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Cardiovascular Sequelae of COVID-19 in Adult Population: A Scoping Review

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ABSTRACT

The COVID-19 pandemic had an unprecedented impact on healthcare systems and the global population. Investigating cardiac complications following COVID-19 recovery holds vital clinical importance, given its scope in the development of post-discharge monitoring programs for patients, as well as the economic and healthcare implication involved. The scoping review aimed to provide a summary of the current and available evidence related to cardiovascular sequelae in adult patients who had COVID-19. Research evidence, published in the last three years (2021 to October 2023), was retrieved in English and Spanish. A total of 746 articles were identified and only 12 that met the inclusion criteria were selected for this review. The most common persistent symptoms reported were dyspnea and fatigue, followed by palpitations and chest pain. Cardiac complications of SARS-CoV-2 virus infection include myocarditis, vasculitis, acute coronary syndrome, right ventricular dysfunction, pericarditis and myocardial infarction. Although the COVID-19 health emergency has ended on an international scale, the consequences of SARS-CoV-2 infection, particularly the cardiovascular sequelae, remain a public health concern due to the associated morbidity and mortality. Documentation and knowledge of the main characteristics of cardiovascular sequelae is crucial for their extent in the development of post-discharge monitoring programs for patients with COVID-19, as well as for health and economic implications.

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KEYWORDS:

COVID-19, SARS-CoV-2, Complications, Post-Acute COVID-19 Syndrome, Cardiovascular Diseases.

INTRODUCTION

The COVID-19 pandemic had an unprecedented impact on healthcare systems and the global population. As COVID-19 is characterized by pulmonary or extrapulmonary manifestations with acute cardiovascular effects that include thromboembolic events, new onset heart failure, myocardial infarction and arrhythmia, the effects related to long COVID-19 can impact different organs and systems, such as pulmonary, cardiovascular, neuromuscular, and hematologic systems, among others.[1]

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The long-term consequences of cardiovascular diseases are of major interest because of the morbidity and mortality they entail.[2] It has been reported that COVID-19 affects the cardiac system by destabilizing the atherosclerotic plaque through severe inflammatory reactions and microvascular thromboembolic events.[3]

It is critical to monitor patients with known cardiovascular complications from acute infection, as well as those who develop cardiovascular problems in the late phase of the disease, occurring weeks or months after the initial infection. Cardiac complications of SARS-CoV-2 viral infection include myocarditis, vasculitis, acute coronary syndrome, right ventricular dysfunction, and myocardial infarction.[3] Major cardiovascular symptoms to be monitored include chest pain, fatigue, dyspnea, palpitations, dizziness, and exercise intolerance.[2]

Even though the global health emergency caused by COVID-19 has ended and almost five years have passed, COVID-19 sequelae have been studied and are expected to persist in patients. Investigating cardiac complications following

COVID-19 recovery holds vital clinical importance, given its scope in the development of post-discharge monitoring programs for patients, as well as the economic and healthcare implication involved. Therefore, this review aims to provide a summary of the current evidence on cardiovascular sequelae in patients who have experienced COVID-19.

METHODOLOGY

Search strategy

A search was conducted following the Preferred Reporting Items for Scoping Reviews (PRISMA-ScR) reference framework[4] and a strategy was developed based on MeSH (Medical Subject Headings) terms in order to identify relevant sources. The search spanned from January 2021 to October 2023 through the following databases: PubMed-Central, Web of Science, and EBSCO. Given the scope of the study, only articles related to cardiovascular complications after COVID-19 that studied risk factors and duration, written in English or Spanish, were included. The search used the following word combinations: (long COVID OR post COVID AND cardiovascular disease) AND (cardiovascular sequelae AND post sequelae COVID).

Selection process

The first step involved screening the titles to remove duplicates. Then, the investigators screened the abstracts found in the search independently based on the predetermined inclusion criteria. Discrepancies between the investigators were resolved through consensus.

The inclusion criteria were as follows: 1) studies involving human populations with confirmed COVID-19 diagnoses through polymerase chain reaction (PCR) test, antibody test, or clinical diagnosis; 2) original research articles indexed in Spanish and English between January 2021 and October 2023; 3) subjects aged 18 years or older of both sexes; 4) patients with cardiovascular sequelae, regardless of type, following COVID-19; and, 5) the primary outcome includes risk factors, duration and/or symptoms after COVID-19. Clinical trial protocols and review articles were excluded.

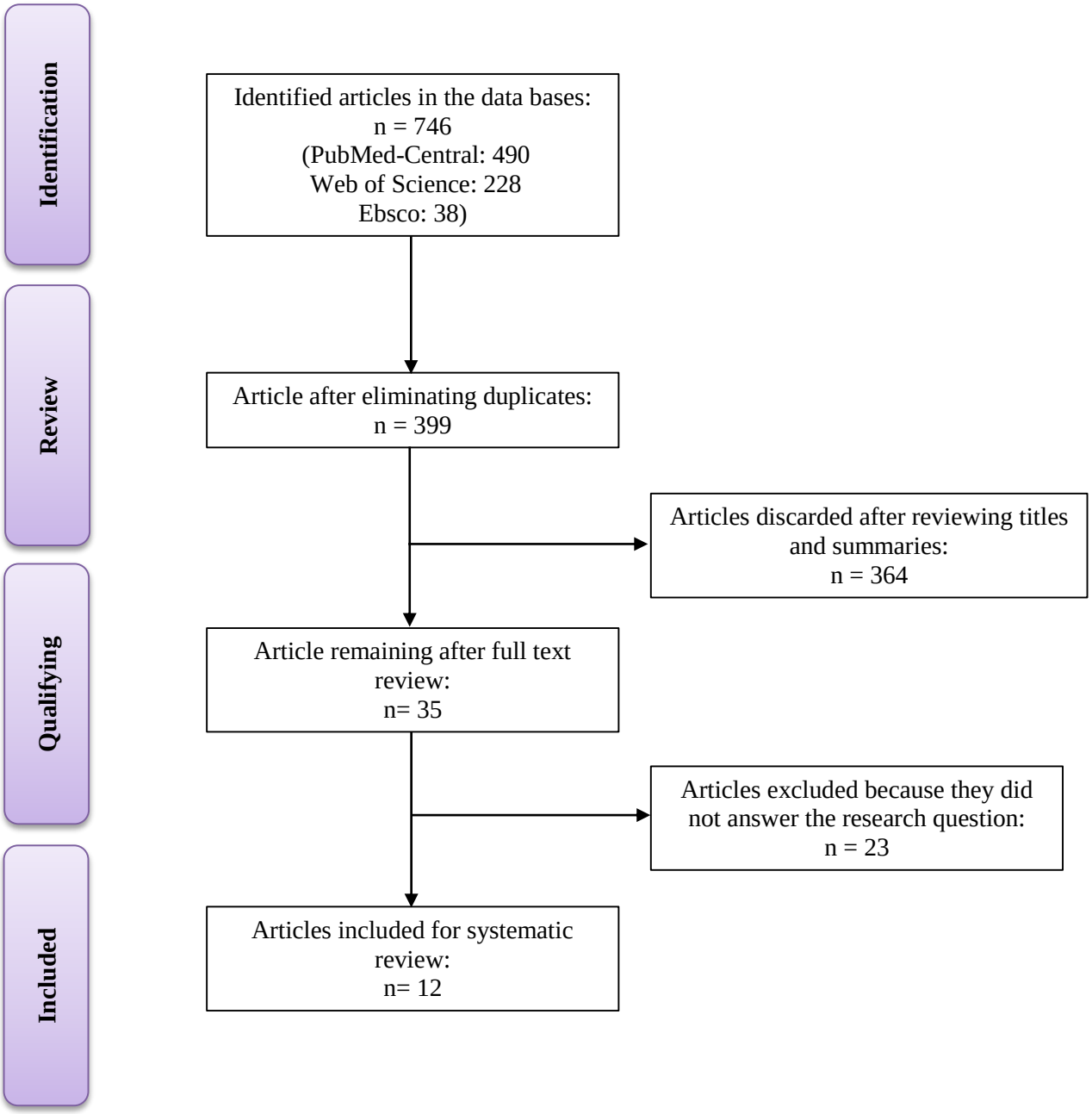
Information extraction

Once the studies were identified and selected, a full-text review was conducted. Reviewers manually extracted the following relevant data: article title, authors, publication date, objective, study design, population, country, sample size, method of COVID-19 confirmation, follow-up period, age, cardiovascular symptoms, and principal findings. Analysis and information extraction were performed using Microsoft Excel.

RESULTS

A total of 746 articles were retrieved from PubMed-Central, Web of Science and EBSCO databases, of which 347 were removed due to being duplicates. 399 articles were evaluated based on title and abstract and, per the aforementioned selection criteria, 364 articles were excluded for being clinical protocols, systematic reviews, or meta-analyses, having a population age different from the proposed criteria, not addressing cardiovascular sequelae of COVID-19, or having a topic unrelated to the research question. This resulted in the retention of 35 articles, which underwent thorough assessment to determine their relevance to the review. Finally, 12 articles were selected for inclusion because directly addressed the research question and contained all the variables of interest. A summary of the search strategy is shown in Figure 1.

Figure 1. Flowchart based on PRISMA criteria.



Of the 12 studies included in the systematic review, 8 were prospective cohorts, [5–12] 2 were case reports[13,14], and 2 were retrospective cohorts.[15,16] The populations studied originated mainly from the United States,[5,6,11,14–16] followed by Spain,[8,12] Egypt,[10] Mexico[9], India,[7] and England.[13]

Subject characteristics

The sample size of the articles varied considerably, ranging from as few as 30 patients[7], to a cohort of 1,357,518 patients.[15] One study did not specify the age range, but it is assumed that they were adults, given that the population studied originated from the database of the United States Department of Veterans Affairs.[5] Most of the articles compared a group of patients with COVID-19 to healthy patients who had not experience COVID-19;[5,6,8,10-14] and two articles studied cardiovascular sequelae in soldiers and veterans.[5,14]

Heart sequelae evolution

All included articles confirmed the presence of COVID-19 through polymerase chain reaction (PCR) testing. Regarding the time from the recovery of COVID-19 to the onset of symptoms reported by the patients, one article mentioned the symptoms occurring 30 days after the diagnosis.[5] Four articles commented on the symptoms persisting to a period of three months,[7,9,10,12] and two articles reported conducting a cardiovascular magnetic resonance within an average of 30 to 90 days after COVID-19 infection[7,14] The remaining articles did not specify the average time elapsed from COVID-19 recovery to the appearance of the symptoms.[6,8,11,13,15]

The most commonly reported persistent cardiovascular symptoms among patients were palpitations (16.7 - 90%), non-exercise related fatigue (36.58 - 87.5%), dyspnea (13.3 - 83%), chest pain (11 - 78%), positional vertigo (4.87 - 62.5%), non-exercise related tachycardia (12.5 - 43%), syncope (41%) and lower limb edema (14%).[7,9-13,16]

The presence of myocarditis was frequently reported as one of the types of cardiovascular sequelae (23.3%).[7,13,14] Similarly, a significant increase in arterial pressure was noted (8.4 - 75.5%).[9,16]

Based on another study that provided a 12-month follow-up, it was found that patients who recovered from COVID-19 had an increased danger of developing cardiovascular complications (HR= 1.52 [1.43-1.62]), transient ischemic attack (HR= 1.503 [1.353-1.670]), inflammatory heart disease such as myocarditis (HR= 4.406 [2.890-6.716]) and pericarditis (HR= 1.621 [1.452-1.810]). Furthermore, there was a higher risk of arrhythmias, including atrial fibrillation and atrial flutter (HR= 2.407 [2.296 -2.523]), tachycardia (HR= 1.682 [1.626-1.740]), bradycardia (HR= 1.599 [1.521-1.681]), and ventricular tachycardia (HR= 1.600 [1.535-1.668]).[6]

Heart sequelae evaluation

Cardiovascular magnetic resonance is one of the main techniques described in the articles for detecting strain and cardiovascular damage among patients with long COVID-19.[7,13,14] In the results of one article, no significant differences were observed in circumferential strain, global longitudinal shortening, or diastolic strain index between the groups (subjects with COVID-19 antecedents compared to healthy subjects). Also, there were no significant differences in global myocardial blood flow at rest (control: 0.7 ± 0.1 ml/min/g, exposed: 0.8 ± 0.3 ml/min/g; p = 0.20).

In contrast, another article identified an active diagnosis of myocarditis in 23.3% of the patients studied based on the revised Lake Lous criteria. However, based on the conventional cardiovascular magnetic resonance parameters of the left ventricle, such as left ventricular ejection fraction, end-diastolic volume, end-systolic volume and systolic volume, no significant differences were found between the patients who recovered from COVID-19 and healthy subjects. Recovered patients had a significantly lower cardiac index of diastolic volume compared to healthy individuals.[7]

Heart sequalae impact in quality of life.

Two articles assessed the quality of life of recovered COVID-19 patients with cardiovascular sequelae. One study used cardiovascular exercise test to evaluate patients with prolonged COVID-19 and revealed that about 58% exhibited evidence of circulatory impairment during maximal exercise performance (maximal oxygen consumption [VO2] <80% prespecified). In addition, 88% displayed ventilatory variability indicative of dysfunctional breathing, hypocapnia at rest, and an excessive ventilatory response to exercise (elevated VE/VCO2 slope).[11]

Another study employed a questionnaire (EQ-5D-5L) to evaluate the quality of life and found that approximately 50% of patients with long COVID-19 experienced difficulties with walking at least at a moderate intensity, while 75% of patients had severe difficulties in carrying out habitual daily activities, such as working, studying or recreational activities.[14]

The main findings of the articles included in this review are summarized in Table 1.

DISCUSSION

In this literature review, 12 articles were identified that explored the presence, types, and magnitude of subsequent cardiovascular sequelae in patients recovered from SARS-CoV-2 infection. The findings of this review indicate a greater risk of clinical cardiovascular sequelae in individuals who have recovered from COVID-19 in comparison to healthy control patients who have never experienced the illness.

Based on these results of the reviewed articles, patients with a history of COVID-19 have an elevated risk of suffering

heart failure, myocardial infarction, myocarditis, pericarditis, and arrhythmias.[17,18]

Per the studies considered and examined in this review, cardiovascular magnetic resonance is one of the screening techniques commonly used for diagnosing patients with symptoms of cardiovascular sequelae. [19,20] Moreover, the minimum follow-up from a period of one year in those patients recovered of COVID-19 in the articles provide an overview and emphasize the importance of a monitoring system aiming to prevent and control the development of the sequalae for all those patients who, at some point in their lives, have been affected by the illness independently from their history of heart diseases.[21]

Two articles examined the impact of cardiovascular sequelae on patients' quality of life, revealing limitations in performing daily activities. These findings are consistent with those published by Tabacof and colleagues, who mentioned that the prevalence of continuing symptoms in patients recovered from COVID-19 negatively impacts physical and cognitive function, quality of life, and social involvement.[22]

Despite the limited number of studies included, the results were consistent regarding the onset of long COVID-19 symptoms and symptomatology.[23] Dyspnea, fatigue, chest pain, and tachycardia where among the most common symptoms reports across the studies.[24,25]

It is recognized that the variety of diagnostic tools used in the studies complicates a specific comparison; nevertheless, in all the reviewed articles is emphasized the presence of cardiovascular symptoms among patients who recovered from COVID-19 within an average timeframe of three months, compared to healthy control patients unexposed to SARS-CoV-2 infection. This observation corresponds to the definition of long COVID-19 and previous research findings. This study has several limitations, amongst which the limited amount of search engines used to identify the articles is emphasized, as it cannot guarantee that the combination of words used includes all the relevant articles. Furthermore, the systematic search only includes articles in English and Spanish, potentially excluding a greater number of studies available in other languages.

CONCLUSION

Although the COVID-19 health emergency has ended on an international scale, the consequences of SARS-CoV-2 infection, particularly the cardiovascular sequelae, remain a public health concern due to the associated morbidity and mortality. Therefore, it is crucial the documentation and the knowledge of the main characteristics of the cardiovascular sequelae in affected populations to support the development of evidence-based post-hospital monitoring programs for COVID-19 patients. This would prevent or, in other cases, control the associated sequelae, while supporting the financial sustainability of healthcare systems and the overall well-being of vulnerable populations.

Table 1. Results of patients who recovered from COVID-19 as described in the included studies.

Number of bibliography reference	Author and year	Country	Design	Size of sample	Population	Age	Time elapsed: recovery – presence of long COVID-19 symptoms	Heart symptoms	Biomarkers
5	Xie et al., 2022	United States	Prospective cohort	-Exposed group: 153,760 -Control group: 5,637,647 (no evidence of COVID infection)	American Veterans	NA	12-month follow-up, the presence of symptoms was reported after 30 days after COVID-19 diagnosis.	NE	NE
6	Wang et al., 2022	United States	Prospective cohort	-Exposed group: 690,892 -Control group: 690,892	Individuals of both sexes who are older than 18 years of age.	Exposed group: 43.2 ± 16.2 Control group: 43.1 ± 16.1	NE	NE	-Troponin I ≥ 0.3ng/ml: Control group: 3713 (00.5) Exposed group: 1412 (00.2) -Hemoglobin ≥12g/dL

									Control group: 327420 (47.4) Exposed group: 312261 (45.2)
7	Kunal et al., 2022	India	Single-center prospective	30 patients recovered from COVID-19	Individuals of both sexes who are older than 18 years of age.	Exposed group: 40.6 ± 12.4 Control group: 39.2 ± 5.3	Average period from COVID-19 infection to the performance of CMR: 30-90 days	All the patients had symptoms at the moment of the CMR: chest pain (60%), dyspnea (13.3%), palpitations (16.7%) and dizziness (6.7%)	-C-reactive protein (mg/L): 40.09 ± 46.42 -Troponin T (µg/L): 3.36 ± 9.04 -Serum creatinine: 0.65 ± .12
8	Ortega-Paz et al., 2022	Spain and Italy	Multicenter, retrospective, international cohort	-Exposed group: 3,578 -Control group: 849	Individuals of both sexes who are older than 18 years of age.	Exposed group: 63.1 (17.3) Control group: 48.8 (19.1)	NE	NE	NE
9	González-Hermosillo, et al., 2023	Mexico	Prospective cohort	23 patients recovered from COVID-19 (15 negative and 8 positive for orthostatic hypertension)	Individuals of both sexes who are older than 18 years of age.	-Exaggerated response to negative orthostatic blood pressure (REPAO) negative: 49.7 ± 9.6 -Exaggerated response to positive orthostatic blood pressure: 54.3 ± 12.9	The onset of symptoms was at least 3 months compared to the 10.8 ± 1.9 months of duration of the study.	Fatigue, dyspnea and non-exercise related tachycardia, chest pain, sleep disorders, positional vertigo.	-C-reactive protein (mmol/L): negative REPAO: 1009 (310–1901) positive REPAO: 1171 (338–2692) -NT-proBNP (pmol/L): negative REPAO 7.6 (3.2–30.12) positive REPAO: 5.2 (3.4-35.1)
10	Hamdy et al., 2023	Egypt	Prospective cohort	-Exposed group: n=30 patients with persistent dyspnea and preserved left ventricular systolic function conserved	Individuals of both sexes who are older than 18 years of age.	-Exposed group: 33.6±7.4 -Control group: 31.3±8.4	3.0±1.7 months	Palpitations (65%), atypical chest pain (53.3%), exertional dyspnea (Average MMRC: 2.4, ± 0.7 Standard deviations)	NE

				after COVID-19, -Control group: n= 30 healthy individuals					
11	Mancini et al., 2021	United States	Prospective	41 patients (23 women and 18 men)	Individuals older than 18 years of age referred to pulmonologists or cardiologists with pulmonary function tests, chest x-rays and chest CT scans, and echocardiograms.	45.2±12.5	8.9±3.3months prior to the cardiovascular exercise.	Dysfunctional breathing, dyspnea.	NE
12	Aranyó et al., 2022	Spain	Prospective cohort	-Group 1: cases, n=40 -Group 2, patients with SARS-COV-2 confirmed by PCR and matched for age and sex without criteria for sinus tachycardia, n=19 -Group 3, patients of the same age and sex without a history of SARS-COV-2, n=17.	Individuals of both sexes who are older than 18 years of age.	-Group 1: 40.1 ± 10 -Group 2: 42.2 ± 11 -Group 3: 39.5 ± 13	Symptoms appeared in an average of three months.	Group 1: Palpitations (90%), dyspnea (83%), chest pain (78%)	-C-reactive protein (mg/L): 1.1 ± 1.3 -NT-proBNP (pg/mL): 67.6 ± 59.6 -Leukocytes: 6.83 ± 1.7 -Ferritin: 50.4 ± 37.4
13	Gorecka et al., 2022	England	Prospective – Case study	-Exposed group: 20 patients with antecedents of COVID-19 -Control group: 10 healthy patients without antecedents.	Individuals of both sexes who are older than 18 years of age.	-Population subsequent to COVID-19: 45±13 -Healthy population: 51±11	ND	-Fatigue (84%), palpitations (69%) and dyspnea (53%). A minority of patients suffered from chest pain (11%).	- C-reactive protein at diagnosis (mg/L): Exposed group= 141 ± 11 -NT-pro BNP: Control group: 35 [35–71] Exposed

									group: 56 [38–68] -White globules: Control group: 6.4 [4.8–8.9] Exposed group: 7.2 [5.9–8.6]
14	Clark et al., 2021	United States	Prospective – Case study	-Exposed group: 50 soldiers with antecedents of COVID-19 -Control group: 50 soldiers without antecedents of COVID-19	Individuals older than 18 years of age.	-Exposed group: 26.5 (23, 31) -Control group: 25 (23, 33)	Average time from COVID-19 infection to cardiovascular magnetic resonance performance (CMR): 71 days	NE	-Normal Troponin-I= 96% at a median of 33 days after the detection of SARS-CoV-2. -Troponin-I > 99%: 4% in patients with abnormal CMR.
15	Wiemken et al., 2023	United States	Retrospective - Cohort	Cohort: 1,357,518	Individuals of both sexes who are older than 18 years of age.	NS	NS	NS	NS
16	Mahmoud et al., 2022	United States	Retrospective	100 patients with a history of COVID-19	Individuals of both sexes who are older than 18 years of age.	46.3±14.7	An average of 99 days from diagnosis of COVID-19 to clinical presentation of sequelae	Chest pain (66%), palpitations (59%), dyspnea with exercise (56%) and syncope (42%)	-C-reactive protein (mg/L): 3.0 [RIC: 1.1–5.3] (13.6%) - Red corpuscles – sedimentation rate (mm/h): 9.0 [6.5–17.5] (13.5%) -Ferritin (ng/mL): 89 [42.4–173] (15%) -Troponin-I: 0 [0–0] (3.4%)

NS: No specified. NA: No available. NT-proBNP: Natriuretic Peptide Tests

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