Sharpening focus through wider collaboration: evolving heterogeneity in the bi-directional relationship between cardiovascular disease and COVID-19

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The recent outbreak of a novel coronavirus illness (coronavirus disease 2019; COVID-19) has emerged as a public health crisis of global proportions. The cardiology community has been captivated by COVID-19, perhaps more than any other systemic disease in history, due to its apparent links with cardiovascular disease (CVD). Researchers rapidly pivoted attention to concentrate on the disease with initial case series and single centre studies suggesting poor outcomes in patients with prior cardiac conditions, and soon after reports of a high prevalence of cardiovascular complications. However now, more than a year since the pandemic's onset, larger studies have emerged that are beginning to refine our understanding of the complex interplay between COVID-19 and CVD.

Previous COVID-19 studies have predominantly evaluated the association between pre-existing chronic cardiac disease and COVID-19 related mortality, where all cardiac conditions are combined and analyzed together.[1,2,3] In this issue of *European Heart Journal*, the CAPACITY-COVID and LEOSS (Lean European Open Survey on SARS-CoV-2 Infected Patients) study groups report on their collaborative retrospective study using coordinated large scale data collection to evaluate heterogeneity in associations between various heart disease subtypes and in-hospital mortality.[4] The authors describe and compare the disease course and outcomes from over 16,000 hospitalized COVID-19 patients across 18 countries admitted between March and May 2021, including more than one-third of patients with pre-existing cardiac disease. Although overall crude mortality was almost twice as high in those with prior CVD when compared to those without, after multivariable adjustment this difference was no longer significant. Furthermore although for patients with heart failure the relative risk of death in hospital was significantly higher and related to severity (NYHA III/IV RR 1.41, 1.20–1.64), for the majority of cardiovascular disorders including ischaemic heart disease and atrial fibrillation outcomes were similar to patients without CVD, This heterogeneity in outcomes between different cardiovascular conditions with COVID-19 provides support for a more stratified public health approach during the pandemic. Examples might include prioritising those

with heart failure at highest risk for early vaccine administration or reducing shielding advice for those considered at lower risk.

The contrast in these findings when compared with those from prior smaller studies highlights the importance firstly of robust adjustment for co-variants when considering the association of CVD on outcomes. Second, and perhaps more importantly, they demonstrate that 'prior CVD' should no longer be considered a single uniform risk factor but should be disaggregated into heart disease subtypes to better stratify risk and inform decision making. This is relevant not only for COVID-19 but should be considered as an approach across other clinical scenarios when analysing the impact of cardiac conditions on outcomes. Unfortunately, although intuitive, in practice this presents challenges with study design requiring significantly larger sample sizes and multi-centre support for delivery.

Here perhaps COVID-19 has provided a unique opportunity for progress. The urgent public health crisis has led to international focus on prioritising large-scale collaborative studies to answer pertinent clinical questions in a timely manner. Both LEOSS and CAPACITY-COVID are examples of such efforts, having received support from national and international professional organizations including endorsement by the European Society of Cardiology (ESC) for international enrolment in CAPACITY-COVID. Similarly combining results from independent (potentially competing) clinical studies to accelerate delivery of results was rare prior to COVID-19, however the expert committees of LEOSS and CAPACITY-COVID should be congratulated for adopting this approach in the current study.

The study also assessed the prevalence of cardiovascular complications of severe SARS-CoV-2 infection, given the presumed bidirectional relationship between CVD and COVID-19. SARS-CoV-2 binds to the ACE2 receptor expressed in cardiac myocytes, has been found in autopsy specimens and hence could potentially cause myocarditis.[5] Elevated troponin levels are both common and prognostic in patients hospitalised with COVID-19, and asymptomatic abnormalities have been reported on cardiovascular imaging studies following severe disease.[6] However, despite targeted

data collection for cardiovascular complications, the current study found clinical cardiac adverse effects to be uncommon, with an overall prevalence of <2%. In contrast, venous thromboembolism was common despite the enhanced antithrombotic prophylactic strategies instituted after the first wave of the pandemic, with pulmonary emboli found in more than one in ten patients admitted to intensive care and overall prevalence 3-4 times higher when compared to seasonal influenza.[7] The multicentre ISARIC study, which prospectively collected in-hospital COVID-19 complications from over 80,000 patients in the United Kingdom starting early during the pandemic, has recently reported cardiac complication rates almost twice higher than those found in the current study,[3] despite lower rates of venous thromboembolism. One common finding however was that thromboembolic complications are unexpectedly less commonly reported among patients with known cardiac disease, possibly related to pre-admission anticoagulant or antiplatelet prescription. The reasons behind the differences between the current study and ISARIC remain unclear, particularly given the similarities in clinical and demographic characteristics of the study cohorts. The one major difference is in the timing of data collection – ISARIC reported findings from patients hospitalised between January and August 2020, whereas the current study included patients hospitalised between March and May 2021. In the interval between these periods the findings of randomised clinical trials and the inevitable growth in clinical experience resulted in changes to the management of patients with severe COVID-19 (including dexamethasone administration,[8] judicious fluid management and empirical anticoagulation for those at highest risk[9]), any of which may have impacted cardiac complication rates. This highlights the changing pattern of patient demographics, clinical manifestations and outcomes as the pandemic progresses – with the additional impact of vaccination likely to result in widening of the geographical and socio-economic differences in COVID-19. The bi-directional relationship between COVID-19 and CVD is therefore likely to evolve, with increasing heterogeneity as time progresses (Figure).

There are several considerations left to be answered in future studies. Despite collaboration between LEOSS and CAPACITY-COVID, the combined dataset lacked sufficient power to draw

conclusions on the interaction of age in the association between COVID-19 and CVD. Second, whilst ethnicity is known to be relevant to SARS-CoV-2 infection, the demographic of this current cohort is narrow (84.5% white), with no adjustment for ethnicity in multivariable models. It is also important to recognise that the scope of this study is relatively narrow, with focus solely on in-hospital survival status and cardiovascular complications following severe COVID-19. Understanding the effect of both severe and (the more prevalent) community COVID-19 on late cardiovascular complications and overall functional recovery requires further investigation, which will demand careful data collection across both hospital and primary care data. Recently resources linking individual person level data across healthcare settings have been developed to address this issue,[10] and the results which will emerge over the coming months are likely to improve our understanding of this complex inter-relationship. Currently however the authors are to be congratulated for coordinating data from such a large number of centres over eighteen countries during a pandemic. Their paper serves to emphasise the strength of scientific collaboration across Europe and beyond, and has highlighted that a 'one-size-fits-all' approach to patients with CVD in the pandemic may no longer be appropriate.

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