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COVID-19

Long COVID and cardiovascular disease: a learning health system approach

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Cardiovascular disease is both a risk factor and potential outcome of the direct, indirect and long-term effects of COVID-19. A recent analysis in >150,000 survivors of COVID-19 demonstrates an increased 1-year risk of numerous cardiovascular diseases. Preventing and managing this new disease burden presents challenges to health systems and requires a learning health system approach.

Refers to Xie, Y. et al. Long-term cardiovascular outcomes of COVID-19. *Nat. Med.* https://doi.org/10.1038/s41591-022-01689-3 (2022).

More than two years into the coronavirus disease 2019 (COVID-19) pandemic, cardiovascular disease (CVD) has emerged as a risk factor and an outcome for both acute SARS-CoV-2 infection (direct and indirect effects[1,2]) and its longer-term effects, known as long COVID, which can affect up to 54% of patients who recover from the acute infection[3]. Long COVID is becoming a major health burden in many countries, including the UK, where 1.1 million people have reported persistent symptoms beyond 12 weeks after the initial infection[4]. The risk of CVD after COVID-19 has been studied in specific settings and cohorts (such as in hospitalized individuals), as well as in patients with a history of CVD. However, until now, the full spectrum of post-acute cardiovascular manifestations of COVID-19 has not been characterized in patients with long COVID. A new study by Xie and colleagues revealed the extent of the 1-year burden of CVD among survivors of acute COVID-19 (REF.[5]). Therefore, further mechanistic research and clinical evidence, as well as improved patient care, are urgently needed: a 'learning health system' approach might effectively mitigate the adverse health effects of long COVID, including long-term cardiovascular complications (FIG. 1).

Xie and colleagues systematically assessed the incidence of numerous CVD subtypes in 153,760 individuals with COVID-19 from the US Department of Veterans Affairs national database who survived beyond 30 days, comparing them with control groups from the same database from before and during the pandemic and w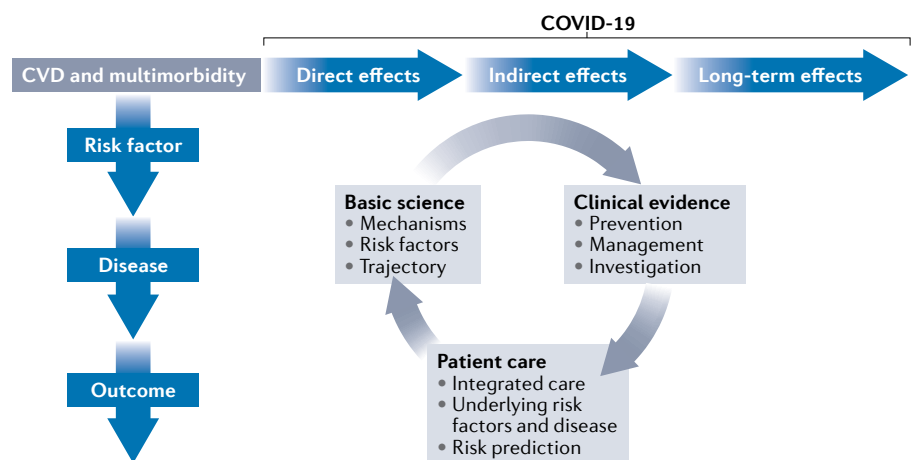ith no evidence of SARS-CoV-2 infection[5]. The investigators found an increased risk and excess burden of incident CVDs among all subgroup of patients with COVID-19 (non-hospitalized, hospitalized and those admitted to the intensive care unit) compared with the control groups. These diseases included atrial fibrillation (HR 1.71, 95% CI 1.64–1.79), ischaemic heart disease (HR 1.72, 95% CI 1.56–1.90), pericarditis (HR 1.85, 95% CI 1.61–2.13), myocarditis (HR 5.38, 95% CI 3.80–7.59), heart failure (HR 1.72, 95% CI 1.65–1.80) and thromboembolic disease (HR 2.93, 95% CI 2.73–3.15)[5].

> COVID-19 can increase the risk of developing CVD after the acute infection, even in individuals who were at low risk of CVD before having COVID-19

The potential mechanisms underlying the cardiovascular consequences of acute SARS-CoV-2 infection include a chronic inflammatory response induced by viral persistence in heart tissue, molecular mimicry that invokes an autoimmune response to cardiac antigens, and persistent endothelial and microvascular dysfunction[6]. A 2022

Fig. 1 | **A learning health system approach for CVD, multimorbidity and long COVID.** A learning health system approach is needed to address gaps in basic science research, clinical evidence and patient care for cardiovascular disease (CVD), multimorbidity and long COVID. Patients with CVD and multimorbidity are at increased risk of the direct, indirect and long-term effects of COVID-19. A coordinated strategy to tackle CVD and multimorbidity, including in the context of COVID-19, requires understanding of the risk factors, the disease processes and the potential outcomes. The learning health system approach allows these knowledge gaps to be addressed effectively.

study involving 70 consecutive patients with SARS-CoV-2 infection in a dedicated post-COVID-19 outpatient clinic in Greece (mean age of 54.5 years, 62.5% male and 32.9% hospitalized for COVID-19) suggested that arterial stiffening, endothelial dysfunction and a persistently high oxidative burden might contribute to cardiac dysfunction, which had not fully recovered at 12 months after the acute infection[7]. Further prospective studies are needed to uncover the underlying biological mechanisms and predisposing risk factors that lead to the cardiovascular sequelae in survivors of COVID-19.

Numerous cardiometabolic risk factors — such as obesity, smoking, hypertension and diabetes mellitus — are implicated in the interaction between COVID-19 and CVD[6], and prevention and management of these risk factors and diseases should be sustained. However, the increased risk of CVD described by Xie and colleagues occurred regardless of age, sex, ethnicity and the presence of cardiovascular risk factors or pre-existing CVD[5]. Therefore, COVID-19 can increase the risk of developing CVD after the acute infection, even in individuals who were at low risk of CVD before having COVID-19 (REF.[5]). In addition, although the study showed that cardiovascular risk increases in parallel with the severity of the acute COVID-19, even individuals with mild COVID-19 (that is, those who were not hospitalized) are at increased risk of CVD[7].

At present, no effective, evidence-based therapies exist for the prevention or management of long COVID. Vaccinations and antiviral medications are effective in reducing complications of acute SARS-CoV-2 infection, and might reduce the risk of long COVID. Future randomized clinical trials and observational studies should include long COVID and CVD as outcomes. In addition, future clinical trials must investigate the effect of strategies for modifying cardiovascular risk factors on the prevention and/or treatment of long COVID, which could offset the increased risk of incident CVD and multiorgan morbidity in the long term.

Long COVID can affect multiple organs over time, but the disease subtypes are yet to be fully characterized. Despite evidence of a high number of clinical investigations with normal findings in individuals with long COVID[8], the study by Xie and colleagues demonstrates that investigative strategies of cardiac and multiorgan function in long COVID — whether the techniques involve imaging or biomarker assessment — need to be evaluated for accuracy and cost-effectiveness[5]. Primary prevention remains the best strategy to avoid long COVID, including the related cardiovascular sequelae. Infection control strategies to avoid SARS-CoV-2 infection are still important, especially in patients at increased risk of CVD, who should continue to be prioritized in receiving the vaccine and subsequent booster doses.

The prevention, treatment and rehabilitation of CVD and long COVID require coordinated approaches. CVD management requires lifelong health-care considerations, whereas the long-term prognosis of and recovery from long COVID are yet to be defined. However, data from the study by Xie and colleagues confirm that long-term follow-up should occur only in certain patients with long COVID[5]. The concept of 'integrated care' has become central to the management of several long-term conditions, including chronic obstructive pulmonary disease and heart failure, and should be evaluated and implemented in patients with long COVID. Research studies (including the LOCOMOTION and STIMULATE-ICP studies) are underway to investigate the optimal management of long COVID, as well as to assess disease mechanisms and trajectories. The diagnosis and treatment of underlying conditions (including CVD) and risk factors are important for the long-term care of patients with long COVID. Multimorbidity is a risk factor for both CVD and long COVID, but was not fully analysed in the study by Xie and colleagues[5]. Multimorbidity and frailty are associated with increased incidence and progression of CVD, and should prompt CVD-risk screening and optimization to ensure evidence-based prevention and management[9]. Studies that focus on interventions for patients with multimorbidity who are at increased risk of CVD are scarce, despite known differences in CVD prognosis by multimorbidity clusters. Such studies are also needed in patients with long COVID, who require multidisciplinary and integrated care pathways.

Finally, personalized risk prediction is recommended in patients with CVD and those with acute COVID-19 (REF.[10]). Informatics and data science approaches are required in population-scale electronic health records, such as the national database used by Xie and colleagues, to develop practical risk-prediction tools for long COVID.

To summarize, bidirectional relationships exist between CVD and COVID-19. Multimorbidity and CVD are key considerations in patients with long COVID, who require multidisciplinary and integrated care. Long COVID, including cardiovascular complications, has potentially far-reaching implications for health system resources, including staffing, infrastructure and funding. The knowledge gaps in basic research, clinical evidence and patient care need to be addressed together to enable effective and timely management of long COVID. Future pandemic planning and preparedness should include modelling and consideration of CVDs and noncommunicable diseases, as well as potential long-term disease sequelae.

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