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EDITORIAL COMMENT

COVID-19: getting to the heart of the matter

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This article refers to 'Heart failure in COVID-19 patients: prevalence, incidence and prognostic implications' by J.R. Rey *et al.*, published in this issue on pages 2205–2215.

The global pandemic of coronavirus disease 2019 (COVID-19) continues to cause unprecedented morbidity and mortality worldwide.[1] Seminal case series demonstrated that 11% to 14% of individuals infected with COVID-19 had pre-existing cardiovascular disease, with these patients being at increased risk of complications.[2,3] These findings have subsequently been confirmed by larger epidemiological studies from North America and Europe noting a considerable proportion of COVID-19 patients had underlying cardiac risk factors and/or disease, and subsequently were at increased risk of morbidity and mortality.[4,5] The prevalence of prior heart failure (HF) in individuals infected with COVID-19 ranges between 4% in certain areas of China to up to 21% in older populations in Europe.[1,6]

In this issue of the Journal, Rey *et al.*[7] report on 3080 consecutive patients with confirmed COVID-19 infections, which in itself is impressive by sheer patient volume. They compared the characteristics and outcomes of those individuals with or without HF. Among the cohort, 4.9% had a prior history of HF, and although it is not surprising that these individuals had higher mortality rates than their non-HF counterparts, it is alarming that almost half (48.7%) of patients died during a median follow-up of 59 days. Similarly high mortality rates for HF patients with COVID-19 have also been noted in other case series.[8] This high mortality rate not only reflects their older age and increased prevalence of comorbidities but the unavoidable decisions in the allocation of limited intensive care resources to those who are more likely to survive – a decision that no physician ever wants to make.

The authors also report the characteristics and outcomes of individuals with and without acute HF; noting older age, atrial arrhythmias, chronic HF and chronic obstructive pulmonary disease being independent predictors. However, most patients (78%) who presented with acute HF after COVID-19 infection did not have a prior history of HF. Even though older age was a predictor of acute HF in this study, it is important to note that younger individuals are also at risk of developing HF following infection with COVID-19.[9]

Trying to diagnose acute HF in individuals with COVID-19 can be difficult because bedside examinations and investigations such as transthoracic echocardiography are less frequently used to avoid risk of transmission to healthcare workers and the use of precious personal protective equipment. In the present study, less than half the patients with a diagnosis of acute HF had echocardiographic confirmation of ventricular dysfunction.

The diagnosis of HF in hospitalized patients with COVID-19 is becoming more dependent on elevations in biomarkers of cardiac injury (troponin) and cardiac congestion (natriuretic peptides). This will lead to both an underdiagnosis of HF in those individuals without clearly elevated biomarkers, such as those patients with HF with preserved ejection fraction; and an overdiagnosis of HF in those individuals with elevations in troponin that may not be related to HF (e.g. type II myocardial infarction). The Cardiac Society of Australia and New Zealand released a position statement to help guide clinicians on the appropriate use and interpretation of the electrocardiogram, biomarkers and transthoracic echocardiogram (TTE) in hospitalized patients with COVID-19 infection. In particular, a TTE should be reserved for those individuals with a single elevated high-sensitivity troponin and abnormal electrocardiogram on presentation or those individuals with high-sensitivity troponins that continue to rise or new-onset tachyarrhythmias, even in the absence of overt HF symptoms.[9]

Although treatment options for COVID-19 are largely centred around best supportive care, trials have now shown that dexamethasone can reduce mortality in patients hospitalized with COVID-19 who are receiving respiratory support.[10] Whether dexamethasone can be safely and effectively used in HF patients with COVID-19 remains unknown. Other medications that have been used in COVID-19 such as hydroxychloroquine, darunavir and remdesivir may also have drug interactions with commonly used HF medications, and their effects on cardiovascular complications remain uncertain.[11]

The increasing rates of HF after COVID-19 infection may be related to several mechanisms. Firstly, COVID-19 may precipitate

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myocardial injury (e.g. fulminant myocarditis) through the release of pro-inflammatory cytokines. Critically ill patients with the severe acute respiratory syndrome virus during the early 21st century displayed activated innate and adaptive immune systems with pro-inflammatory cytokinaemia.[12] It follows that members of the interleukin family and tumour necrosis factors mediate cardiotoxicity by precipitating oxidative stress and activating apoptotic pathways.[13] A second postulated mechanism is that the virus directly infiltrates cardiomyocytes, which may trigger local damage to the myocardium. A series of 22 autopsies of COVID-19 patients demonstrated cardiac viral infiltration in the majority of patients.[14] The third mechanism for HF in COVID-19 may be related to increased thrombotic events. It is possible that elevations in troponin and natriuretic peptides in critically unwell individuals infected with COVID-19 are secondary to right heart strain from multiple pulmonary emboli. This hypothesis is further supported by a recent analysis that showed anticoagulation is associated with lower mortality and intubation rates in patients hospitalized with COVID-19.[15] In this respect, it may be right (rather than left) ventricular remodelling and/or dysfunction that is observed on a limited point of care TTE in such patients.

The consequent local inflammation may persist after resolution of viral symptoms and pose ongoing risks of arrhythmia and progression to clinical HF. A recent study found that 78% of patients with recently recovered COVID-19 infections had evidence of cardiac involvement, with 60% of patients having ongoing myocardial inflammation, independent of pre-existing conditions.[16]

Rey *et al.*[7] also demonstrated that withdrawal of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor II blockers (ARB) and mineralocorticoid receptor antagonists was associated with increased mortality. Although this analysis is heavily subject to selection bias, the results are consistent with prior trials that have shown that withdrawal of beta-blockers and ACE inhibitors/ARBs in patients hospitalized with HF is associated with worse outcomes. Concerns about withdrawal of ACE inhibitors and ARBs are particularly relevant to the COVID-19 pandemic, where initial laboratory studies suggested that COVID-19 invades the lung cells through binding of its spike protein S to ACE2 of lung cells.[17] Importantly, large registry studies have shown that ACE inhibitor and ARB use does not increase the risk of COVID-19 infections, and their use in infected individuals with COVID-19 is also safe.[18] The Chinese Heart Failure Association & National Heart Failure Committee and the Heart Failure Association of the European Society of Cardiology position statement guidelines recommend initiation and continuation of HF therapies in individuals with COVID-19 in the same manner as for non-COVID-19 infected patients. In fact, the guidelines advise that oral HF medications should be re-started before intensive care unit discharge in patients on mechanical ventilation.[11]

From a public health perspective, the current study by Rey *et al.*[7] serves as strong reminder that previously healthy individuals are still at risk of morbidity and mortality from COVID-19 infection and should seek medical attention early. Of course, prevention is the best cure.

Conflict of interest: none declared.

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