Weekly Journal Scan

SARS-CoV-2 infection markedly increases long-term cardiovascular risk

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Comment on 'Long-term cardiovascular outcomes of COVID-19' which was published in *Nat Med*. https://doi.org/10.1038/s41591-022-01689-3.

Key Points

- To characterize the post-acute cardiovascular (CV) manifestations of coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, the study analysed the national healthcare databases from the United States Veterans Health Administration (VHA) system.[1] A cohort of 153 760 individuals who survived the first 30 days of COVID-19 was identified. The analysis regarded the time frame between 1 March 2020 and 15 January 2021, preceding the delta and omicron variants of SARS-CoV-2, as well as the wide availability of vaccines.
- Two large control cohorts were also built: a contemporary cohort consisting of 5 637 647 veterans with no clinical evidence of COVID-19 and a historical cohort from 2017 including an additional 5 859 411 veterans. The risks and 12-month burdens of a set of pre-specified incident CV outcomes were estimated in the overall COVID-19 cohort and according to care setting of the acute infection [non-hospitalized ($n = 131\,612$), hospitalized ($n = 16\,760$)], and admitted to intensive care unit ($n = 5388$)], and compared with those of the control cohorts.
- Patients who had COVID-19 had a 63% higher risk of developing any of the 20 pre-specified CV outcomes over 12 months than the contemporary control cohort [hazard ratio (HR), 1.63; 95% confidence interval (CI), 1.59–1.68]. The adjusted excess burden of CV outcomes due to COVID-19 per 1000 persons at 12 months was 45.3 (95% CI, 42.2–48.4).
- Compared with the contemporary control group, COVID-19 patients experienced a 55% higher rate of major adverse cardiovascular events, a composite of myocardial infarction (MI), stroke, and all-cause mortality (HR, 1.55; 95% CI, 1.50–1.60; burden 23.5, 95% CI 21.5–25.5). They were more likely to have a stroke (HR, 1.52; 1.43–1.62; burden 4.0, 3.3–4.8), dysrhythmias (in particular atrial fibrillation: HR, 1.71; 1.64–1.79; burden 10.7, 9.6–11.9), myocarditis and pericarditis (HR, 2.02; 1.77–2.30; burden 1.2, 0.9–1.6), ischaemic heart disease including acute coronary syndrome (HR, 1.72; 1.56–1.90; burden 5.3, 4.1–6.7), and MI (HR, 1.63; 1.51–1.75; burden 2.9, 2.4–3.5), heart failure (HF) (HR, 1.72; 1.65–1.80; burden 11.6, 10.5–12.8), thromboembolic disorders including pulmonary embolism (HR, 2.93; 2.73–3.15; burden 5.5, 4.9–6.1).
- These results were consistent in all subgroups. The risks and 12-month burdens of CV outcomes increased according to the severity of the acute infection but were also observed in those with mild COVID-19 symptoms. Consistent results were found when the historical control cohort instead of the contemporary control cohort was used as reference.

Comment

Cardiac injury is common during acute COVID-19.[2,3] Accordingly, imaging abnormalities of the heart, including inflammation, or inflammation plus scarring, are commonly found irrespective of the severity of the acute illness.[4] Acute cardiac involvement has a multifactorial aetiology,[5–7] and is associated with worse short-term outcomes.[2,3]

The analysis of the VHA healthcare databases revealed a surprisingly broad array of CV abnormalities beyond the acute phase of COVID-19, including coronary and cerebrovascular events, dysrhythmias, pericarditis, myocarditis, HF, thromboembolic disease, and other cardiac disorders whose incidence was amplified in 12 months.[1] These results add to a growing body of data highlighting a broad variety of symptoms from brain fog and exercise fatigue to heart-related issues that some patients experience past the initial phase of SARS-CoV-2 infection.[8–10] In the current analysis of VHA, risks of CV events were higher in those with pre-existing CV disease and those suffering from more severe COVID-19. However, the risks were evident across

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all subgroups, including people who had mild COVID-19 and did not need to be hospitalized during the acute phase of the disease, and those who did not have a known CV condition before their infection.[1] These risk estimates were remarkably higher than those related to other viral infections, including seasonal flu.[11] Considering the CV damage likely suffered by patients who postponed medical care, who switched to more sedentary lifestyles and unhealthy diets, and the stress of the pandemic itself, a surge in new-onset CV diseases directly or indirectly linked to the SARS-CoV-2 infection would be expected, in addition to a worsening of pre-existing CV disease.

While the large sample size, the scrutiny of the VHA extensive electronic health record system, and the multiple sensitivity analyses performed to challenge the robustness of results are clear strengths of the study, the VHA cohort—largely male and white—is not representative of the entire population. Moreover, as the study analysed electronic databases, misclassification bias and residual confounders cannot be excluded; in addition, information on causes of death was not available.[1] Also, subjects in the contemporary control group had not been tested for SARS-CoV-2 infection, so it cannot be excluded that some of them suffered mild infections while being asymptomatic.[1] The reduced access to primary and secondary CV prevention facilities and drug treatment for those who had COVID-19 might also have influenced CV disease development and complications. Finally, the data of this study were obtained before vaccines were widely available. As vaccination has been linked to a significant decrease in the onset of severe COVID-19 symptoms, hospitalizations, and serious complications, the data presented here suggest that vaccination may play an important role in preventing or limiting CV disease.

Much remains to be learned about the natural history of post-COVID-19 CV complications and the clinical implications of these findings. The mechanisms that underlie the association between COVID-19 and development of CV diseases in the post-acute phase are still unknown. Several mechanisms have been proposed, including direct viral infection of cardiac tissue and endothelial cells, inflammation and persistent hyperactive immune response following the disease, complement-mediated coagulopathy and microangiopathy, and dysregulation of the renin–angiotensin–aldosterone system.[8,9] Further research is needed to characterize specific causes and identify optimal prevention and treatment strategies. It is also unclear if different variants of the virus causing different disease severity may carry different levels of CV risks. As the virus continues to mutate and new variants emerge, as treatment strategies of acute and post-acute COVID-19 evolve and vaccine uptake improves, it is likely that CV complications of COVID-19 might be reduced.

Regardless of the mechanisms, variants, and vaccines, with the enormous number of patients infected, cardiologists should be prepared to deal with an unpredicted wave of CV diseases related to COVID-19 over the next years.[10] Because of their chronic nature, these conditions may have long-lasting consequences for patients and represent a growing burden for the health care systems. Therefore, this study emphasizes the importance of including CV screening in the healthcare of patients who survived the acute episode of COVID-19, with a focused follow-up plan.

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