Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Systematic review

Cardiac sequelae after coronavirus disease 2019 recovery: a systematic review

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has been implicated in a wide spectrum of cardiac manifestations following the acute phase of the disease.
Objectives: To assess the range of cardiac sequelae after COVID-19 recovery.
Data sources: PubMed, Embase, Scopus (inception through 17 February 2021) and Google scholar (2019 through 17 February 2021).
Study eligibility criteria: Prospective and retrospective studies, case reports and case series.
Participants: Adult patients assessed for cardiac manifestations after COVID-19 recovery.
Exposure: Severe acute respiratory syndrome coronavirus 2 infection diagnosed by PCR.
Methods: Systematic review.
Results: Thirty-five studies (fifteen prospective cohort, seven case reports, five cross-sectional, four case series, three retrospective cohort and one ambidirectional cohort) evaluating cardiac sequelae in 52 609 patients were included. Twenty-nine studies used objective cardiac assessments, mostly cardiac magnetic resonance imaging (CMR) in 16 studies, echocardiography in 15, electrocardiography (ECG) in 16 and cardiac biomarkers in 18. Most studies had a fair risk of bias. The median time from diagnosis/recovery to cardiac assessment was 48 days (1–180 days). Common short-term cardiac abnormalities (<3 months) included increased T1 (proportion: 30%), T2 (16%), pericardial effusion (15%) and late gadolinium enhancement (11%) on CMR, with symptoms such as chest pain (25%) and dyspnoea (36%). In the medium term (3–6 months), common changes included reduced left ventricular global longitudinal strain (30%) and late gadolinium enhancement (10%) on CMR, diastolic dysfunction (40%) on echocardiography and elevated N-terminal proB-type natriuretic peptide (18%). In addition, COVID-19 survivors had higher risk (risk ratio 3; 95% CI 2.7–3.2) of developing heart failure, arrythmias and myocardial infarction.
Conclusions: COVID-19 appears to be associated with persistent/*de novo* cardiac injury after recovery, particularly subclinical myocardial injury in the earlier phase and diastolic dysfunction later. Larger well-designed and controlled studies with baseline assessments are needed to better measure the extent of cardiac injury and its clinical impact. **Mohammad Said Ramadan, Clin Microbiol Infect 2021;27:1250**

Introduction

By 12 May 2021, more than 130 million individuals had confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection worldwide with more than 3.3 million related deaths [1]. Although it primarily affects the respiratory system,

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increasing reports imply that SARS-CoV-2 has extrapulmonary manifestations, including renal, gastrointestinal, neurological and cardiovascular [2]. SARS-CoV-2 and its interaction with the cardiovascular system is not entirely recognized and knowledge of the pathophysiological mechanisms behind such an interaction is still evolving [3–5]. These mechanisms include direct SARS-CoV-2 cardiac and endothelial injury, and indirect heart damage by induced cytokine storm, hypercoagulable state and hypoxia [4], all of which are increasingly reported in individuals with COVID-19, especially severe cases.

Cardiac manifestations in COVID-19 seem to occur over different time-points: acutely during COVID-19 and/or after apparent COVID-19 recovery [4,6–8]. Described cardiac complications in the acute phase (pre-recovery) include myocardial/pericardial inflammation, arrythmias, heart failure and sudden cardiac death, which are more commonly observed with increasing COVID-19 severity, presence of co-morbidities and older age [4]. Much less is known about the cardiac manifestations after apparent COVID-19 recovery [9,10]. Several studies found that more than half of patients still complain of cardiac symptoms many weeks post-COVID-19, with a similar proportion showing structural and functional cardiac abnormalities on diagnostic investigations [5,11,12].

Despite the advancing of COVID-19 treatments, long-term sequelae of this disease, including those pertinent to the heart, are expected to endure in survivors [13]. Hence, investigating cardiac involvement after COVID-19 recovery has a crucial clinical role to direct the development of post-discharge surveillance programmes along with public health, economic and social policies [14].

For these reasons, we performed a systematic review of the current literature data addressing cardiac sequelae in adults after COVID-19 recovery.

Materials and methods

All procedures used in this systematic review were consistent with PRISMA guidelines (see Supplementary material, Table S1).

Selection criteria and case definition

For this systematic review, we included retrospective and prospective studies, case series, cross-sectional studies and case reports that described adult patients who underwent any type of cardiac assessment (both objective and subjective) after COVID-19 recovery. We defined COVID-19 recovery, in line with experts' and the World Health Organization's (WHO) definition [15–17], as follows: (a) un-hospitalized patients: (i) asymptomatic/mild: 2 weeks after SARS-CoV-2 infection diagnosis, (ii) moderate-severe: 3 weeks after first COVID-19 diagnosis/evidence; (b) hospitalized patients: (i) after discharge for COVID-19 illness.

Search strategy and data sources

We conducted a comprehensive literature search of PubMed, Embase, Scopus and Google Scholar. PubMed, Embase and Scopus were searched from inception to and including 17 February 2021. Google Scholar was searched from 2019 to 2021 to minimize irrelevant results, as SARS-CoV-2 first appeared in 2019 so limiting results to 2019–2021 would not exclude any relevant studies. Individual journal searches were done for *Clinical Microbiology and Infection*, *The Lancet* and *JAMA*. *MedRxiv* was also searched for preprints, and Clinicaltrials.gov to identify COVID-19 treatments that may cause long-term cardiac effects. Study investigators (MSR and LB) designed the search strategies and conducted the searches. We used controlled vocabulary along with keywords to search for studies that investigated cardiac sequelae after the recovery of COVID-19 patients. Full search strategies are provided in the Supplementary material (Table S2). Email alerts were set to be received weekly on PubMed and were reviewed until 26 February 2021. The protocol has not been previously published.

Two authors (MSR and LB) independently reviewed the titles and abstracts of the identified studies, and those not complying with the study inclusion criteria (Table 1) were excluded. Reference lists of included studies were reviewed for relevant studies.

Data items and collection process

Two investigators (MSR and LB) independently extracted data from included articles into a developed form. Collected variables from each study included: study design, year of publication, country, number of patients, patient characteristics (age, setting, co-morbid conditions, cardiac disease history), methods of COVID-19 diagnosis and cardiac assessment, medications used, time between COVID-19 diagnosis/discharge and cardiac assessment, cardiac symptoms/diagnoses, results of cardiac magnetic resonance imaging (CMR), echocardiography, electrocardiography (ECG) and cardiac biomarkers, in addition to any other reported cardiac assessment method.

After removal of duplicates, two authors (MSR and LB) performed the study selection process, including the initial search for the identification of references, the selection of potentially relevant titles for review of abstracts and, among them, of those chosen for review of the full-length report, according to prespecified inclusion and exclusion criteria (Table 1). Conflicts in data abstraction were resolved by consensus. The screening and selection process are presented in Fig. 1.

Risk of bias

The Newcastle–Ottawa Scale was used to assess the quality of cohort non-randomized studies (see Supplementary material, Table S3). This scale is an ongoing collaboration between the Universities of Newcastle, Australia and Ottawa, Canada. The tool assesses risk of bias in selection of participants, comparability of study groups and ascertainment of either exposure or outcome of interest in case–control or cohort studies, respectively. Alternatively, we used the Joanna Briggs Institute critical appraisal checklist to assess the quality of cross-sectional studies (see Supplementary material, Table S4) [6], case reports (see Supplementary material, Table S5) [18] and case series (see Supplementary material, Table S6) [19]. The Joanna Briggs Institute is an independent, international, not-for-profit research and development organization based in the Faculty of Health and Medical Sciences at the University of Adelaide, South Australia. This was done at the outcome level for each study.

Analytical approach

Outcomes of interest included both subjective or reported cardiac symptoms and objectively measured outcomes. Data for cardiac sequelae were counted by patient. Where data were reported for multiple time-points, we presented the whole data set according to the time of assessment. Extracted outcomes included only those reported during the post-recovery period. For that purpose, we assessed the lower limit of the reported time range between COVID-19 and cardiac assessment. The lower limit needed to be equal to or greater than our pre-specified time to assessment criteria. Where outcomes were reported earlier than our inclusion criteria with no possibility of retrieving the relevant outcomes, the article was excluded.

Table 1
Inclusion and exclusion criteria for identified published studies

Inclusion	Exclusion
Population: Adult patients (≥18 years) post COVID-19 recovery Exposure: SARS-CoV-2 infection, diagnosed by PCR *Outcome:* Cardiac sequelae after recovery including symptoms, functional or structural changes *Study:* primary studies of COVID-19 recovered patients	*Population:* studies including participants <18 years old *Outcome:* cardiac manifestations before recovery (during acute infection) or studies investigating non-cardiac complications *Study:* Non primary studies including review articles and studies examining previous coronavirus strains, such as SARS-CoV and MERS-CoV

Abbreviations: COVID-19, coronavirus disease 2019; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2;

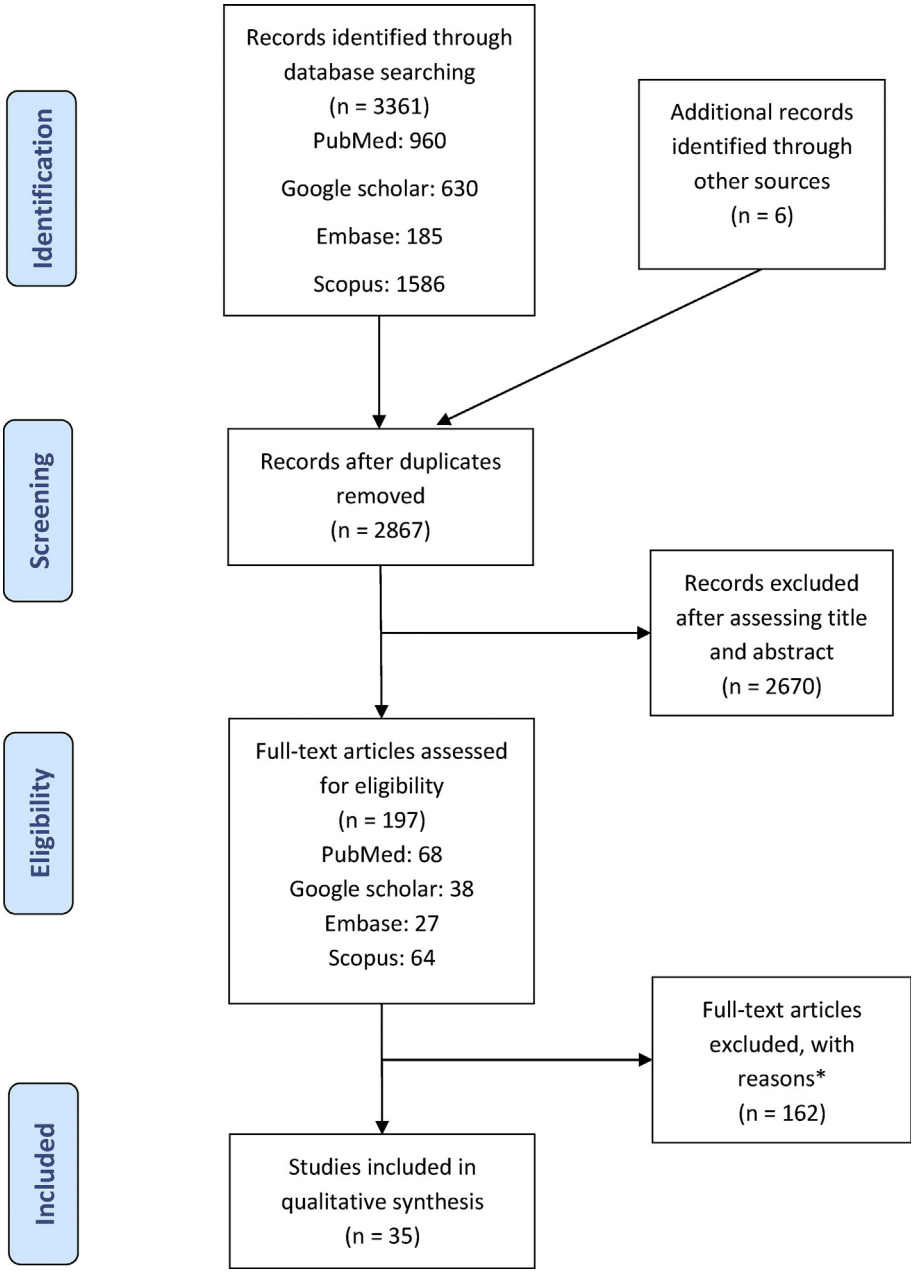

Fig. 1. PRISMA study flow diagram.

Similar outcomes from original studies were summarized in a proportion (observed cases/number of tested participants), median (in percentage), and range of reported findings (in percentage), excluding results from case reports. We present also outcomes stratified by COVID-19 severity, and short-term (<3 months) or medium-term (≥3 months) cardiac sequelae in per cent

proportions. COVID-19 severity was determined, if not explicitly stated in the study, using the WHO scale for COVID-19 severity [15]. All statistical analyses were carried out with SPSS V.26 (IBM, Armonk, NY, USA) or Microsoft Excel. Owing to the differences in design of the studies, we were not able to perform a meta-analysis.

Results

Results of the search

The database search identified 2867 records after removing duplicates. Through screening of titles and abstracts, we excluded 2670 records, leaving 197 to be assessed as full text. Of these, we finally included in this review 35 studies [5,8,11,12,20–50], of which three were pre-prints [5,23,50], three were presented as research letters [21,30,43] and three were presented as research communications [22,31,44]. The reasons for excluding 162 articles are listed in the PRISMA flow chart (see Fig. 1) [51].

Of the 35 studies included in this review, 15 were prospective cohort [8,12,22,29–31,34,35,40–42,44,45,47,50], seven were case reports [21,25,28,36,37,39,48], five had a cross-sectional design [5,20,24,26,38], four were case series [23,32,43,46], three were retrospective cohort [11,27,49] and one was an ambidirectional cohort study [33].

Findings

The main characteristics of all included studies are listed in the Supplementary material (Table S7).

Participants' characteristics

The number of included patients totalled 52 609 with a median age of 53 years (range 19–74 years) and one study not specifying the age, but inferring adults because they are collegiate athletes [23]. No study included children.

Twenty-two articles (63%) included patients previously hospitalized for COVID-19 (n = 51 117, 97.2%) [11,21,24,25,31–46,48,49], eight studies contained a mixed population of discharged patients and outpatients (n = 1330, 2.5%) [5,8,12,22,26,29,47,50] among which one included health-care workers [5], five included only outpatients (n = 122; 0.3%) [20,23,27,28,30], among which four included solely athletes [20,23,27,30].

Severity of COVID-19 was not clearly demarcated in 14/35 studies (n = 51 100 participants) [5,8,12,25,29,33,38,42–46,48,49]. Using the WHO scale for COVID-19 severity [15], we divided the latter population into severity categories and then combined them with other studies with pre-specified groups. Studies included participants with a majority of asymptomatic-mild (13/35 studies; n = 1359 participants) [5,12,20–24,26–30,50], moderate-critical (21/35 studies; n = 51 234 participants) [8,11,25,31–45,47–49] and one remaining study (n = 16 participants) with no clear demarcation [46].Most studies were from Europe (n = 19/35; 54.3%), followed by Asia (10/35; 28.6%), North America (5/35; 14.3%) and Africa (1/35; 2.9%).

Outcome assessment

For cardiac sequelae assessment, utilized methods included CMR (n = 16 studies, 45.7%) [5,11,12,20,23,25,27–30,34,35,37,39,40,46], echocardiography (n = 14, 40%) [20–23,25,28,30,32,36,38,44,45,47,48], ECG (n = 16, 45.3%) [5,20–23,25,27,28,30,32,34,36–39,48], troponin (n = 17, 48.5%) [5,11,20,23,27–30,32,34–37,39,44–46], questionnaire (n = 9, 25.7%) [8,12,24,26,32,33,41–43], N-terminal proB-type natriuretic peptide (NT-proBNP) (n = 9, 25.7%) [5,11,28,29,32,34,39,45,47], endomyocardial biopsy (n = 2, 5.7%) [28,29], 24-hour ECG (n = 2, 5.7%) [21,45], clinical assessment (n = 3, 8.6%) [31,43,50], coronary angiography (n = 4, 8.6%) [21,28,36,39], registry analysis (n = 1, 2.9%) [49].

Median time to follow up in all studies totalled to 48 days (1–180 days). Fifty-two days (range 1–180 days) in studies with discharged patients [11,21,24,25,31–46,48,49], 66.5 days (range 28–103 days) in those with mixed discharged patients and outpatients [5,8,12,22,26,29,47,50] and 28 days (range 23–104 days) in those with outpatients [20,23,27,30]. In one study, the reported range was 11–53 days, but this was kept in the analysis as individual data for those assessed ≥14 days were available [30]. Another study included only the time since admission (74–88 days), and was also included because the maximum hospitalization time was 17 days [31].

Outcomes

The main outcomes of all included studies are presented in Table 2.

Cardiac sequelae on CMR

In 12 studies with CMR (excluding four case reports) [5,11,12,20,23,27,29,30,34,35,40,46], median time to assessment was 63 days (range 14–124 days) and participants totalled 1018 (785 patients; 233 controls). Reported outcomes included increased T1 intensity (n = 193/785; median 19%; range 0%–73%), late gadolinium enhancement (n = 86/785; median 12%; range 0%–46%), increased T2 intensity (n = 106/785; median 7%; range 0%–60%), pericardial effusion (n = 99/785; median 2%; range 0%–58%), decreased global longitudinal strain (n = 54/785; median 5%; range 0%–70%), decreased left ventricular ejection fraction (n = 17/785; median 1.5%; range 0%–8%), myocardial enhancement (n = 65/785; median 0%; range 0%–54%), pericardial enhancement (n = 63/785; median 0%; range 0%–40%) and elevated extracellular volume (n = 20/785; median 0%; range 0%–31%). No study reported completely normal CMR results on all included patients.

Only four of the studies above provided formal figures of CMR-based clinical diagnoses. Reported clinical diagnoses using CMR from these studies included myocarditis (n = 84/785, median 0%, range 0%–37%), myopericarditis (n = 15/785; median 0%; range 0%–11%) pericarditis (n = 4/785; median 0%; range 0%–3%) and myocardial infarction (n = 1/785; median 0%; range 0%–2%).

Cardiac sequelae on echocardiography

In nine studies using echocardiography for cardiac assessment (excluding five case reports) [20,22,23,30,32,38,44,45,47], median time to assessment was 41 days (23–104 days) and participants totalled 936 (811 patients; 125 controls). Reported outcomes included reduced left ventricular ejection fraction (n = 23/811; median 0%; range 0%–16%), pericardial effusion (n = 12/811; median 0%; range 0%–6%), global hypokinesis (n = 1/811; median 0%; range 0%–2%), left ventricular hypertrophy (n = 1/811; median 0%; range 0%0.5%), (n = 1/811; median 0%; range 0%–2%), diastolic dysfunction (n = 80/811; median 0%; range 0%–55%), pulmonary hypertension (n = 15/811; median 0%; range 0%–10%), and reduced global longitudinal strain (n = 6/811; median 0%; range 0%–11%). Four articles with 374/936 participants (40%) and a median time to assessment of 33 days (23–56 days), did not report any abnormality on echocardiography [30,32,38,44].

One article reported formal clinical diagnoses by echocardiography including pulmonary hypertension (0.5%), pericarditis (0.5%) and hypertrophic cardiomyopathy (0.5%) [22].

Table 2
Post-COVID-19 recovery outcomes described in included studies

Ref.	Hos.	CMR findings	Echo	ECG	Biomarkers and other tests	Cardiac Symptoms	Clinical cardiac diagnoses
Arnold [31]	100%	NA	NA	NA	NA	Chest pain: 12.7%	None
Ayoubkhani [49]	100%	NA	NA	NA	NA	NA	Major cardiovascular events (MACE)*: 4.8%, 126 per 1000 patient-years New onset MACE: 66 per 1000 patient-years RR of MACE: 3
Brito [20]	None	Late pericardial enhancement: 40%; Pockets of pericardial effusion: 58%; Increased T1: 19%	Reduced GLS: 11%; Pericardial effusions: 6%; EF < 50% Global Hypokinesis: 2%	Sinus tachycardia, ST changes: 2%	Elevated troponin: 2%	None	None
Carfi [43]	100%	NA	NA	NA	NA	Chest pain: 21.7%	None
Carvalho-Schneider [8]	35.30%	NA	NA	NA	NA	d30: chest pain (18%), palpitations (7%); d60: chest pain (13%); palpitations (11%)	NA
Catena [44]	100%	NA	No evidence of cardiac abnormalities: 100%	NA	Troponin: within normal range	NA	None
Daher [32]	100%	NA	No evidence of cardiac abnormalities: 100%	Within normal	Troponin and NT-proBNP: within normal range	Angina: 18%	None
de Graaf [45]	100%	NA	Decreased LVEF from baseline: 16%	No new changes observed	Elevated Troponin: 19%; Elevated NT-proBNP: 15%	Chest pain: 19%; palpitations: 15%	None
Dennis [12]	18.4%	LVEF <50%: 4%; high T1: ≥3 segments: 10.9%	NA	NA	NA	Chest pain: 73.1%;	Myocarditis: 11%
Eiros [5]	16%	Increased T1-relaxation time, ECV: 42%, 37%; T1 LGE: 7%; Increased T2-relaxation time: 4%, edema: 4%; Pericardial effusion: 30%; systolic left ventricular wall motion abnormalities: 5%	NA	STJ depression: 10%; T-wave flat, negative or diphasic: 11%; Incomplete RBBB: 5%; Sinus bradycardia: 4%; Low QRS amplitude: 4%; Other: 13%	Elevated troponin: 1%; Elevated NT-proBNP: 8%	Chest pain: 19%; palpitations: 14%	Pericarditis: 14%; myocarditis: 37%; myopericarditis: 11%
Fan [21]	100%	NA	No evidence of cardiac abnormalities: 100%	25%: anterolateral ST-Elevation. 24-hour ECG: within normal	Angiography: LAD occlusion:25%; no abnormalities: 75%	Chest pain: 25%	Cardiac arrest and acute myocardial infarction: 25%
Hall [22]	89.5%	NA	Inferior regional wall motion abnormality: (0.5%); LV hypertrophy: (0.5%); atrial septal defect with new reversal of shunt: (0.5%)	Persistent sinus tachycardia: (0.5%)	NA	NA	Pericarditis: (0.5%); hypertrophic cardiomyopathy: (0.5%); pulmonary hypertension: (0.5%); worsening of pre-

							existing heart failure: (0.5%)
Huang [33]	100%	NA	NA	NA	NA	Chest pain: 5%; Palpitations: 9%	None
Huang [11]	100%	Myocardial oedema: 54%; LGE (focal linear subepicardial and patchy midwall): 31%; elevated T1, T2, ECV: 31%; decreased RVEF, CO, CI, SV: 31%; decreased LVEF: 3.8%	NA	NA	Troponin I: within normal range	Precordial chest pain: 12%; Palpitations: 88%; Chest distress: 23%	None
Hwang [23]	None	Global hypokinesis with dilated LV and RV: 2% Pericardial effusion: 2%	Borderline/reduced EF: 7%; biventricular dysfunction: 2%	Diffuse ST elevation: 2%; diffuse ST depression: 2%	Within normal range	None	None
Iqbal [24]	100%	NA	NA	NA	NA	Chest pain: 35.4%	None
Jagia [25]	100%	Subepicardial LGE suggestive of myocardial fibrosis	Within normal range	Within normal limits	Within normal range	Atypical chest pain and palpitations	Myocardial fibrosis
Kamal [26]	20%	NA	NA	NA	NA	Chest pain: 30%	Myocarditis: 1.4%
Li [34]	100%	LGE (mid inferior wall): 3%; elevated ECV: 30%; reduced GLS: 70%	NA	Within normal	Within normal range	NA	None
Malek [27]	4%	Borderline or decreased LVEF: 8%; Pericardial effusion: 8%, LGE: 4%, increased T2: 19.2%	NA	Within normal limits	Within normal range	None	None
Ng [46]	100%	LGE: 19%; elevated T1: 25%, T2: 6%, T1 and T2: 6%	NA	NA	Elevated troponin: 20%	Chest pain: 13%	None
Nicol [28]	None	Myocardial inflammation; subepicardial LGE; Small pericardial effusion	LVEF: 45%	Sinus tachycardia	Elevated Troponin I and BNP. EMB: necrosis and inflammation, no viral genome. Coronary angiogram: no obstructive lesions	None	Myocarditis
Puntmann [29]	33%	Increased T1: 73%, T2: 60%; LGE: myocardial (32%), pericardial (22%); pericardial effusion (20%) Decreased LVEF: 3%	NA	NA	Elevated troponin T: 5% EMB: lymphocytic inflammation, no viral genome	Atypical chest pain: 17%; palpitations: 20%	None
Rajpal [30]	None	LGE: 46%; Pericardial effusion: 8%	Within normal range	Within normal limits	Within normal range	None	Myocarditis: 15.4%
Raman [35]	100%	LVEF: Normal; Increased T1: 26%, 8%, 2% in basal, mid and	NA	NA	Within normal range	NA	Myocarditis (CMR): 12%;

(*continued on next page*)

Table 2 (*continued*)

Ref.	Hos.	CMR findings	Echo	ECG	Biomarkers and other tests	Cardiac Symptoms	Clinical cardiac diagnoses
		apical myocardium T2, ECV: no significant difference LGE: myocarditis pattern (12%), LV/RV insertion point (14%) Pericardial effusion: 2%					Myocardial infarction (CMR): 2%
Rivera-Morales [36]	100%	NA	Pericardial effusion; LVEF: 40%–50%; concentric hypertrophy	Widespread ST elevation and PR depression	Toponin: within normal range; Left heart cath: non obstructive CAD	Chest pain	Acute myopericarditis
Santis [50]	Unspecified	NA	NA	NA	NA	Chest pain: 25.9%; Palpitations: 22.2%	None
Sardari [37]	100%	LVEF: 50%; T2: oedema/ inflammation in the mid inferoseptal and inferior wall; LGE: subepicardial fibrosis in the mid inferior wall	Mild LV dysfunction	Normal	Troponin: within normal range	None	None
Sechi [64]	100%	NA	No abnormalities as compared to controls	RBBB: 18.1%; LBBB: 1%; ST segment elevation/ depression: 9.5%; T wave abnormalities: 26.7%	NA	Chest pain: 10.5%	None
Sonnweber [47]	75%	NA	Diastolic dysfunction: 55% (d63), 60% (d103); reduced LVEF: 3%; pulmonary hypertension: 10%; pericardial effusion: 6% (d63), 1% (d103)	NA	Elevated NT-proBNP (23%, d103)	None	None
Tschope [39]	100%	Normal LVEF; T2: elevated and oedema at anterior/ lateral wall; LGE of 75% transmurality; T1 and ECV: elevated	NA	Within normal	Troponin: slightly elevated; NT-pro-BNP: within normal range; angiography: two vessel CAD with severe reduction of mid LAD	Not specified	Silent MI
Vervaat & Houthuizen [48]	100%	NA	Severely dilated RV, decreased systolic function, large, mobile, thrombus in apex	Sinus tachycardia, right axis, incomplete RBBB, prolonged QTc interval (520 ms), and negative T-waves	NA	Shock	Ventricular thrombus
Wang [40]	100%	Oedema: none; LGE: 30% (77% in inferior wall of the basal segment); decreased LVpGCS, RVpGCS, RVpGLS: 30%; no difference in LVEF, EDV, ESV	NA	NA	NA	Not specified	None

Wang [41]	100%	NA	NA	NA	NA	Chest tightness (d7,14,21,28): 4.6%,3.8%,0.8%, 0.8%. chest pain: (d7,14,21,28): 3.1%,0.8%,0%, 0%. palpitations: (d7,14,21,28): 2.3%,0.8%,0%, 0%	None	
Xiong [42]	100%	NA	NA	NA	NA	Resting heart rate increase: 11%; chest pain: 12%; Chest distress: 14.1%. Palpitations: 4.8%	None	

Abbreviations: BNP, B-type natriuretic peptide; CI, cardiac index; CMR, cardiac magnetic resonance; CO, cardiac output; Echo, echocardiography; ECG, electrocardiography; EMB, endomyocardial biopsy; GLS, global longitudinal strain; Hos, hospitalization; hs, high sensitivity; LGE, late gadolinium enhancement; LVpGCS, left ventricle peak global circumferential strain; LV, left ventricle; LVEF, left ventricle ejection fraction; RBBB, right bundle branch block; RV, right ventricle; RVEF, right ventricular ejection fraction; RVpGCS, right ventricle peak global circumferential strain; RVpGLS, right ventricle peak global longitudinal strain.

* MACE: composite outcome of heart failure, myocardial infarction, stroke, and arrhythmia.

Cardiac sequelae on ECG

In nine studies that reported ECG results (excluding seven case reports) [5,20,22,23,27,30,32,34,38], median time to assessment was 41 days (23–124 days) and participants totalled 828 (678 patients; 150 controls). Outcomes included T-wave changes ($n = 43/678$; median 0%; range 0%–27%) ST segment changes including elevation and depression ($n = 26/678$; median 0%; range 0%–10%), right bundle branch block ($n = 26/678$; median 0%; range 0%–18%) and sinus tachycardia ($n = 2/678$; median 0%; range 0%–2%).Four studies with 150/828 participants (18.1%) and a median time to assessment of 44 days (23–124 days) did not report any abnormality on ECG [27,30,32,34].

Cardiac biomarkers

In 13 studies (excluding four case reports), which included troponin level assessment [5,11,20,23,27,29,30,32,34,35,44–46], median time to assessment was 48 days (14–124 days) and participants totalled 968 (766 patients; 202 controls). Elevated levels were observed in 27/766 patients, with a median of 0% and range 0%–20%. In contrast, eight studies with 444/968 participants (45.9%) and a median time to assessment of 44.5 days (14–124 days) reported no increased troponin levels [11,23,27,30,32,34,35,44].

In seven studies (excluding two case reports) which included NT-pro-BNP level assessment [5,11,29,32,34,45,47], median time to assessment was 71 days (14–124 days) and participants totalled 723 (571 patients; 152 controls). Increased NT-pro-BNP levels were reported in 57/571, with a median of 0% and range 0%–23%. Four studies with 351/723 participants (48.5%) and a median time to assessment of 64 days (range 14–124 days) did not report NT-pro-BNP level increase [11,29,32,34].

Coronary angiography and endomyocardial biopsy

In studies that reported coronary angiogram ($n = 4$) [21,28,36,39], of which three were case reports [28,36,39] and one a case series [21], median time to angiogram was 54 days (28–180 days) for a total of seven patients. Results included two-vessel coronary artery disease including left anterior descending artery occlusion in one patient [39] and left anterior descending artery occlusion in another patient ($n = 1$ of 4; 25% of participants) [21].

In one study (excluding one case report), which reported endomyocardial biopsy 71 days after recovery, results showed inflammation in all (100%) of three patients, with no viral genome recovered [29].

Cardiac symptoms

Twenty studies (excluding two case reports) reported cardiac symptoms [5,8,11,12,20,24,26,29,31–33,35,38,41–43,45–47,50] with a median time to assessment of 52 days (range 14–153 days), and total of 4789 (4323 patients; 466 controls). Outcomes included chest pain ($n = 625/4323$; median 17.5%; range 0%–73%), dyspnoea ($n = 763/4323$; median 33%; range 0%–87%) and palpitations ($n = 327/4323$; median 0.77%; range 0%–88%).

Major cardiovascular adverse events

One study reported a composite outcome (major cardiovascular adverse event), which includes heart failure, myocardial infarction, stroke and arrhythmia, with a median follow up of 140 days and a total of 95 560 participants (47 780 patients; 47 780 controls) [49].

Outcomes included a major cardiovascular adverse event in 4.8% of patients, with new-onset major cardiovascular adverse events totalling 66 per 1000 patient-years (compared with 12.3 per 1000 patient-years), translating into an increased relative risk compared to controls (relative risk 3, 95% CI 2.7–3.2).

Timeline of cardiac sequelae

Data on cardiac sequelae timeline are presented in Fig. 2; 646/785 (82.3%), 611/811 (75.3%) and 583/678 (86%) individuals with COVID-19 were tested using CMR, echocardiography and ECG, respectively, at <3 months. Moreover, troponin and NT-proBNP were measured in 671/766 (88%) and 386/571 (68%) at <3 months, respectively, and symptoms were assessed in 1907/4323 (44%) at <3 months. The remaining patients in each group were assessed at 3–6 months after COVID-19 recovery (inclusive).

As shown in Fig. 2, CMR and ECG changes were mostly observed in studies assessing patients <3 months after COVID-19 recovery; in contrast, echocardiography changes and NT-proBNP elevation were more likely in those assessing patients 3–6 months after recovery.

Discussion

The issue of cardiac sequelae of COVID-19 remains a highly clinically relevant topic, which prompted us to perform a systematic review of cardiac manifestations in adults after COVID-19 recovery. Cardiac abnormalities were common and were detected more frequently when higher accuracy diagnostic tests were employed. Indeed, cardiac abnormalities were observed in decreasing rates on CMR, echocardiography, ECG and biomarker assessment. This was in contrast to a very high rate of reported symptoms of cardiac disease, mostly chest pain and palpitations.

Included studies were observational in nature, and most had a fair risk of bias, the latter being primarily due to absence of a comparison group in cohort studies [8,12,22,27,30,31,33,41,44,45,47,50]. The studies included a variety of patients with diverse baseline health profiles, demographic characteristics and COVID-19 severities. One study [49], included most participants (89.9%); however, as the sole study reporting on major cardiovascular adverse events, it is unlikely to alter the pooled results of other studies. The studies used a range of methods, with most using CMR, echocardiography, ECG and biomarker measurement. However, most positive findings came from CMR, which has higher sensitivity for detecting myocardial damage [52] and in line with studies using these methods concomitantly to detect cardiac pathology [20,29,34].

Included studies demonstrate increased risk of clinical and subclinical cardiac sequelae in individuals who have recovered from COVID-19. Clinically, these patients seemed to be at a greater risk than controls who had never had COVID-19 for a range of cardiac diseases, including heart failure, myocardial infarction, myocarditis, pericarditis and arrythmia. This was evident in a high-quality study with matched control groups assessing a large UK cohort of COVID-19 patients at 140 days after hospital discharge, where the authors found a three times higher risk of developing heart failure, myocardial infarction, stroke and arrhythmia in the COVID-19 cohort, compared with matched controls with similar baseline characteristics [49]. On the other hand, evidence for clinical myocarditis and pericarditis was more variable across studies, and many did not report them as explicit diagnoses despite findings suggesting myocardial involvement on imaging [11,20,29]. Alarmingly, myocarditis was reported in groups with asymptomatic/mild COVID-19 [5,12,30], and in healthy populations such as athletes [30], but without evidence of a greater arrythmia risk. Increased risk for cardiac injury was also observed in other respiratory viral illnesses [53], such as with severe acute respiratory syndrome coronavirus (SARS-CoV), whose genomic sequence is 79.6% homologous to that of SARS-CoV-2 [4]. Both SARS-CoV and SARS-CoV-2 attach to the angiotensin-converting enzyme 2 receptor, found on the surface of host cells, and highly expressed in the heart, kidneys, lungs and blood vessels. This could explain direct damage though cell invasion, translating into increased inflammation and coagulation [4], which could provide a pathophysiological basis for cardiac injury due to both viruses.

Short-term cardiac sequelae after COVID-19 (<3 months after diagnosis/discharge) clustered in increased CMR test parameters (T1, T2, pericardial/myocardial enhancement), ECG abnormalities

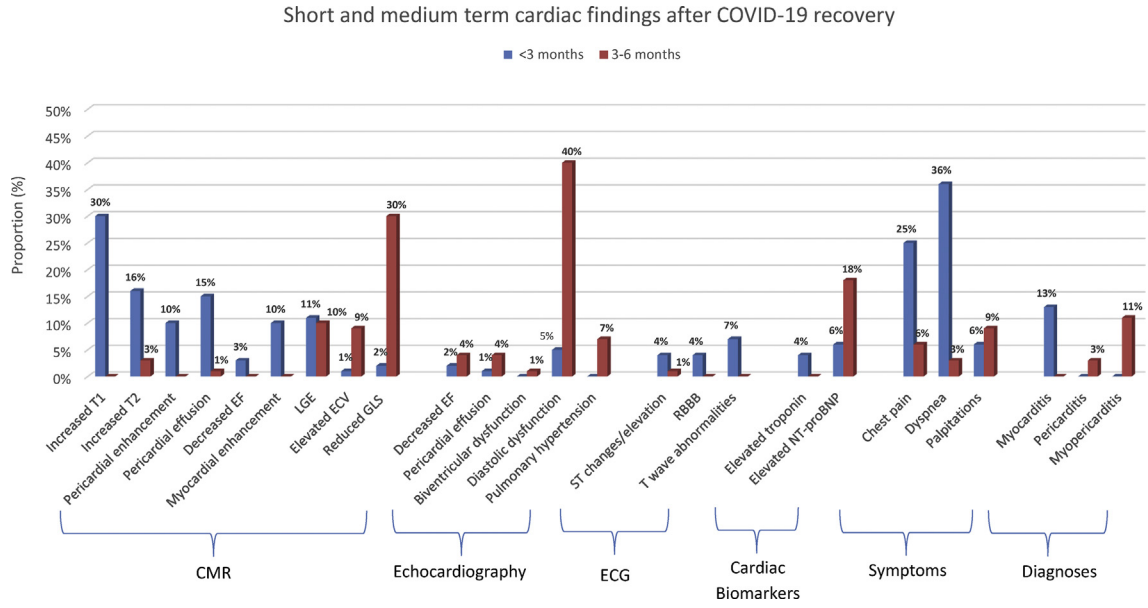

Fig. 2. Graphical representation of the proportions of patients with specific cardiac involvement features according to the timing of evaluation (<3 months versus 3–6 months). Abbreviations: CMR, cardiac magnetic resonance; ECG, electrocardiography; EF, ejection fraction; GLS, global longitudinal strain; LGE, late gadolinium enhancement; RBBB, right bundle branch block.

(T-wave abnormalities and ST segment changes), and persistent symptoms (chest pain and dyspnoea) (Fig. 2). These short-term findings could point towards an active inflammatory process of the myocardium (evidenced by an increase in both T1 and T2) [20,29,54,55]. The latter observation is further strengthened by endomyocardial biopsy, performed in the short-term post-recovery period, showing active inflammatory infiltrate [28,29]. Medium-term cardiac sequelae (3–6 months after COVID-19 recovery), on the other hand, mostly included reduced global longitudinal strain and elevated extracellular volume on CMR, diastolic dysfunction and pulmonary hypertension on echocardiography, and elevated NT-proBNP (Fig. 2). In one study with two-point follow ups, chest pain, diastolic dysfunction and pulmonary hypertension observed at day 60 persisted at day 100 [47], whereas in another study, chest pain (3%) and palpitations (2.3%) reported in the first week subsided on the third week of follow up (0%) [41]. These findings could indicate later development of myocardial scarring and fibrosis, subclinical left and right ventricular dysfunction and non-ischaemic cardiomyopathy [20,29,34,54,55]. Diastolic dysfunction and pulmonary hypertension could result from direct viral injury and/or indirectly from chronic pulmonary disease and ongoing inflammation caused by COVID-19, increasing the long-term risk of developing sub-clinical/clinical heart failure with preserved ejection fraction [56]. Moreover and outside COVID-19, ongoing myocardial inflammation associates with more severe complications such as heart failure [57], and late gadolinium enhancement may be associated with life-threatening arrythmias and sudden cardiac death [58]. However, properly determining the clinical significance of CMR findings and their evolution with time requires follow up over multiple time-points, which was not evident in most included studies.

Research on cardiac involvement after COVID-19 is evolving at a fast-pace, given the possible clinical impact of such an interaction on increased morbidity and mortality rates. Evidence from current studies suggests a higher risk of cardiac involvement in patients with severe COVID-19 than those with a milder disease (see Supplementary material, Table S8). Assessment of other risk factors for cardiac involvement was not possible because of individual limitations of the studies and limited available data. Moreover, symptoms did not seem to correlate with cardiac involvement, as shown by the high percentage of cardiac findings on CMR in asymptomatic patients in the moderate–severe COVID-19 group compared with the mild COVID-19 group. This finding could be due to the non-specific nature of these symptoms, which could be explained by non-cardiac causes such as pulmonary or psychiatric involvement (depression, anxiety), which have been increasingly reported with COVID-19 [24,26,42]. Nonetheless, these studies suggest that cardiac assessment in the short-term and long-term is warranted, irrespective of symptoms, and more importantly in high-risk groups, including those with severe COVID-19 and/or baseline comorbidities, and those who could be at a high risk for cardiac dysfunction and/or arrythmias with subclinical myocarditis, such as athletes.

Cardiac workup should take the urgency, cost and availability into account, among other considerations. Included studies suggest that CMR was the most sensitive method for cardiac sequelae detection, especially in the short-term (<3 months) period after COVID-19 recovery. Detection in this period could be further improved when combining CMR with ECG, cardiac biomarker evaluation and symptom assessment. In the medium-term recovery period (3–6 months), the combination of echocardiography, CMR, cardiac biomarkers and symptom assessment could be a relevant strategy for cardiac assessment.

Studies assessing cardiac sequelae after COVID-19 to date included heterogeneous populations, variable assessment methods and timeline, and most did not include baseline cardiac study and/or control groups. As a result, we could not exclude the presence at baseline of at least part of the observed cardiac findings in some studies. Moreover, cardiac sequelae, in turn, could be part of increasingly reported syndromes after COVID-19, such as long COVID syndrome, with symptoms such as palpitations and dyspnoea stretching past the acute phase [59], and/or multisystem inflammatory syndrome, which causes multi-organ damage, many weeks after COVID-19 [60]. Also, despite the fact that current trials did not conclude any significant burden of cardiac sequelae with major utilized drugs for COVID-19 treatment [61–63], these should be considered in sequelae assessment. In order to categorize cardiac findings as either occurring alone, as part of these syndromes, or due to COVID-19 treatment, proper assessment of other organ systems and drug effects could be warranted.

To improve the current understanding of cardiac sequelae after COVID-19, we believe future studies should include larger numbers of participants, with prospective serial and long-term follow up. Assessments should be made at different time-points up to several months after recovery, with standard questionnaires for cardiac symptoms, and objectively by multiple modalities including ECG, cardiac biomarkers (NT-proBNP, troponin I), echocardiography and possibly CMR. We believe that it is important to perform inter-group analyses to identify risk factors for cardiac involvement after recovery. Moreover, the presence of recent pre-COVID-19 cardiac assessments optimal to compare the progression of cardiac manifestations and the inclusion of one or more control groups, matched to baseline characteristics, with negative SARS-CoV-2 swabs and serologies, is crucial to control for possible confounders.

Additional limitations of our study stem from the variable study types and broad range of populations, assessment methods and outcomes. Moreover, most studies had a single measurement of outcome, fair risk of bias and were uncontrolled. Because of these limitations, the quality of current evidence remains low.

Conclusions

COVID-19 appears to be implicated in *de novo* post-recovery cardiac structural and functional changes and cardiac related symptoms. Larger controlled studies with baseline and serial assessments are required to better characterize the association of cardiac sequelae after COVID-19 and improve the quality of evidence.

Transparency declaration

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Authors contributions

MSR and EDM conceptualized the idea and planned the methodology of this review. MSR and LB designed and conducted the search and extracted relevant data. MSR performed the statistical analysis and wrote the first draft of the paper. LB, RZ and EDM contributed to the writing of the paper. EDM supervised this work and corrected the final version. All authors contributed to the data interpretation, revised each draft for important intellectual content, and read and approved the final manuscript.

Appendix. Members of the Monaldi Hospital Cardiovascular Infection Study Group

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.06.015.

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