Cardiovascular disease and COVID-19: implications for prevention, surveillance and treatment

Neal A Chatterjee 1, Richard K Cheng 2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogenic cause of COVID-19, an ongoing global pandemic. In addition to anticipated respiratory mortality, there is an increasing recognition of cardiovascular morbidity and mortality in this population.1-4 In hospitalised patients with COVID-19, prevalent cardiovascular disease (CVD) and the presence of cardiac injury have each been associated with in-hospital mortality (table 1). While similar associations have been reported in other coronavirus epidemics, including SARS and Middle East respiratory syndrome,1 the potential impact of CVD and injury in COVID-19 remains a critical knowledge gap. Further clarity would not only facilitate the identification of at-risk populations who qualify for closer monitoring but additionally frame investigation of shared pathophysiology that could guide development of targeted therapies.

In this issue of Heart, Zhang and colleagues5 present a retrospective, cohort study of patients with COVID-19 admitted to a single hospital in Wuhan, China between 11 January and 6 February 2020. The authors examine the prevalence of CVD among admitted patients and compare clinical characteristics in those with and without CVD. Using logistic regression models, they evaluate the association between CVD and a range of clinical outcomes including all-cause mortality and clinical recovery from infection.

After excluding 119 patients with incomplete clinical history and laboratory data, the study cohort was comprised of 541 patients in whom approximately one-quarter had a history of prevalent CVD. The most common cardiovascular morbidity was hypertension (HTN; 23% of total cohort) followed by coronary artery disease (8%) and arrhythmia (2%). A minority (7%) of patients had more than one CVD type at baseline. When compared with patients without CVD, those with CVD were older and had a greater prevalence of severe infection, end-organ injury (acute kidney injury, acute liver injury) and inflammation (higher C-reactive protein). Overall mortality was higher in those with prevalent CVD (22%) when compared with those without (5%) and those with CVD had an approximate twofold increased odds of presenting with critical illness (defined as respiratory failure, shock or intensive care unit (ICU) admission).

WHAT DOES THIS STUDY PROVIDE?

While the authors of this study6 should be congratulated for the focused evaluation of prevalent CVD and outcomes in COVID-19, there are several important considerations when evaluating the implications of these findings. First, the prevalence data in this study reflects a single region in China. Previous population-based studies highlight important differences in the prevalence and control of cardiovascular risk factors between China and other regions of the world, including the USA.7 For example, while the prevalence of HTN and dyslipidaemia were lower in China compared with the USA, treatment and control of these factors were substantially lower in China (eg, HTN control 20% vs 50% in China vs US). In addition, HTN was more likely to cluster with other cardiovascular and metabolic risk factors in China when compared with the USA. These epidemiological differences have major implications for the generalisability of the findings of this study.6 For example, given the higher rates of risk-factor clustering, it is not clear if CVD or subtypes of CVD as a single risk factor carries the same prognostic implications in other regions of the world. Likewise, the marked variability in both treatment and control of risk factors frames similar ambiguity regarding the prognostic weight of the identified associations. Future data from other geographic epicentres of COVID-19, including the USA and Europe, will be critical to refining our understanding of the implications of CVD in this population.

Second, we would highlight that the study from Zhang and colleagues6 was circumscribed to hospitalised patients. Given the authors’ own findings that patients with CVD were more likely to present with severe illness and thus require hospitalisation, the prevalence of CVD in all patients with COVID-19 may be lower than that reported in this study. Whether prevalent CVD carries the same magnitude of risk in ambulatory patients with COVID-19 remains uncertain. Third, studies to date including this one from Zhang et al6 have employed variable definitions of CVD when evaluating its association with clinical outcomes in COVID-19 (table 1). While the authors of this study should be commended for exploratory analyses examining the association of specific types of CVD with clinical outcomes, the findings noted are likely to be underpowered in light of the sample size and number of endpoints. Looking ahead, evaluation of distinct subtypes of CVD is of specific interest as the clinical implications and types of morbidity are likely to differ between disease conditions. For example, a patient with severe systolic heart failure and pulmonary HTN would be predicted to be at different risk of cardiovascular morbidity when compared with a patient with stage I HTN or paroxysmal atrial fibrillation. While this study6 was underpowered to perform such stratified analyses, future efforts should focus on employing systematic and harmonised definitions of CVD in patients with COVID-19. Finally, in addition to the variability in phenotyping CVD, there remains similar heterogeneity in the adjudication of cardiovascular outcomes in COVID-19. While endpoints such as all-cause mortality are of value, future work delineating both mode of death (respiratory, cardiovascular) as well as specific cardiovascular outcomes (heart failure, malignant brady-arrhythmia or tachyarrhythmia, acute coronary syndrome, myocarditis) will be key to inform both surveillance and therapeutic strategies. Certain risks, such as arrhythmic sudden death, may accrue during the convalescent phase of COVID-19 and studies examining longitudinal outcomes in patients with CVD will be important to understand both the mechanisms and timeline of risk.

MECHANISMS BY WHICH CVD WORSENS OUTCOMES IN COVID-19

There are several possibilities by which CVD could be associated with adverse clinical outcomes in patients with COVID-19. First, prevalent CVD could be a surrogate...
Caring for the patient with CVD during the COVID pandemic

- Additional isolation measures skin to immunosuppressed patients
- Closer monitoring for symptoms of COVID
- Frequent assessment for clinical deterioration
- Threshold for hospitalization
- Additional data on risk vs benefit of angiotensin axis inhibition
- Heightened surveillance with cardiac and inflammatory biomarkers
- Threshold for cardiac diagnostic testing
- Early consideration for COVID-targeted therapies
- Consider imaging to establish cardiac function post-COVID infection
- Re-administration of cardiac medications that may have been held during infection
- Additional data on post-discharge sequelae of COVID infection (e.g. arrhythmias) needed

Figure 1 Caring for the patient with CVD during the COVID-19 pandemic. CVD, cardiovascular disease; ICU, intensive care unit.

Table 1 Increased risk of adverse outcomes with underlying CVD and COVID-19 infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>N for total cohort</th>
<th>Age (Years)</th>
<th>Pre-existing cardiac disease</th>
<th>Association of baseline CVD with outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo et al</td>
<td>Wuhan, China</td>
<td>187</td>
<td>Mean 58.5±14.7</td>
<td>35.3% any CVD: 4% cardiomyopathy 11% coronary heart disease 33% HTN</td>
<td>In-hospital mortality: CVD+elevated TnT: 69.4% No CVD+elevated TnT: 37.5% CVD+normal TnT: 13.3% No CVD +normal TnT: 7.6%</td>
</tr>
<tr>
<td>Shi et al</td>
<td>Wuhan, China</td>
<td>416</td>
<td>Median 64.0 (range 21.0–95.0)</td>
<td>4% chronic heart failure 11% coronary artery disease 31% HTN</td>
<td>Adjusted HR for CVD and mortality (adjustment included TnT and NT-proBNP): From symptom onset 1.51 (95% CI: 0.70 to 3.30) from admission 1.40 (95% CI: 0.65 to 3.03)</td>
</tr>
<tr>
<td>WHO-China report</td>
<td>Wuhan, China</td>
<td>55924</td>
<td>Median 51.0 (IQR 39.0–63.0)</td>
<td>Not reported</td>
<td>No comorbidities: CFR 1.4% CVD: CFR 13.2% HTN: CFR 8.4%</td>
</tr>
<tr>
<td>Yang et al</td>
<td>China</td>
<td>Eight studies: Total n=46248</td>
<td>Median 46.0</td>
<td>HTN in studies: 0%–31.2% CVD in studies: 0%–33.3% Mean prevalence: 17%±7% (95% CI: 14% to 22%) HTN 5%±4% (95% CI: 4% to 7%) CVD</td>
<td>Pooled OR for risk for severe disease: HTN 2.36 (95% CI: 1.46 to 3.83) CVD 3.42 (95% CI: 1.88 to 6.22)</td>
</tr>
<tr>
<td>Zhang et al</td>
<td>Wuhan, China</td>
<td>541</td>
<td>Mean (no CVD): 54.3±16.3 Mean (CVD): 69.7±10.9</td>
<td>26.6% any CVD: 23.1% HTN 7.6% coronary artery disease 1.5% cerebrovascular disease 2.2% arrhythmia</td>
<td>Adjusted OR for CVD and ordinary/severe versus critical disease: 2.74 (95% CI: 1.50 to 5.00) No CVD in-hospital mortality: 5.3% CVD in-hospital mortality: 22.2%</td>
</tr>
<tr>
<td>Zhou et al</td>
<td>Wuhan, China</td>
<td>191</td>
<td>Median 56.0 (IQR 46.0–67.0)</td>
<td>8% coronary artery disease 30% HTN</td>
<td>Multivariable OR for CVD: 2.14 (95% CI: 0.3 to 17.8) In-hospital mortality: HTN non-survivor (48%), survivor (23%) Coronary heart disease non-survivor (24%), survivor (1%)</td>
</tr>
</tbody>
</table>

CFR, case-fatality rate; CVD, cardiovascular disease; HTN, hypertension; N, number; NT-proBNP, N-terminal proB-type natriuretic peptide; TnT, troponin T.

for other conditions (e.g., smoking, diabetes mellitus, obesity) that could impact pulmonary and infectious reserve and thus account for higher mortality. Second, CVD and associated risk factors such as diabetes mellitus may result in functional immunosuppression and thus predispose to more severe manifestations of infectious disease. Previous work has highlighted the relationship between CVD and immune dysregulation, and this association has been proposed as a mechanism of worse outcomes in other infection paradigms including sepsis and influenza. Third, prevalent CVD has been linked to chronic activation of inflammatory pathways. Whether such basal activation of the inflammatory cascade acts synergistically with the reported inflammation-mediated organ injury in COVID-19 remains unknown. Fourth, limited reports have suggested the presence of direct infection of vascular endothelium by SARS-CoV-2. Endothelial dysfunction and associated microvascular injury may be deleterious in patients with prevalent CVD, particularly those with coronary artery disease. Indeed, inflammation and endothelial dysfunction have been linked to acceleration of atherogenesis and induction of coronary plaque instability in the setting of other viral infections such as influenza, which has similarly been associated with increased cardiovascular mortality. Fifth, SARS-CoV-2 employs the ACE 2 receptor (ACE2) to gain cellular entry. Emerging data suggests that myocardial ACE2 expression may be increased in patients with prevalent CVD, particularly those with coronary artery disease. Indeed, inflammation and endothelial dysfunction have been linked to acceleration of atherogenesis and induction of coronary plaque instability in the setting of other viral infections such as influenza, which has similarly been associated with increased cardiovascular mortality. Looking ahead, how can we leverage the evidence provided by studies like this?
one to improve clinical outcomes for our patients with CVD (figure 1)? In terms of primary prevention, one approach may be to recommend additional isolation measures and social distancing for those with pre-existing CVD, akin to recommendations for other ‘high-risk’ cohorts such as immunosuppressed patients. Given the suggested propensity for clinical deterioration, ambulatory CVD patients diagnosed with COVID-19 may warrant heightened outpatient monitoring coupled with a lower threshold for hospitalisation. For patients who are hospitalised, those with prevalent CVD may benefit from greater frequency of cardiac and inflammatory biomarker monitoring, lower threshold for diagnostic testing (eg, point-of-care ultrasound) to identify early signs of cardiac injury, modified clinical care pathways including a lower threshold for ICU transfer, and earlier consideration for disease-modifying COVID-19 therapies. To the extent that CVD-associated inflammation may act synergistically with the inflammatory and cytokine injury of SARS-CoV-2 infection, the role of targeted anti-inflammatory therapies in patients with CVD and COVID-19 remains an important unanswered question. More broadly, given the potential effect modification of CVD on the effectiveness of clinical therapies for COVID-19, we would advocate stratifying analyses of investigational COVID-19 therapies by CVD status.

Ultimately, operationalising these approaches will require engagement from a range of stakeholders including federal and local governments, healthcare systems, clinical trialists, the pharmaceutical industry, care providers and most importantly, patients. For the more than 400 million people across the globe with CVD, including the disproportional burden in low and middle income countries, these partnerships will be nothing short of vital to their health and lives. We must act now.

Twitter Neal A Chatterjee @NChatterjee_md

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