading to inflammation and multi-organ failure. Especially, the infection of endothelial cells or pericytes could lead to severe microvascular and macrovascular dysfunction. Furthermore, in conjunction with the immune over-reactivity can potentially destabilize atherosclerotic plaques and explain the development of the acute coronary syndromes. Infection of the respiratory tract, particularly type-2 pneumocytes, by SARS-CoV-2 is manifested by the progression of systemic inflammation and immune cells over-activation leading to "cytokine storm", which results in an elevated level of cytokines such as IL-6, IL-7, IL-22 and CXCL10. Subsequently, it is possible that activated T cell and macrophages may infiltrate infected myocardium resulting in the development of fulminant myocarditis and severe cardiac damage. This process could be further intensified by cytokine storm. Similarly, the viral invasion could cause cardiac myocyte damage directly leading to myocardial dysfunction and contribute to the arrhythmia development.

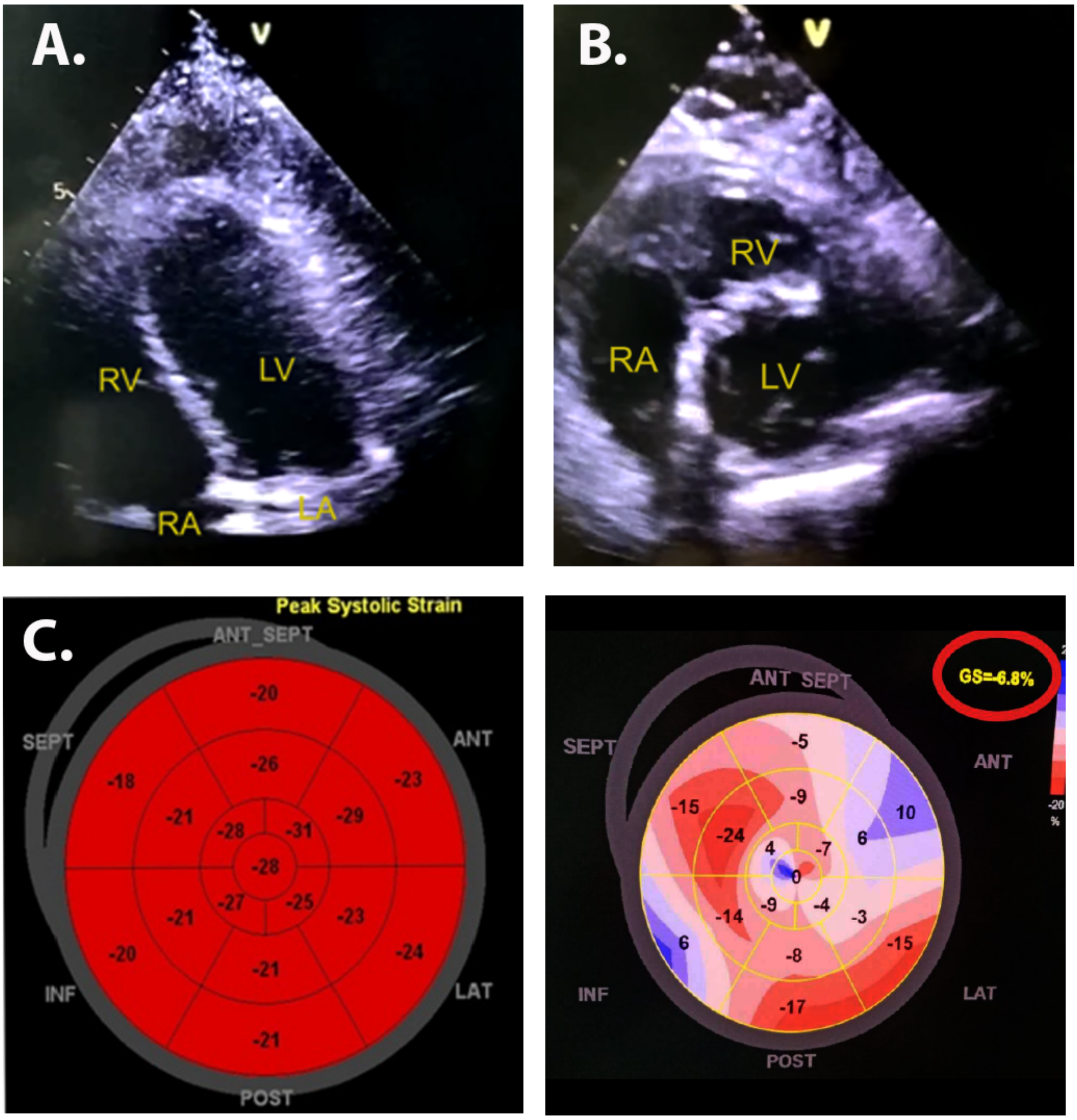

Figure 6. Representative real-life transthoracic echocardiography frames (selected from cine loop images) from a patient with COVID-19. **A.** Apical four chamber view showing globally reduced left ventricle contraction, especially in the apical segment. The right ventricle is dilated and an echo free space, indicating pericardial effusion is present. **B.** Parasternal short axis view showing markedly reduced left ventricle contraction, enlarged right ventricle, and a mural thrombosis in the right ventricle outflow tract. **C.** Two-dimensional speckle tracking echocardiography based on speckle tracking imaging technology (2D STE). Left panel showing a normal 2D STE, right showing a 2D STE from a patient with COVID-19 and myocarditis, depicting reduced regional peak systolic strain rates. Data were collected as part of retrospective study retrospective study, Wuchan, China, consent was waived and collection of these data was approved by local ethics committee. Kindly provided by Prof. Dao Wen Wang.