

## EDITORIAL

# Getting to the heart of the matter of COVID-19

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The coronavirus disease 2019 (COVID-19) has become a global pandemic which has had a major impact on hundreds of countries across the world. In less than 6 months, we have seen millions of people infected by the virus and over a quarter of a million deaths. The speed and rapidity of the spread of COVID-19 has left many countries scrambling to initiate public health interventions and to cope with the impact on healthcare provision in hospitals. In spite of this, the majority of people who are infected have either no symptoms or mild self-limiting disease. Understanding and identifying those at risk of severe manifestations or death has therefore become an imperative.

Our understanding of COVID-19 continues to evolve but it was clear early on that, like other viral pandemics, the severity of disease and mortality are greatest in older people. Going beyond age alone, further exploration of the co-morbidities has suggested an influence of co-existing cardiovascular disease. In this issue of *Heart*, Li and colleagues present a systematic review and meta-analysis of studies looking at the outcomes of patients with COVID-19 in relation to their history of cardiovascular disease and the presence of myocardial injury.<sup>1</sup> This is a rapidly evolving field and it is amazing to observe that this systematic review has already distilled data from over 3,000 patients in as little as a 3-month period, such is the global scientific impetus to share knowledge. Their findings confirm a strong and largely consistent association of an increased risk of mortality with hypertension and especially cardiovascular disease which has a 4-5-fold increased risk. They also report a near 20-fold increased mortality associated with the presence of myocardial injury defined as a rise in plasma cardiac troponin concentrations, albeit with much greater uncertainty and between-study variability.

What underlies these associations? There is the strong association of age with increasing cardiovascular disease. This means that the link with cardiovascular disease may either be a mediator of the influence of age on outcome or is co-associated but not causally related to the adverse outcome. The authors aim to shed light on this by providing information about the level of adjustment for the studies included. Reassuringly, the larger studies that give greater weight to the pooled estimates seem to have reported adjusted estimates. Together with the relatively consistent pattern for mortality across studies, this suggests that differences in age are unlikely to explain fully the excess risk associated with cardiovascular disease. Indeed, the findings seem broadly consistent with another report that showed a 2-3-fold risk of death for several subcategories of cardiovascular disease.<sup>2</sup>

Another possible explanation for these associations is that the presence of cardiovascular disease is not only an indicator of older age but a marker of other non-cardiovascular comorbidities. Indeed, as shown by others, the burden of major comorbidities in people presenting with cardiovascular diseases is high, even when age is taken into account, and about half are due to unrelated conditions such as depression, asthma and arthritis.<sup>3</sup> Thus, in absence of systematic ascertainment of all major comorbidities, it is possible that the reported associations are a reflection of incomplete adjustment for the poorer health status of patients with cardiovascular disease.

Nonetheless, there are a number of reasons to indicate that cardiovascular disease is mechanistically related to adverse outcome of COVID-19. The first well described mechanism is the known association of cardiovascular events with respiratory tract infections whereby acute infections in people with prior cardiovascular disease can trigger

myocardial infarction and cardiovascular events.<sup>4,5</sup> This will occur irrespective of a viral or bacterial aetiology of the chest infection. Alternatively, COVID-19 could directly cause cardiovascular events and hence explain the excess mortality in patients with prior disease. The mode of viral infection includes the binding of the severe acute respiratory syndrome coronavirus 2 to the angiotensin-converting enzyme type 2 (ACE2) which is highly expressed on endothelial cells. This could plausibly lead to dysfunction or denudation of the endothelium throughout the circulation. As such, widespread exposure of the vascular intima or erosion of atherosclerotic plaque following endothelial denudation is highly likely to result venous and arterial thrombosis. Indeed, there are growing reports of systemic and disseminated thromboembolism in patients affected by COVID-19.<sup>6,7</sup> This has led some to suggest antithrombotic interventions in these patients could have a beneficial impact on patient outcome.

The powerful impact of the presence of myocardial injury on subsequent mortality is an extremely important finding that will assist in identifying patients at greatest risk. On one level, this should not be surprising since troponin is an excellent marker of prognostic risk in a number of diverse settings and will be a further measure of multiorgan failure.<sup>8</sup> However, given the association of mortality with prior cardiovascular disease, there are many other considerations to take into account. There have undoubtedly been cases of acute coronary syndrome, type 2 myocardial infarction, takotsubo cardiomyopathy and myocarditis that have occurred in patients with COVID-19. Some of these cases have been precipitated by the illness and others have happened concurrently, some without a causal association. Therefore, it is important to be vigilant for primary cardiac disease since it is important not to miss the opportunity to treat reversible causes of cardiovascular disease. However, the

overall prevalence of primary cardiac problems appears to be modest and the majority of problems increasingly appears to be related to left and right ventricular systolic dysfunction. The latter in particular seems to be an adverse prognostic sign and is likely to be indicative of severity of the viral pneumonia or pulmonary thromboembolism.

Overall, the systematic review by Li and colleagues has confirmed that, in patients with COVID-19, there are strong associations between mortality and cardiovascular disease or cardiac injury. These observed associations lend major support to the hypothesis of direct and indirect cardiovascular consequences as being a contributor to or mediator of the increased mortality seen in patients with COVID-19. What therapeutic interventions can be used to limit or to prevent these adverse cardiovascular consequences has yet to be established although there are currently an overwhelming number of therapeutic interventions being proposed to try and address these questions.

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