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Health Review

Development of cardiac arrhythmias in patients with Long COVID-19 Syndrome

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Abstract: To analyze the scientific evidence of the main factors that are associated with the development of cardiac arrhythmias in patients with Long COVID-19 Syndrome. An Integrative review, was carried out in November 2023, using the digital library Scientific Electronic Library Online (SciELO), the Virtual Health Library (VHL) and PUBMED in the databases, the Boolean operators were used: AND and OR. The results were obtained through management with the Rayyan 16 QCRI application and were structured in PRISMA flowcharts. Thirty-seven articles were found in the databases, 5 articles that made up the sample were selected, repeated articles were excluded, which were 24. It is concluded that there is a need for more specific studies, to guide the impact on the care and clinical management of patients, considering that the development of this syndrome may be related to the spectrum of possible cardiac arrhythmias, from benign ventricular extrasystoles even atrial fibrillation and sudden death due to ventricular arrhythmias, probably due to the different pathogenic mechanisms of the virus that require further exploration.

Keywords: Development cardiac arrhythmias; Long COVID-19 Syndrome; Review.

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1. Introduction

COVID-19 has presented an unprecedented challenge to public health around the world. According to the 'WHO Coronavirus (Covid-19) Dashboard' (updated on 10/18/23), the disease affected 770 million people and caused 6.9 million deaths. In terms of number of cases, Brazil ranks 8th (38 million), rising to 2nd in number of deaths (more than 700 thousand) and, unfortunately, reaches 1st in the fatality rate with approximately 368 deaths/ 100 thousand inhabitants. These data indicate that, if the pandemic was devastating for the world, it was even more drastic for the Brazilian population. The lethality of the disease worldwide was around 1% and, also in this indicator, Brazil stands out negatively with lethality close to 1.9%. As the disease affected a huge number of individuals, the number of survivors of the disease is also large [1].

The persistence of symptoms led the World Health Organization to define post-Covid syndrome or long Covid as a new clinical entity that appears in patients recovered from SARS-CoV-2 infection. The syndrome is characterized by the persistence, for more than 3 months, of symptoms that cannot be explained by a condition prior to the viral infection. Adopting this definition, several studies show that up to 30% of cases

develop the syndrome. The difficulty of characterizing a syndrome occurs due to a wide variety of symptoms [1].

Among cardiovascular manifestations, arrhythmias were the second most common change, among pathologies related to COVID-19, cardiac arrhythmias were observed in 16.7% of hospitalized patients, being present in 7% of patients who are not observed in intensive care and 44% in those admitted to the intensive care unit. It ranges from benign arrhythmias such as atrial fibrillation to atrioventricular blocks and ventricular tachycardia/fibrillation. Furthermore, metabolic dysfunctions, stimulants, and activation of the nervous system are the main predisposing factors for heart rhythm changes [2, 3].

2. Material and methods

This study is characterized as an integrative review, which allows the search, evaluation and synthesis of evidence on a given phenomenon [4]. To construct this study, the topic was first chosen and the guiding question was defined: "*What factors are associated with the development of cardiac arrhythmias in patients with Long COVID-19 Syndrome?*". We sought to answer the main guiding question based on the PICO strategy (acronym for Patient, Intervention, Comparison and Outcome), that is, given this, PICO corresponds to, respectively, P= Patients with long COVID-19; I= factors associated with the development of arrhythmias in Long COVID-19 Syndrome; CO= Cardiac arrhythmias.

The established inclusion criteria: primary research article published in Portuguese, English or Spanish, with a time limit in the last 3 years (2020-2023). Letters to the editor, expert opinions, reviews, books, book chapters, experience reports, case studies, theoretical reflections, theses, dissertations, monographs and summaries published in event annals were excluded. The search was carried out in November 2023. In this step, terms in Portuguese were chosen through the Health Sciences Descriptors (DeCs) and terms in English through Medical Subject Heading (MeSH). The locations where the search would take place were established, as well as the inclusion and exclusion criteria for studies.

The articles were selected via online access using the digital library Scientific Electronic Library Online (SciELO), the Virtual Health Library (VHL), in addition to the following health database: PUBMED, available on the Periodicals portal of the Coordination of Improvement of Higher Education Personnel (CAPES) obtained through the Federated Academic Community (CAFe). To search the databases, the following Boolean operators were used: AND and OR, to improve the search in the databases. Therefore, we will use the following descriptors in Health Science (DeCS) and Medical Subject Headings (MESH): Cardiac arrhythmias OR (Cardiac arrhythmias) AND Long COVID-19 syndrome OR (long COVID-19 Syndrome) AND Myocardial injury SARS-COV- 2 OR (myocardial injury SARS-COV-2), which were performed in different combinations.

To manage the results, Rayyan16 QCRI (http://rayyan.qcri.org/) was used to exclude duplicate articles, identify those that were related to the guiding question and applicability of the exclusion and inclusion criteria. Studies were identified from selected information sources by two independent researchers, previously trained to evaluate titles and abstracts, through a free single-version web review program called Rayyan Qatar Computing Research Institute (Rayyan QCRI) [5]. For better understanding and transparency in the selection method, it was decided to present the flowchart of scientific articles through the Main Items for Reporting Systematic Reviews and Meta-Analyses (PRISMA) guide.

3. Results and discussion

According to the results found in the study, for better understanding and transparency in the selection method, the flowchart of scientific articles was used through the Main Items for Reporting Systematic Reviews and Meta-Analyses (PRISMA) guide (Figure 1). The first phase consisted of searching the databases, totaling 37 articles. In the second phase, repeated articles were excluded, which were 12. In the third, titles and ab-

stracts were read, 25 articles were selected. In the last phase of construction, an exploratory, selective and analytical reading of all studies and stratification of excerpts that answered the guiding question was carried out, totaling 8 articles that make up the sample.

The data is presented in a descriptive way, aiming to gather and organize knowledge on the topic investigated. Table 1 presents an overview of the articles selected for the study and (Figure 2) a summary of the main conclusions reached.

Figure 1. Schematic representation of synthesis and analysis of results (PRISMA).

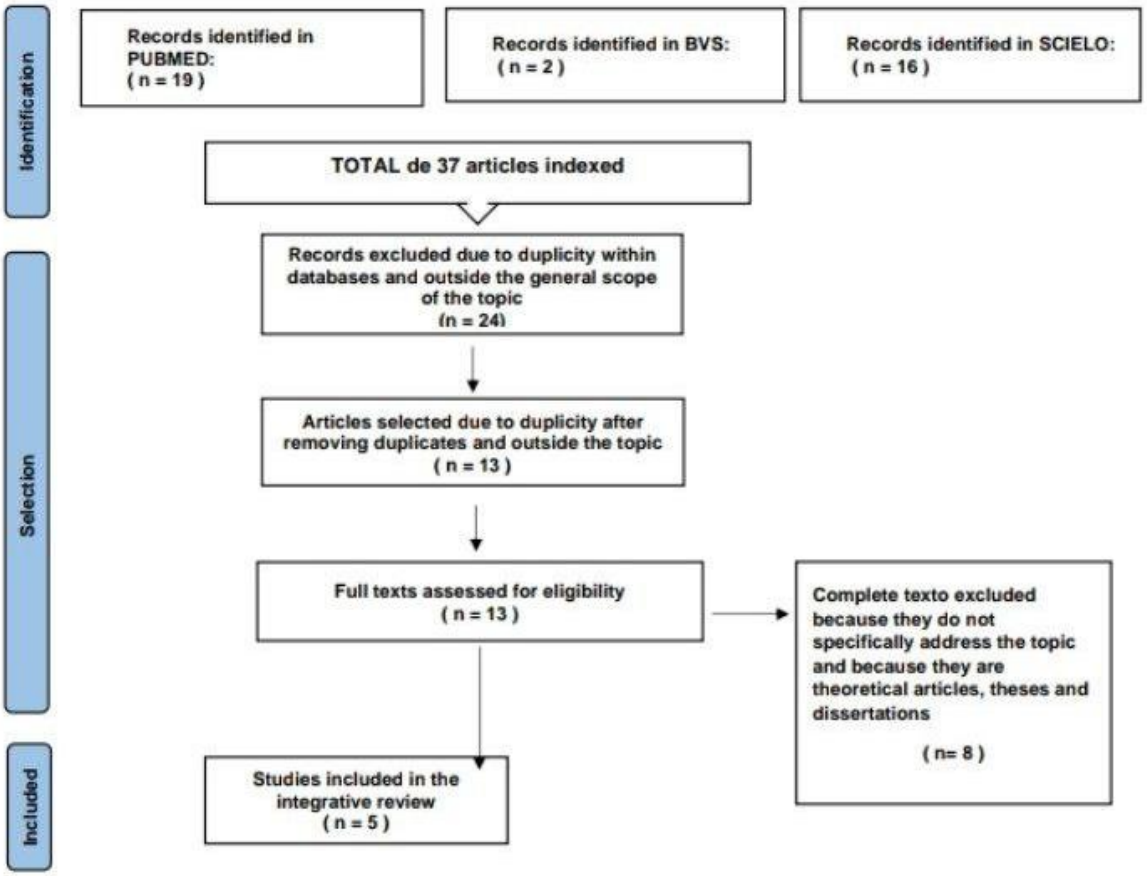

Table 1. Studies selected for sample, according to rayyan identification, title, authors, objectives, and main results.

Title	Objectives	Main results
[6]	This Editorial aims to present the current situation of long COVID, or post-COVID syndrome, and its global impact on health and healthcare provision.	The clinical manifestations of long COVID and its prevalence in all age groups that initially appear to have recovered from acute SARS-CoV-2 infection are now recognized. However, the effects on society, the economy and the provision of healthcare have not yet been realized.
[7]	This Editorial aims to present the current situation of long COVID, or post-COVID syndrome, and	The propensity for the occurrence of potentially fatal ventricular arrhythmia may be a consequence of several con-

	its global impact on health and healthcare provision. COVID-19 can directly exacerbate underlying cardiac disease and is often worsened by cardiovascular complications, including arterial and venous thromboembolic events, malignant arrhythmia, and myocardial injury.	tributing factors. In addition to myocardial injury, patients with COVID-19 frequently develop metabolic disorders and electrolyte disturbances in addition to the hyperinflammatory state, creating an environment that may favor the occurrence of cardiac arrhythmia. It should be emphasized that several drugs initially used to treat COVID-19 have pro-arrhythmic potential, for example hydroxychloroquine and azithromycin.
[8]	To evaluate the incidence of cardiac arrhythmias (atrial tachyarrhythmia, bradyarrhythmia and sustained ventricular tachycardia) and cardiac arrest (CPA) in a cohort of patients hospitalized with COVID-19 in a tertiary university hospital.	We included 241 consecutive patients diagnosed with COVID-19 (mean age, 57.8 ± 15.0 years; 51.5% men; 80.5% white), 35.3% of whom received invasive mechanical ventilation (MV). . Overall mortality was 26.6%, 58.8% among those on MV. Cardiac arrhythmias were identified in 8.7% of patients, the most common being atrial tachyarrhythmia (76.2%).
[9]	Assess the range of cardiac sequelae after recovery from COVID-19.	Twenty-nine studies used objective cardiac assessments, primarily cardiac magnetic resonance (CMR) in 16 studies, echocardiography in 15, electrocardiography (ECG) in 16, and cardiac biomarkers in 18. Most studies had a reasonable risk of bias. The median time from diagnosis/recovery to cardiac evaluation was 48 days (1-180 days). Common short-term (<3 months) cardiac abnormalities included increased T1 (proportion: 30%), T2 (16%), pericardial effusion (15%), and late gadolinium enhancement (11%) on CMR, with symptoms such as pain chest (25%) and dyspnea (36%).
[10]	We aimed to investigate whether there are changes in the QT, QTc and Tpe ratios and in the Tpe/QT and Tpe/QTc ratios in	It was found that basal heart rate, the presence of hypertension and diabetes, leukocyte count, blood urea nitrogen, creatinine, potassium, aspartate ami-

patients with COVID-19.	notransferase, and alanine aminotransferase, NT-proBNP, C-reactive protein high sensitivity, D-dimer, TncI-as, Tpe interval, Tpe/QT ratio and Tpe/QTc ratio increased from group I to group IV and were significantly higher in all patients in group IV ($p < 0.05$). QT and QTc segments were similar between groups. It was determined that elevated heart rate, calcium, D-dimer, NT-proBNP, and hs-CRP levels were significantly related to Tpe, Tpe/QT, and Tpe/QTc.

The declaration of a pandemic by the World Health Organization (WHO) in March 2020 marked the beginning of an unprecedented global crisis triggered by the coronavirus SARS-CoV-2, the causative agent of COVID-19. Since then, this disease has emerged as one of the most serious contemporary public health challenges, impacting millions of individuals in all corners of the globe and resulting in a significant number of fatalities. The relevance of addressing both preventive strategies and complications of COVID-19 is undeniable, given its high transmission rate and the serious consequences associated with its rampant spread. On the one hand, preventive measures such as social distancing, use of face masks and mass vaccination play a crucial role in containing the spread of the virus and reducing morbidity and mortality rates related to the disease.

According to Parums [6], it is crucial to investigate the effects of COVID-19 on the cardiovascular system, especially considering serious cardiac complications, such as arrhythmias, which significantly increase patient mortality. The author highlights the importance of evaluating specific ventricular repolarization parameters, such as the QT interval and the Tpe interval, in patients with COVID-19, in order to predict and prevent arrhythmic events.

On the other hand, understanding and managing the complications of COVID-19, as described in the study by Mevlut Koc [10], is crucial to ensure adequate treatment of affected patients and minimize the negative impact of the disease on their health and well-being. Therefore, a holistic approach that includes both prevention and management of complications is essential to effectively address the pandemic and protect global public health. Both highlight the importance of understanding cardiovascular complications and the need to monitor specific parameters to prevent serious events, such as arrhythmias. While the article by Parums [6] focuses on the theoretical importance of this investigation, the study by Mevlut Koc [10] provides concrete data on these parameters in real patients.

Pre-existing cardiovascular disease is an important risk factor for a severe clinical course of COVID-19 and is associated with adverse outcomes. COVID-19 can directly exacerbate underlying cardiac disease and is often worsened by cardiovascular complications, including arterial and venous thromboembolic events, malignant arrhythmia, and myocardial injury [7]. In the case of cardiac arrhythmias, the possibility of pro-arrhythmic effects of drugs used to treat COVID-19, hypoxia caused by pulmonary viral involvement, myocardial ischemia, fluid and electrolyte disorders, myocardial "*tension*" and changes in intravascular volume can also be considered. The unbalanced inflammatory response by T helper cells of types 1 and 2 constitutes yet another mecha-

nism proposed to explain inflammation and arrhythmogenesis in patients with COVID-19 [11].

The interaction of the virus with the host occurs through the virus's S (spike) protein and its entry receptor angiotensin-converting enzyme 2 (ACE2); however, invasion requires the initiation of a cellular serine protease called Transmembrane Serine Protease 2 (TMPRSS2). This receptor is present on several cells in the body, mainly type II pneumocytes, and is also present at a systemic level, including in the heart and in blood vessels, organs frequently involved in complications presented during infection [12]. Cardiac involvement is multifactorial in patients with COVID-19. Since cardiac involvement is associated with mortality, it is possible to predict an increase in mortality due to arrhythmia in these patients. In fact, patients with COVID-19 had fatal arrhythmias. Despite this, no clear parameters or classifications have been reported to provide information about the frequency of arrhythmias or to predict these patients [10].

However, care must be taken when interpreting the data obtained: the greater the diagnostic accuracy, the more frequently structural changes in the heart are detected. Likewise, the symptoms reported by patients may have other non-cardiac causes. We can therefore conclude that, in light of the studies analyzed, SARS-CoV-2 infection may be associated with clinical or subclinical cardiac sequelae, which include myocarditis, pericarditis, myocardial infarction, arrhythmias and pulmonary hypertension. Chronologically, the sequelae that occur in the first three months tend to be more serious than those occurring after this period [9].

In a cohort study carried out on patients hospitalized with a diagnosis of COVID-19, in a tertiary hospital [1] the most common patterns found were: Cardiac arrhythmias occurred in 8.7% of patients, the most common being atrial tachyarrhythmia (76.2 %). Patients with arrhythmias had higher mortality, 52.4% versus 24.1% ($p=0.005$). In multivariate analysis, only the presence of heart failure was associated with a higher risk of arrhythmias (hazard ratio, 11.9; 95% CI: 3.6-39.5; $p<0.001$). During hospitalization, 3.3% of patients were treated for CPA, with a predominance of non-shockable rhythms. All those treated for PCR died during hospitalization. In conclusion, to better understand the real clinical impact of cardiovascular disease caused by COVID-19, controlled studies with more defined outcomes would be necessary [9].

4. Conclusion

Cardiac arrhythmias in Long Covid-19 Syndrome are a possible complication that affects patients infected by the SARS-CoV-2 virus. Its clinical forms do not depend on whether the patient had a mild manifestation or even severe forms. They can manifest themselves both in those who have suffered a mild illness and in those who have suffered a more serious form. Symptoms such as palpitations and tachycardia are commonly reported by patients [13]. Persistent cardiac arrhythmias may have different pathogenesis, such as primary cardiac damage, secondary cardiac injury, or deterioration of preexisting cardiovascular disease [3].

There is currently increasing evidence that cardiovascular disorders generated by SARS-CoV-2 may lay a foundation for the development of subsequent cardiac arrhythmias in patients who have suffered a previous infection. However, the mechanisms triggering cardiac arrhythmias after COVID-19 are not yet well defined, but a chronic inflammatory response and a possible autoimmune response to cardiac antigens due to molecular mimicry are suspected [11]. The spectrum of possible cardiac arrhythmias is broad and ranges from benign ventricular extrasystoles to atrial fibrillation and sudden death due to ventricular arrhythmias, probably due to different pathogenic mechanisms that require further exploration [14].

In general, more research is needed to better understand the impact of arrhythmias on Post-Covid Syndrome and, thus, develop effective strategies for their prevention and treatment. Furthermore, it is necessary for doctors to be alert to the possibility of this

complication in patients who have suffered from COVID-19, and the work of the multidisciplinary team in the follow-up and rehabilitation of these patients is important.

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