This report focuses on Cardiovascular Disease and COVID19

1. **Old age, being male and CVD co-morbidity are risk factors for mortality**
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Whilst the lungs are the primary site of infection for SARS-CoV-2, in more severe cases its effects can be detected in multiple organ systems. The cardiovascular (CV) system is not only important from an underlying disease and risk factor standpoint, but also in that many COVID-19 positive patients purportedly develop cardiovascular complications, such as myocardial injury (https://jamanetwork.com/journals/jamacardiology/fullarticle/2763524), cardiac arrhythmia (https://jamanetwork.com/journals/jama/fullarticle/2761044) and thromboembolism (https://pubs.rsna.org/doi/10.1148/radiol.2020201561, https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.047430). CV system involvement is associated with higher mortality rates and is largely indicated by elevated inflammatory biomarkers, including D-dimer, cardiac troponin, ferritin and interleukin (IL)-6 (https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.046941).

1. In a retrospective, multicentre cohort study it was shown **old age, being male and CVD co-morbidity are risk factors for mortality of COVID19**. Zhou et al. (2020) showed that 191 patients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital), of whom 137 were discharged and 54 died in hospital, the median age was 56·0 years (IQR 46·0–67·0), ranging from 18 years to 87 years, and most patients were male. 91 (48%) patients had a comorbidity, with hypertension being the most common (58 [30%] patients), followed by diabetes (36 [19%] patients) and coronary heart disease (15 [8%] patients). Multivariable regression showed increasing odds of in-hospital death associated with older age (odds ratio 1·10, 95% CI 1·03–1·17, per year increase; p=0·0043), higher Sequential Organ Failure Assessment (SOFA) score (5·65, 2·61–12·23; p=0·0001), and d-dimer greater than 1 μg/mL (18·42, 2·64–128·55; p=0·0033) on admission. In univariable analysis, odds of in-hospital death was higher in patients with diabetes or coronary heart disease. Age, lymphopenia, leucocytosis, and elevated ALT, lactate dehydrogenase, high-sensitivity cardiac troponin I, creatine kinase, d-dimer, serum ferritin, IL-6, prothrombin time, creatinine, and procalcitonin were also associated with death. **In this study, increased high-sensitivity cardiac troponin I during hospitalisation was found in more than half of those who died.** The potential risk factors of older age, high SOFA score, and d-dimer greater than 1 μg/mL could help clinicians to identify patients with poor prognosis at an early stage. (Zhou et al. (2020) Lancet, https://doi.org/10.1016/S0140-6736(20)30566-3)

In a retrospective case series involving 1591 critically ill COVID19 patients admitted from February 20 to March 18, 2020 in Lombardy, Italy, who required treatment in an intensive care unit (ICU), the median (IQR) age was 63 (56-70) years and 1304 (82%) were male. Of the 1043 patients with available data, 709 (68%) had at least 1 comorbidity and 509 (49%) had hypertension. The second most common comorbidities were cardiovascular disease (223 patients, 21% [95% CI, 19%-24%]) and hypercholesterolemia (188 patients, 18% [95% CI, 16%-20%]). ICU mortality was higher in those who were older (≥64 years). **The prevalence of hypertension was higher among patients who died in the ICU (63%, 195 of 309 patients) compared with those discharged from the ICU (40%, 84 of 212 patients)**.
(difference, 23% [95% CI, 15%-32%]; P < .001) (Grasselli et al. (2020), JAMA [https://doi:10.1001/jama.2020.5394])

Guo et al. (2020) showed that cardiac injury (increased cTnT levels) was associated with worse outcome. In a case series study of 187 patients with COVID-19, 27.8% of patients had myocardial injury, which resulted in cardiac dysfunction and arrhythmias. Myocardial injury has a significant association with fatal outcome of COVID-19, while the prognosis of patients with underlying CVD but without myocardial injury were relatively favourable. Among 187 patients with confirmed COVID-19, 144 patients (77%) were discharged and 43 patients (23%) died. The mean (SD) age was 58.50 (14.66) years. Overall, 66 (35.3%) had underlying CVD including hypertension, coronary heart disease, and cardiomyopathy, and 52 (27.8%) exhibited myocardial injury as indicated by elevated TnT levels. The mortality during hospitalization was 7.62% (8 of 105) for patients without underlying CVD and normal TnT levels, 13.33% (4 of 30) for those with underlying CVD and normal TnT levels, 37.50% (6 of 16) for those without underlying CVD but elevated TnT levels, and 69.44% (25 of 36) for those with underlying CVD and elevated TnTs. Patients with underlying CVD were more likely to exhibit elevation of TnT levels compared with the patients without CVD (36 [54.5%] vs 16 [13.2%]). Plasma TnT levels demonstrated a high and significantly positive linear correlation with plasma high-sensitivity C-reactive protein levels ($\beta = 0.530$, P < .001) and N-terminal pro–brain natriuretic peptide (NT-proBNP) levels ($\beta = 0.613$, P < .001) (Guo et al. JAMA Cardiology [https://doi:10.1001/jamacardio.2020.1017])

2. Myocardial Damage: The Role of Cardiac Troponin and other relevant markers

A number of studies show that a high proportion of COVID-19 patients exhibit elevated levels of cardiac damage biomarkers, such as cardiac troponin (cTn), with reports of up to 38% of patients testing positive for COVID-19 displaying high circulating levels of cTn (Deng et al., [https://doi.org/10.1016/j.jicard.2020.03.087]). COVID-19 patients who exhibit high levels of cTn are at significantly greater risk of requiring admission to ICU, diagnosis with acute respiratory disorder syndrome (ARDS), cardiac arrhythmias, in need of mechanical ventilation, are hospitalised for longer and subsequent higher risk of mortality (Santoso et al,[https://doi.org/10.1016/j.ajem.2020.04.052]) than COVID-19 patients with low levels of cTn. In a study comparing clinical characteristics between survivors of COVID-19, and those who succumbed to the disease, researchers found that elevated levels of cTn were found in 77% of patients who subsequently died, compared to only 14% of patients who had survived (Chen et al., [https://doi.org/10.1136/bmj.m1091]). In addition, patients with underlying CVD are more likely to present with high cTn levels with the poor prognosis for those with elevated levels, further compounded if the patient has underlying CVD, compared to those without underlying CVD (69.4% vs. 37.5% mortality rate, respectively) (Guo et al., [https://doi.org/10.1001/jamacardio.2020.1017]). A recent meta-analysis showed that cardiac injury (taken as high sensitivity cTn >99th percentile) was associated with greater risk of ICU admission (7.94 risk ratio [RR], n=3 studies), and mortality (7.95 RR, n=7 studies) (Santoso et al., [https://doi.org/10.1016/j.ajem.2020.04.052]). In a study published in the Lancet, the highest odds ratio (OR) for mortality in COVID-19 patients (n=191) was for elevated cTn (>28pg/mL, OR: 80.1) compared to other biomarkers, including circulating lymphocyte count (OR: 0.02) and D-Dimer (OR: 20.04) (Zhou et al., [https://doi.org/10.1016/S0140-6736(20)30566-3]).

It is also evident that throughout hospitalisation, levels of cTn rise, and importantly, survivors showed no rise in this biomarker during the hospital stay, whereas patients
with COVID-19 who died from complications, showed a steady upward rise in cTn until death (Zhou et al., https://doi.org/10.1016/S0140-6736(20)30566-3) (see Figure 1). In another study, a significant predictor of mortality due to COVID-19 was the peak cTn during hospitalisation, not the level measured upon admission (Deng et al., https://doi.org/10.1016/j.jicard.2020.03.087), suggestive that risk stratification should include serial cTn measurements.

![Figure 1](image.png)

**Figure 1.** Serum cardiac troponin I (cTnI) in patients with COVID-19 in Jinyintan Hospital and Wuhan Pulmonary Hospital, China. Figure displays cTnI measurements in patients who died of COVID-19 (red) with levels significantly increasing from admission through hospitalization and a few days before death, and in COVID-19 patients survived (blue), with no change in cTnI in these patients. From Zhou et al. (https://doi.org/10.1016/S0140-6736(20)30566-3).

Besides cTn, other biomarkers, such as **creatine kinase (CK), electrocardiographic (ECG) changes, and imaging** might also reveal cardiac pathology in COVID-19 patients. Plasma lactate dehydrogenase and CK levels are correlated with COVID-19 severity and ICU admissions, reaching 26.1% and 70.5%, shown from data acquired by multicentres (Guan et al., https://www.nejm.org/doi/10.1056/NEJMoa2002032). CK isoenzyme-MB (CK-MB), myohaemoglobin (MYO), and N-terminal pro-brain natriuretic peptide (NT-proBNP) are elevated above normal ranges in 3.7%, 10.6%, and 12.4% confirmed cases, respectively (Han et al., https://doi.org/10.1002/jmv.25809). When stratified by disease severity, patients with abnormal CK-MB, MYO, and NT-proBNP increased to 6.7%, 26.7%, and 33.3% respectively in the critical cases, underscoring underlying ischaemia and cardiac dysfunction. This is further supported by ECG findings characteristic of ischaemia, such as T-wave depression and inversion, ST depression, and presence of Q waves (Shi et al., doi:10.1001/jamacardio.2020.0950). In a case report, the presence of acute pulmonary embolism in COVID-19 was associated with right ventricular dilatation and dyskinesis on echocardiography, indicating that some patients develop ventricular hypertrophy. (Danzi et al., https://doi.org/10.1093/eurheartj/ehaa254).

3. **ACE2 expression, hypertension and ACE2 inhibitors**

The main receptor required for SARS-CoV2 entry into host cells is considered to be angiotensin-converting enzyme 2 (ACE2), with binding facilitated via its glycosylated outer membrane protein, TMPRSS2. Coexpression and distribution of ACE2 and TMPRSS2 are thus considered key determinants for viral entry into the host cell (Hoffman et al., https://doi.org/10.1016/j.cell.2020.02.052).
In the heart, examination of myonuclei obtained from human donors revealed ACE2 expression in cardiac pericytes, which exhibit cross-talk with endothelial cells, as well as cardiomyocytes (Chen et al., https://doi.org/10.1093/cvr/cvaa078; Nicin et al., https://doi.org/10.1093/eurheartj/ehaa311). The degree of cardiac ACE2 expression, assessed at the mRNA and protein level, was increased in failing hearts compared to normal donors (Chen et al., https://doi.org/10.1093/cvr/cvaa078).

However, ACE2 expression may not always correlate with degree of infection, as examination of SARS-CoV viral uptake revealed high uptake in cell types exhibiting low ACE2 expression (Gu et al., https://doi.org/10.2353/ajpath.2007.061088). This therefore highlights the importance of considering the coexpression of factors, such as the serine protease TMPRSS2, alongside ACE2 when assessing cell types vulnerable to SARS-CoV-2 uptake.

Hypertension has been identified as a risk factor for increased COVID-19 disease severity, being reported as the most frequent coexisting condition across 1099 patients in China with an estimated prevalence of 15% (Guan et al., https://doi.org/10.1056/NEJMoa2002032). Yet thus far, no data shows hypertension as an independent risk factor of fatal outcome (Kuster et al., https://doi.org/10.1093/eurheartj/ehaa235; Mehra et al., https://doi.org/10.1056/NEJMoa2007621). Prevalence of hypertension is highest in the elderly population and advanced age remains the strongest predictor of COVID-19 related death (Vaduganathan et al., https://doi.org/10.1056/NEJMsr2005760; Mehra et al., https://doi.org/10.1056/NEJMoa2007621).

Concerns have been raised regarding the use of RAAS blockers (ACE inhibitors (ACEi) and Angiotensin receptor blockers (ARBs)) in COVID-19 patients, with variation in ACE2 purported to increase SARS-CoV-2 disease severity (Sommerstein et al., https://doi.org/10.1136/bmj.m810). Patients receiving ACEi treatment (N=4) demonstrated increased cardiac ACE2 and ACE:ACE2 ratio relative to patients taking ARBs (N=2) and a healthy control (N=1) (Nicin et al., https://doi.org/10.1093/eurheartj/ehaa311). Higher urine ACE2 levels, indicative of kidney ACE2 level, have also been reported in 13 patients taking the ARB Olmesartan (Furuhashi et al., https://doi.org/10.1093/ajh/hpu086). However, other cross sectional cardiovascular disease studies have not demonstrated higher plasma ACE2 activity in those patients taking ACEi (Vaduganathan et al., https://doi.org/10.1056/NEJMsr2005760).

Currently, there is no data proving causal relationship between ACE2 activity and SARS-CoV-2 associated mortality (Kuster et al., https://doi.org/10.1093/eurheartj/ehaa235). In 8910 patients across Asia, Europe and North America, no association was found between risk of in-hospital death and the use of either ACEi or ARBs (Mehra et al., https://doi.org/10.1056/NEJMoa2007621). Indeed, the risk of severe disease onset was lower across 205 patients taking ACEi in the UK, with a lower rate of death or transfer to ICU within 7d of symptom onset in patients on an ACEi compared to those not on ACEi. This association was adjusted for age, gender and comorbidities including hypertension and heart failure (Bean et al., https://doi.org/10.1101/2020.04.07.20056788) (Note: not yet peer reviewed and they are continuing to increase subject numbers to this trial dataset). This is in accordance with experimental mouse models that demonstrate protective effects of ACE2 expression against severe acute lung injury (Imai et al., https://doi.org/10.1038/nature03712) and SARS-CoV infection (Kuba et al. https://doi.org/10.1038/nm1267).

4. Renal dysfunction

There is emerging evidence of COVID-19-associated renal dysfunction. The incidence of elevated baseline serum creatinine concentrations have been reported to be between 14.4% and 22.3% and seem to progressively increase as COVID-19 severity progresses, with a higher chance of being admitted to the ICU (Wang et al., https://doi.org/10.1001/jama.2020.1585; N = 138 [COVID-19-associated pneumonia], China). Cheng et al. (https://doi.org/10.1016/j.kint.2020.03.005; N = 701, China), reported renal abnormalities, such as proteinuria, haematuria, and acute kidney injury (AKI) were associated with in-hospital death, even after adjusting for confounders, such as age and comorbidities status. The incidence of AKI has been reported in as high as 23% (Huang et al., https://doi.org/10.1016/S0140-6736(20)30618-5; N = 41 [N = 13 for ICU patients], China) of patients with COVID-19 who were admitted to ICU. Whilst not fully elucidated, there are a number of competing mechanisms for this apparent COVID-19-associated renal dysfunction. Firstly, hypoxaemia is a hallmark consequence in patients with COVID-19, which may drive renal dysfunction due to the kidneys operating under low oxygen tensions and are therefore susceptible to hypoxic insult (Shu et al., http://dx.doi.org/10.3390/cells8030207). Secondly, a cytokine storm-induced inflammatory response, which has been reported in COVID-19 patients, may cause sepsis-induced AKI (Li et al., https://doi.org/10.1016/S0140-6736(20)30920-X). Lastly, specialised renal cells, called podocytes, co-express ACE2 and TMPRSS2 (Pan et al., https://doi.org/10.1007/s00134-020-06026-1). Therefore, it could be postulated that SARS-CoV-2 may bind to host ACE2 expressing podocytes and subsequently alter the structure and function of glomeruli. This is similar to other viral related nephropathies, mainly human immunodeficiency virus-associated nephropathy (Wyatt et al., https://dx.doi.org/10.1016%2Fj.semnephrol.2008.08.005). In support of this, two case studies have reported severe collapsing glomerulopathy, acute tubular necrosis and severe proteinuria (Kissling et al., https://doi.org/10.1016/j.kint.2020.04.006; Larsen et al., https://doi.org/10.1016/j.ekir.2020.04.002) in patients with COVID-19 and AKI. Of note, both case studies were in individuals of African descent who may be at higher risk of kidney disease as a result of the APOL1 risk allele (Limou et al., https://doi.org/10.1053/j.ackd.2014.06.005). Further research is required to elucidate the mechanism of renal dysfunction in patients with COVID-19, however, due to disease severity, ethnicity factors, and pre-existing comorbidities, the mechanisms are likely heterogeneous. Close and early monitoring of renal function throughout the course of COVID-19 may be recommended (Pan et al., https://doi.org/10.1007/s00134-020-06026-1).

5. Cytokine Storm and the cardiovascular system.

A hallmark of more severe cases of SARS-CoV-2 in patients with acute respiratory distress syndrome (ARDS) appears to be a virally-induced over-activation or unregulated response of the immune system, termed a “cytokine storm”, featuring elevated levels of pro-inflammatory cytokines such as IL-2, IL-6, IL-7, IL-22, CXCL10 and tumour necrosis factor-α (TNFα).
The ‘cytokine storm’ theory is that the activation of lung-resident immune cells via pattern-recognition receptors drives the release of pro-inflammatory cytokines and extravasation of blood neutrophils and monocytes into the bronchi. These cells may disrupt the air–blood barrier by causing collateral tissue damage, particularly to airway epithelial cells and vascular endothelial cells, which express the ACE2 entry receptor for SARS-CoV-2; the damage of vascular endothelial cells may account for thrombotic microangiopathies (Risitano et al. 2020, https://www.nature.com/articles/s41577-020-0320-7).


Furthermore, dysregulated inflammatory responses, as seen in a cytokine storm, are implicated in the pathogenesis of heart failure and dysfunctional peripheral circulation (Mann, 2015, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4380242/#R23), which is consistent with the relatively high prevalence of acute cardiac injury observed in severe cases of COVID-19, with elevated levels of IL-6, neutrophils and CRP (Wu et al., https://www.medrxiv.org/content/10.1101/2020.02.26.20028589v1), troponin (Lala et al., https://www.medrxiv.org/content/10.1101/2020.04.20.20072702v2) and IL2, IL7, IL10, granulocyte-colony stimulating factor (GCSF), interferon-γ inducible protein (IP)-10, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1-α, and TNFα (Huang et al., https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30183-5/fulltext).

A recent study has demonstrated involvement of the vascular endothelium in COVID-19, with an accumulation of inflammatory cells across multiple organs (e.g. lungs, heart, gut, kidneys, liver) observed in three patients (Varga et al., https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30937-5/fulltext#%20). These findings suggest that endotheliitis across several organs is largely due to the inflammatory response induced by SARS-CoV-2. Considering endothelial dysfunction leads to impaired systemic microvascular function, it seems likely that involvement of the vascular system’s first line of defence (endothelial cells) precipitates the systemic damage observed in severe COVID-19. However, further retrospective studies are required to advance this theory although interestingly, SARS-CoV-2 has been shown to directly infect engineered human blood vessel organoids and human kidney organoids (Monteil et al., https://www.cell.com/pb/assets/products/coronavirus/CELL_CELL-D-20-00739.pdf).

Drug and cell therapies targeting immunosuppression have been suggested to help combat the cytokine storm (Mehta et al., https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext). Early studies demonstrate encouraging outcomes for targeted IL-6 blockade via administration of Tocilizumab (Roumier et al., https://www.medrxiv.org/content/10.1101/2020.04.20.20061861v1, Xu et al., https://www.pnas.org/content/early/2020/04/27/2005615117) and α1-AR antagonists such as Prazosin are undergoing further investigation (Konig et al., https://www.medrxiv.org/content/10.1101/2020.04.02.20051565v2). However, drug therapies
such as the immunomodulator hydroxychloroquine, should be monitored carefully due to associated CV disturbance, including myocardial damage and arrhythmia. Furthermore, given the potential role of the endothelium in facilitating systemic disease of COVID-19, ACE inhibitors and statins are also suggested as potentially relevant therapies (Varga et al., https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30937-5/fulltext#%20).

Mesenchymal stromal cells (MSCs), owing to their powerful immunomodulatory ability, have also shown promise in early clinical studies to avoid, prevent or attenuate the cytokine storm. Leng et al. 2020 (https://doi.org/10.14336/AD.2020.0228) showed that i.v. transplantation of 1 x 10^6 kg/body weight of MSCs into seven patients with COVID-19 pneumonia has proved to be safe and effective. Indeed, before the transplantation, all patients had COVID19-pneumonia with symptoms of high fever, weakness, shortness of breath and low oxygen saturation. All symptoms had disappeared by two to four days after the transplantation. This was not the case for the 3 placebo control patients. The study found improvement was particularly dramatic for an elderly male patient in a severe critical condition, who made a recovery and was discharged 10 days after treatment (Leng et al. 2020 https://doi.org/10.14336/AD.2020.0228). Therefore, it was postulated that MSC transplantation restored the balance of the immune system enabling patients to make a recovery, be discharged more quickly from hospital and reduce overall mortality.

On April 8th 2020 Mesoblast announced that its adult human allogenic MSC product, remestemcel-L, will be formally evaluated in a randomized, placebo-controlled trial in up to 300 ventilator-dependent patients in intensive care units with moderate to severe COVID-19 acute respiratory distress syndrome (ARDS) in the US. This multi-center Phase 2/3 trial will be conducted as a public-private partnership in a collaboration with the Cardiothoracic Surgical Trials Network (CTSN), which was established by the United States National Institutes of Health’s National Heart, Lung and Blood Institute (NHLBI) as a flexible platform for conducting collaborative trials. (http://investorsmedia.mesoblast.com/static-files/e63bf0d5-7dd5-46c0-8381-c2e24babc130; http://investorsmedia.mesoblast.com/static-files/336699fe-c5ab-41f2-801e-404c3739275c).

Recent preliminary data from Mesoblast (http://investorsmedia.mesoblast.com/static-files/337e723a-340d-493e-a4a1-0971d2c71460) show 83% survival in ventilator-dependent COVID-19 patients (10/12) with moderate/severe ARDS treated with two infusions of Mesoblast’s allogeneic cell therapy remestemcel-L within the first five days under emergency compassionate use at New York City’s Mt Sinai hospital during the period March-April 2020. 75% (9/12) have successfully come off ventilator support within a median of 10 days. These results contrast with only 9% of ventilator-dependent COVID-19 patients being able to come off ventilators with standard of care treatment and only 12% survival in ventilator-dependent COVID-19 patients at two major referral hospital networks in New York during the same time period (Petrilli CM et al. MedRxiv 2020 doi: https://www.medrxiv.org/content/10.1101/2020.04.08.20057794v1.full.pdf; Richardson S et al. JAMA 2020. https://jamanetwork.com/journals/jama/fullarticle/2765184).

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