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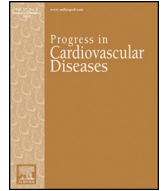
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## The acute and chronic implications of the COVID-19 virus on the cardiovascular system in adults: A systematic review

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### ABSTRACT

Despite coronavirus disease 2019 (COVID-19) primarily being identified as a respiratory illness, some patients who seemingly recovered from initial infection, developed chronic multi-system complications such as cardiovascular (CV), pulmonary and neurological issues leading to multiple organ injuries. However, to date, there is a dearth of understanding of the acute and chronic implications of a COVID-19 infection on the CV system in adults. A systematic review of the literature was conducted according to PRISMA guidelines and prospectively registered via Prospero (ID: CRD42022360444). The MEDLINE Ovid, Cochrane Library and PubMed databases were searched from inception to August 2022. The search strategy keywords and MeSH terms used included: 1) COVID; 2) coronavirus; 3) long COVID; 4) cardiovascular; and 5) cardiovascular disease. Reference lists of all relevant systematic reviews identified were searched for additional studies. A total of 11,332 records were retrieved from database searches, of which 310 records were duplicates. A further 9887 were eliminated following screening of titles and abstracts. After full-text screening of 1135 articles, 9 manuscripts were included for review. The evidence of CV implications post-COVID-19 infection is clear, and this must be addressed with appropriate management strategies that recognise the acute and chronic nature of cardiac injury in COVID-19 patients. Efficacious management strategies will be needed to address long standing issues and morbidity.

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Abbreviations: ACE2, Angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; cTn, Cardiac troponin; CV, Cardiovascular; CVD, Cardiovascular disease; IQR, Interquartile range; PRISMA, Preferred reporting items for systematic review and meta-analyses; vWF, von Willebrand factor; WHO, World Health Organization.

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## Introduction

In December 2019, the first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection COVID-19 was reported in Wuhan, China and rapidly spread worldwide.<sup>1,2</sup> In fact, coronavirus disease 2019 (COVID-19) is the most prevalent pandemic of the century with 3.5 million cases reported worldwide by May 2020.<sup>3</sup> The World Health Organization (WHO) declared Europe the epicentre of the pandemic on March 13th, 2020, based on more cases and deaths than the rest of the world.<sup>4</sup> To date, the WHO has recorded 618 million confirmed cases of COVID-19 worldwide and over 6.5 million deaths.<sup>5</sup> Clinical manifestation and features of acute COVID-19, including pathophysiology, diagnosis and symptom profiling have been carefully researched,<sup>6,7</sup> with a growing research agenda focused on the chronic multi-system impacts of COVID-19.<sup>8,9</sup>

Initially, COVID-19 was primarily identified as a respiratory illness with varying degrees of clinical manifestation and symptoms, including fever, cough, shortness of breath, loss or change in smell or taste, fatigue, sore throat, chill, and nasal congestion.<sup>10,11</sup> High-resolution chest computed tomography was established as the gold standard for identifying lungs that had been damaged by COVID-19 (with 90% sensitivity and 91% specificity) and helped identify patients requiring mechanical ventilation.<sup>12–14</sup> It quickly became evident that patients with underlying comorbidities were at an increased risk of more serious complications upon initial COVID-19 infection. A study by Kompaniyets and colleagues (2021) found that compared to people with no underlying conditions, the risk of death was 1.5 and 3.8 times higher for those with one comorbidity and over 10 comorbidities, respectively, therefore, demonstrating that the total number of underlying conditions is strongly associated with severity of COVID-19 illness.<sup>15</sup> Further, a meta-analysis involving 1527 patients with COVID-19 reported hypertension (17.1%), diabetes (9.7%), and cardiac and cerebrovascular disease (16.4%) were the most prevalent comorbidities and concluded that patients with previous cardiometabolic disease face a greater risk of infection and infection-related cardiac damage.<sup>3,16</sup>

Despite COVID-19 primarily being identified as a respiratory illness, some patients who seemingly recovered from the initial infection developed chronic issues and multi-system complications such as cardiovascular (CV), pulmonary and neurological, leading to multiple organ injuries.<sup>8,9</sup> It has been reported that many patients suffer CV complications both during and after COVID-19 infection including, myocarditis, acute coronary syndrome, myocardial injury, arrhythmia, impaired ventricular function, heart failure, multi-system inflammatory syndrome, venous and arterial thrombotic events, stroke, and coagulopathy.<sup>8,12,17,18</sup> COVID-19 infection is caused by the binding of a viral protein to human transmembrane angiotensin-converting enzyme 2 (ACE2) which is expressed in the lungs, as well as in the heart and blood vessels.<sup>3,19,20</sup> This 'cytokine storm' that is observed in COVID-19 patients contributes to endothelial damage, thrombosis and chronic inflammation leading to multi-organ failure and death.<sup>21–23</sup> Additionally, it has also been observed that 8–62% of patients hospitalised with COVID-19 have elevated cardiac troponin (cTn) that is suggestive of myocardial injury alongside being associated with greater disease severity, need for mechanical ventilation, and mortality.<sup>22,24,25</sup> Despite these clear associations between COVID-19 and the CV system, there is currently little consensus on the acute and chronic CV impacts and therefore uncertainty as to how best to treat and rehabilitate patients.<sup>9</sup> Accordingly, this systematic review aimed to synthesise the acute and chronic implications of COVID-19 infection on the CV system in adults.

## Methods

The preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines were followed when conducting and reporting this prospectively registered systematic review (PROSPERO ID: CRD42022360444).<sup>26</sup>

## Eligibility criteria

We included trials published in the English language that studied the effect of COVID-19 on the CV system. Manuscripts were excluded if they were protocols, reports, position statements or case series reports. Participants must have been aged >18 years and have suspected or confirmed SARS-CoV-2 infection. Studies involving specific clinical populations e.g., HIV, organ transplantation, asthma and post-vaccination cohorts were excluded. Studies that included at least one of the following cardio-metabolic health outcomes or clinical end-points were eligible: 1) micro- or macrovascular function; 2) bloodborne biomarkers of cardiometabolic health; 3) CV mortality; 4) resting blood pressure or heart rate; 5) all-cause mortality; 6) non-fatal CV end-points (e.g., myocardial infarction, coronary artery bypass grafting); 7) percutaneous transluminal coronary angioplasty; angina or angiographically-defined coronary heart disease; 8) stroke; 9) carotid endarterectomy; and 10) peripheral arterial disease.

## Search strategy

The MEDLINE Ovid, Cochrane Library and PubMed databases were searched from inception to August 2022. The search strategy keywords, and MeSH terms used included: 1) COVID; 2) coronavirus; 3) long COVID; 4) cardiovascular; and 5) cardiovascular disease. Reference lists of all relevant systematic reviews identified were searched for additional studies. All searches were conducted by the same author (RA), with search results collated using Rayyan software,<sup>27</sup> and duplicates removed. All titles and abstracts were screened by one reviewer (RA). Screening of full texts was performed by two independent reviewers (RA and MF) with disagreements resolved through consensus.

## Data extraction

Two authors (RA and MF) independently extracted data using Microsoft Excel. Any disagreements were resolved via consensus. Extracted data included study design, participant demographics, intervention details and data for all outcomes.

## Results and discussion

A total of 11,332 records were retrieved from database searches, of which 310 records were duplicates. A further 9887 were then eliminated following a screening of titles and abstracts. After the full-text screening of 1135 articles, 9 manuscripts were found to be eligible for inclusion in this review (Fig. 1).

## Characteristics of studies

The 9 studies included comprised 2616 participants, with sample sizes of 10–659 per study. Summary details of the included studies and populations are presented in Table 1.

Five studies (55%) were conducted at a single site with the remaining four studies (45%) recruiting patients from multiple sites. The duration of the trials varied from 3 to 52 weeks with one study not stating the trial duration. Six studies (66.5%) involved drugs being administered to patients and three studies (33.5%) involved patients being instructed to exercise.

## Risk of bias

Risk of bias was assessed by one author (RA) using the Cochrane Risk of Bias tool<sup>28</sup> with risk of bias on the study level classified as 'low', 'unclear' or 'high' risk.<sup>29</sup> All trials were deemed to have some concerns for the overall risk of bias. Table 2 shows a summary of the risk of bias for each of the included studies.

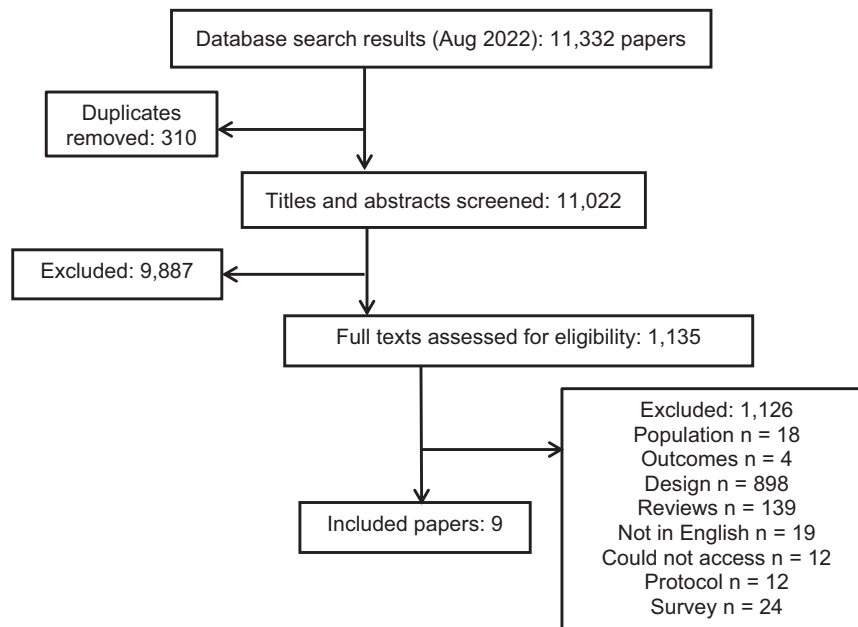


Fig. 1. PRISMA flow diagram.

An acceptable randomisation method was used in seven studies whilst two studies were deemed to have some concerns regarding bias due to insufficient information to determine randomisation methods. Six studies were deemed to be at low risk of deviation from the intervention whereas three studies were deemed to have some concerns. All studies were at low risk of bias due to missing data. Acceptable measurement of outcomes was evident in eight studies, one study had some concerns regarding bias due to missing information. All studies were deemed to have some concern surrounding the selection of reported results as it was not clear whether the data had been analysed by a pre-trial plan.

#### Acute implications

Eight papers examined the acute (<12 weeks) implications of COVID-19 infection. Five studies involved pharmacological interventions; two studies used anticoagulants,<sup>30,31</sup> one study used lipase-releasing units (Sulodexide),<sup>32</sup> one study used monoclonal antibodies<sup>33</sup> and one study used angiotensin inhibitors and receptor blockers.<sup>34</sup> In a study conducted by Connors et al., patients were randomised to either Aspirin (81 mg a day) with a matching placebo, prophylactic-dose apixaban (2 × 2.5 mg a day), apixaban at the therapeutic dose (2 × 5 mg a day), or placebo (2 × day) for 45 days, with a 30-day follow-up.<sup>30</sup> The study reported no deaths, myocardial infarction, or major bleeding. There was one deep vein thrombosis reported in the aspirin group and three hospitalisations due to cardiopulmonary issues (1 patient in the Apixaban 2 × 2.5 mg and 2 patients in the Apixaban 2 × 5 mg).<sup>30</sup>

Gonzalez-Ochoa and colleagues randomised patients to a treatment dose of 500 lipase releasing units (Sulodexide) twice daily or a placebo group for three weeks.<sup>32</sup> Three deaths were reported in the treatment group compared to 7 in the placebo. The study also reported D-dimer and c-reactive protein (CRP) at day 14. D-dimer levels were significantly different at  $465 \pm 630$  ng/dL and  $898 \pm 1215$  ng/dL in the treatment and placebo groups respectively. CRP level was also significantly different at day 14 with  $12.5 \pm 10.2$  mg/dL in the treatment group and  $17 \pm 11.5$  mg/dL in the placebo group.<sup>32</sup>

In a further study conducted by Leuker et al., patients were randomly assigned in a 1:1 ratio to receive double-blind treatment with a single intravenous dose of crizanlizumab 5 mg/kg or placebo.<sup>33</sup> They reported

change from baseline to day 14 in P-selectin, D-dimer, CRP and von Willebrand factor (vWF). P-selectin was significantly different in the treatment group compared to the placebo group at day 14 ( $12 \pm 10$  ng/mL and  $48 \pm 24$  ng/mL respectively). D-dimer concentration was reported as median (IQR) and at day 14 was 1.5 (0.5–1.9) mg/L and 0.7 (0.5–0.8) mg/L in the treatment and placebo groups respectively. CRP was 2.5 (1.1–5.1) mg/dL in the treatment group compared to 1.3 (0.6–4.9) mg/dL in placebo and vWF was 2.7 (1.9–4.2) IU/mL and 4.6 (2.6–7.4) IU/mL in the treatment and placebo groups, respectively.<sup>33</sup>

In a study conducted by Lopes and colleagues, patients were randomised to either discontinue or continue angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers therapy for 30 days.<sup>34</sup> Following the 30-day intervention, 9 deaths were reported in each group alongside 25 and 15 myocardial infarctions in the discontinue and continue groups respectively. Additionally, new, or worsening heart failure was reported in 14 patients who discontinued use and in 16 patients who continued use. The study also reported median (IQR) CRP levels as 4.3 (1.6 to 8.9) mg/L and 4.2 (1.4–7.4) mg/L in the discontinue and continue groups respectively.<sup>34</sup>

The final study involving a pharmacological intervention was conducted by Sholzberg et al., which randomised patients to a therapeutic or prophylactic dose of heparin (low molecular weight or unfractionated heparin), to be continued until hospital discharge, day 28, or death (whichever was soonest).<sup>31</sup> Four deaths were reported in the therapeutic group compared to 18 in the prophylactic group. Furthermore, two cases of thromboembolism were reported in the therapeutic group compared to 7 in the prophylactic group.<sup>31</sup>

A further three studies involved exercise interventions. In a study by Teixeira do Amaral et al., patients were randomly assigned to either a 12-week (tele-supervised and home-based) exercise training group or a control group.<sup>35</sup> Following the intervention period, the heart rate was  $80 \pm 13$  bpm in the intervention group and  $77 \pm 13$  bpm in the control group. Systolic blood pressure was  $118 \pm 21$  mmHg and  $114 \pm 18$  mmHg in the intervention and control groups respectively and diastolic blood pressure was  $82 \pm 9$  mmHg in the intervention group and  $75 \pm 10$  mmHg in the control group.<sup>35</sup>

Foged and colleagues conducted a randomised cross-over trial of three different supervised high-intensity interval training protocols: 1) 4 intervals of 4 min starting at 75% max workload; 2) 6 intervals of

**Table 1**  
Study characteristics.

Author (Year)	Title	Country	Number of centres	Total sample size (n = male, n = female)	Trial duration	Age (Mean + –SD)	Ethnicity	Intervention
Barco et al., (2022) <sup>45</sup>	Enoxaparin for Primary Thromboprophylaxis in Symptomatic Outpatients with COVID-19 (OVID): A Randomised, Open-Label, Parallel-Group, Multicentre, Phase 3 Trial	Switzerland, Germany	8	472 (M = 255, F = 217)	90 days	Median (IQR) Intervention = 56 (53–62) Comparator = 57 (53–62)	Stated	Receive either enoxaparin or standard of care (no thromboprophylaxis).
Connors et al., (2021) <sup>30</sup>	Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients with Clinically Stable Symptomatic COVID-19: The ACTIV-4B Randomised Clinical Trial	USA	52	657 (M = 388, F = 269)	11 weeks	Median (IQR) Aspirin = 54.0 (46.0–59.0) Apixaban 2.5 mg = 55.0 (46.0–61.0) Apixaban 5 mg = 52.0 (47.0–58.0) Placebo = 54.0 (45.0–59.0)	Stated	Aspirin (81 mg a day) with a matching placebo, prophylactic-dose apixaban (2 × 2.5 mg a day), apixaban the therapeutic dose (2 × 5 mg a day), or placebo (2 × day) for 45 days, with a 30-day follow-up.
Foged et al., (2021) <sup>36</sup>	Fidelity, Tolerability and Safety of Acute High-Intensity Interval Training After Hospitalisation for COVID-19: Randomised Cross-Over Trial	Denmark	Single	10 (M = 5, F = 5)	3 weeks	61 ± 8	Not stated	Randomised cross-over to three supervised high intensity interval training protocols: 4 × 4, 6 × 1, 10–20-30.
Gonzalez-Ochoa et al., (2021) <sup>32</sup>	Sulodexide in the Treatment of Patients with Early Stages Of COVID-19: Randomised Controlled Trial	Mexico	Single	243 (M = 115, F = 128)	36 days	Intervention = 55.3 ± 10.3 Comparator = 54 ± 10.9	Not stated	The treatment dose of 500 LRU (lipase releasing units) 2 x day.
Leucker et al., (2021) <sup>33</sup>	Effect Of Crizanlizumab, a P-Selectin Inhibitor, in COVID-19: Placebo-Controlled, Randomised Trial	USA	Single	50	30 days	Intervention = 54.6 ± 13.4 Comparator = 58 ± 17.7	Stated	Treatment with 1 intravenous dose of crizanlizumab 5.0 mg/kg or placebo.
Lopes et al., (2021) <sup>34</sup>	Effect of Discontinuing Vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of The Hospital in Patients Admitted with COVID-19: Randomised Clinical Trial	Brazil	Multiple	659 (M = 393, F = 266)	30 days	Median (IQR) Discontinue = 55 (46.1–36.1) Continue = 56.0 (46.1–66.1)	Not stated	Randomised to either discontinue or continue angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers therapy for 30 days.
Poncin et al., (2022) <sup>37</sup>	Impact of Surgical Mask on Performance and Cardiorespiratory Responses to Submaximal Exercise in COVID-19 Patients Near Hospital Discharge: Randomised Crossover Trial	Belgium	Single	28 (M = 19, F = 9)	Not stated	Median (IQR) 55 (47–59)	Not stated	Randomised to perform a 1-min sit-to-stand test while wearing a surgical mask followed by a 1-min sit-to-stand test without wearing a surgical mask.
Sholzberg et al., (2021) <sup>31</sup>	Effectiveness of Therapeutic Heparin Versus Prophylactic Heparin on Death, Mechanical Ventilation, or Intensive Care Unit Admission in Moderately Ill Patients with Covid-19 Admitted to Hospital: RAPID Randomised Clinical Trial	Brazil, Canada, Ireland, Saudi Arabia, United Arab Emirates, USA	28	465 (M = 264, F = 201)	28 days	Intervention = 60.4 ± 14.1 Comparator = 59.6 ± 15.5	Stated	Therapeutic dose or prophylactic dose heparin (low molecular weight or unfractionated heparin), is to be continued until hospital discharge, day 28, or death.
Teixeira do Amaral et al., (2022) <sup>57</sup>	Cardiovascular, Respiratory, and Functional Effects of Home-Based Exercise Training After COVID-19 Hospitalisation	USA	Single	32 (M = 7, F = 12)	12 weeks	Intervention = 51.9 ± 10.2 Comparator = 53.3 ± 11.6	Stated	Tele-supervised and home-based, exercise training protocol.

1 min at 100% max workload; and 3) 3 sets of 5 repeated 30 s/20 s/10 s intervals at varying paces in individuals recently discharged after hospitalisation for severe COVID-19.<sup>36</sup> There were no cases of angina reported and no changes were seen in echocardiograms following exercise. Time spent at >85% heart rate maximum was significantly different between exercise conditions 1 and 2 described above.<sup>36</sup>

Finally, Poncin et al., randomised patients to perform a 1-min sit-to-stand test while wearing a surgical mask followed by a 1-min sit-to-stand test without wearing a surgical mask, or vice versa.<sup>37</sup> Heart rate 120 s post-exercise was 85.3 ± 16.6 bpm and 84.2 ± 17.6 bpm with and without a mask respectively.<sup>37</sup>

Existing data indicate an increased risk of severe complications and mortality in those who contract COVID-19 with pre-existing CV disease (CVD) or who present with one or more risk factors such as hypertension, diabetes mellitus, hypercholesterolaemia, or obesity.<sup>38–40</sup> A report of 393 patients hospitalised with COVID-19 in the USA demonstrated that ~50% of patients had underlying hypertension (54% of ventilated patients), 36% were obese (43% of ventilated patients), 25% had diabetes mellitus (28% of ventilated patients) and 14% were diagnosed with coronary artery disease (19% of ventilated patients).<sup>41</sup> The high prevalence of obesity among those hospitalised with COVID-19 was also deemed to be a considerable risk factor for respiratory failure, prompting the need for mechanical ventilation.

**Table 2**  
Risk of bias assessment.

Author (Year)	Bias arising from the randomisation process	Bias arising from deviations from the intervention	Bias due to missing data	Bias in the measurement of outcome	Bias in the selection of reported result	The overall risk of bias
Barco et al., (2022)	–	–	–	–	?	?
Connors et al., (2021)	–	–	–	–	?	?
Foged et al., (2021)	–	?	–	–	?	?
Gonzalez-Ochoa et al., (2021)	–	–	–	–	?	?
Leucker et al., (2021)	–	–	–	–	?	?
Lopes et al., (2021)	–	–	–	–	?	?
Poncin et al., (2022)	?	?	–	–	?	?
Sholzberg et al., (2021)	–	?	–	–	?	?
Teixeira do Amaral et al., (2022)	?	–	–	?	?	?

During the initial stages of the COVID-19 pandemic, cardiac injury/insult was not part of routine clinical assessments. As the evidence and incidence of the multi-system nature of COVID-19 became apparent it became clear that acute myocardial injury (e.g., myocarditis, pericarditis, and impaired ventricular function) following infection with COVID-19 was common. Observed in around 20% of hospitalisations via imaging and investigative approaches, it is now apparent that the risk of cardiac injury occurs irrespective of pre-COVID-19 performance status and quality of life,<sup>42</sup> and is related to worse clinical outcomes and in-hospital mortality.<sup>20</sup> As a result of emerging evidence, cardiac screening is warranted among those that were asymptomatic or had a mild COVID-19 infection, and even those without traditional CV risk factors.<sup>43</sup> Common methods for this screening and to characterise cardiac injury include cardiac affectation with echocardiography and cardiac magnetic resonance. This has yielded mixed results to date and has limited generalisability due to a broad and often conflicting incidence of myocarditis criteria. Research has attempted to document the mechanisms associated with myocardial injury, but detailed investigative research is still required. Studies of inflammatory profiles, cardiac biomarkers, and detailed imaging studies, highlight the risk of COVID-19 on long-term CV outcomes,<sup>44</sup> and should now prompt investigations that use pharmacological interventions to offset and reduce the risk of acute CV illness and prolonged complications.

Despite the progress of knowledge in relation to managing acute COVID-19 infection, there remains a paucity of research that highlights effective treatment and management options to reduce associated CVD risk factors. To this date, research has investigated the use of pharmacological approaches in the management of acute COVID-19, however, what is clear from this review is that there is a lack of follow-up data to determine change in patient outcomes and performance status following a clinical intervention. There is also a dearth of literature that provides substantive evidence of effective treatment options with many studies being pilot, safety, tolerability, and feasibility work (see Table 1), which needs to be scaled-up to address the persistent and substantial burden in healthcare settings. Whilst the risk factors of CVD are well established, the association between acute COVID-19 infection and the progression to chronic requires further investigation.

### Chronic implications

Only one study followed patients for >12 weeks.<sup>45</sup> This study was a randomised control trial involving a pharmacological intervention with Enoxaparin (anticoagulant medication). The drug was administered to patients daily for 14 days with patients followed up at 3, 7, 14, 30, and 90 days for both CV events and major bleeding. However, this manuscript only presents data up to the 30-day follow-up, so it is not possible to extract data on chronic CV implications over a longer period.<sup>45</sup>

Chronic implications of COVID-19 often referred to as post-COVID-19 syndrome/condition and/or Long COVID which is defined by the WHO as an episodic condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection. Typically, this occurs

after 3 months following COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. The presentation of Long COVID is highly variable among patients with a broad profile and severity of symptoms that are undulating in nature which is underpinned by a series of complex manifestations. Prevalence data on Long COVID is scarce, but recent projections suggest that >144 million people are living with it globally, with long-term, disabling symptoms that broadly impact quality of life and functional status.<sup>46</sup> In the absence of efficacious treatment and interdisciplinary support services, the burden on healthcare settings is rising at an alarming rate<sup>47</sup> and may be considered the next global health crisis.<sup>48</sup> Puntmann et al., reported cardiac involvement in 78%, and ongoing inflammation in 60% of patients ( $n = 100$ ) in the months following COVID-19 infection.<sup>49</sup> The data here also demonstrates various cardiac symptoms which include but are not limited to; atypical chest pain (17%), palpitations (20%), and dyspnoea and exhaustion (36%). For those with CVD, Long COVID is of concern due to its association with high morbidity and exacerbation of underlying CV disorders. Studies examining patients with Long COVID have reported dyspnoea, joint pain and muscle weakness, chest pain, sleep difficulties and reduced quality of life,<sup>50</sup> but what remains unclear is the link between symptom prevalence and severity during the acute infection and subsequent progression to chronic issues.

With respect to CVD related issues, there remains a dearth of literature that demonstrates and documents the impacts on CV health. This is due to the time-course nature of the chronic disease which has yet to be realised in its entirety but is also confounded by a lack of knowledge and understanding of how COVID-19 impacts CV function and progression to chronic disease. In respect of the status of knowledge and understanding, most interventions are medicinal trials that look to offset, and prevent the progression of acute clinical manifestations, and investigate the efficacy of pharmaceutical approaches. Research until this point has attempted to elucidate the causes and cellular mechanisms to develop informed diagnostic and therapeutic strategies which have been the focus of multi-centre/national research groups (e.g., European Society of Cardiology) who produced a Scientific Statement on COVID-19-related CV complications covering myocardial and pericardial disease.<sup>51</sup> Whilst the need to establish effective methods is recognised, the role of interdisciplinary rehabilitation approaches to address long standing morbidity in Long COVID patients requires urgent consideration.<sup>52,53</sup> The role of increasing and promoting pro-active healthy living behaviours at this stage in the pandemic is essential in the prevention of chronic disease.<sup>54</sup> In the context of Long COVID and public health, the widespread implementation of national lockdown protocols to reduce viral transmission had a widespread impact on population health and well-being.<sup>55</sup> Whilst effective at addressing the immediate threat, the long-term behavioural determinants and their link to increased CVD are yet to be realised<sup>56</sup> and are likely to be complex.

From our review of the literature, it is apparent that there is a plethora of research that has conducted cohort analysis observations, cross-sectional studies, and retrospective analysis however to date, there

remains a lack of insight that can inform the development and testing of intervention approaches. From the available literature, it is apparent that a paucity of well-controlled, multi-centre and placebo-controlled intervention studies, are needed to profile and document changes in CVD prevalence and prognosis in relation to COVID-19.

### Future directions

This systematic review has highlighted that, whilst many studies are exploring the effects of COVID-19 on the CV system, many of these are observational or take a case-study design approach and as such, there is currently a lack of high-quality research investigating the acute and chronic implications of COVID-19 infection on the CV system. As we move into a period of living with COVID-19, more studies investigating the long-term consequences of COVID-19 infection are needed alongside more detailed studies regarding the management of acute and chronic cardiac injuries caused by COVID-19 infection. Additionally, future studies should also address, and consider, the issues surrounding long-standing morbidity that will likely lead to an increase in the prevalence of CVD in the future.

### Conclusion

The severity, extent, and long-term CV effects of COVID-19 and its treatments are yet to be understood in their entirety. Research demonstrating the acute and chronic implications of COVID-19 on CVD is limited and in need of increased recognition as we attempt to understand and develop effective treatment approaches. The evidence of CV involvement post-COVID-19 infection is clear, and this must be addressed with appropriate management strategies that recognise the acute and chronic nature of cardiac injury in COVID-19 patients whilst efficacious management strategies will also be needed to address long standing issues and morbidity.

### Declaration of Competing Interest

None.

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