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MYOCARDIAL INJURY DUE TO COVID-19 EXPRESSED THROUGH BIOMARKERS AND ECHOCARDIOGRAPHIC PARAMETERS: AN INTEGRATIVE REVIEW OF THE LITERATURE

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ABSTRACT

The high risk of cardiovascular complications during and after infection with SARS-CoV-2, a virus that causes COVID-19, is well documented in the world literature. Through cardiac changes, the role of echocardiography and biomarkers of myocardial injury is exalted as useful tools that can affect the morbidity and mortality of these patients. For a better understanding of the subject, an integrative review was performed from bibliographic data arranged in indexed databases. The objective of this study was to answer the following question: What is the role of biomarkers, conventional echocardiography and the Speckle Tracking analysis by the occurrence of myocardial injury caused by the SARS-CoV-2 virus? We concluded with the analysis of 10 studies eligible for the review that there is an intimate relationship between troponin and brainnatriureticpeptide with echocardiographic findings of myocardial injury by COVID-19. Moreover, these biomarkers were easy and widely available for screening patients eligible for echocardiography. Therefore, more studies are necessary to assess the validity and consolidation of this simple screening method that can predict cardiovascular complications in advance, often fatal.

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INTRODUCTION

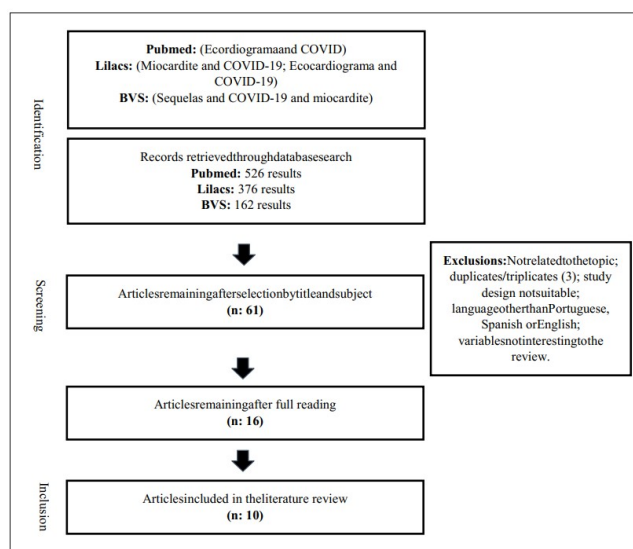
According to the World Health Organization, more than 765 million cases and more than 6.9 million deaths from COVID-19 have been confirmed in the world since the pandemic began in December 2019. Brazil is the sixth country with the highest number of confirmed cases, with almost 37.5 million notifications (World Health Organization, 2023). Previously thought as an airway disease, it is now known to be widely inflammatory in several organs, including the cardiovascular system (Farnaz et al., 2021). As knowledge about the relationship between SARS-Cov-2 infection and cardiac impairment increased, the laboratory and cardiac imaging role gained more prominence (Messina et al., 2021).

In this scenario, the conventional and the speckle tracking echocardiogram (STE) analysis, together with the biomarkers of myocardial injury, are tools for the early detection of changes that may influence the morbidity and mortality of patients with COVID-19. Given the above, the objective of this study was to conduct an integrative review to search for articles that showed the value of echocardiography and biomarkers to predict cardiovascular complications in patients infected with SARS-CoV-2. The relevance of this research is based on the possibility of early detection of negative outcomes and the reduction of morbidity and mortality.

MATERIALS AND METHODS

This is an integrative review study from bibliographic data arranged in indexed databases. The objective of this study was

to answer the following question: What is the role of biomarkers, conventional echocardiography and STE through the occurrence of myocardial injury caused by the SARS-CoV-2 virus?. Therefore, a survey of articles published until October 2021 was carried out. The searches were performed in the following databases: National Library of Medicine National Institutes of Health (PUBMED)/Medical Literature Analysis and Retrieval System on-line (MEDLINE), Latin American and Caribbean Health Sciences Literature (LILACS) and Virtual Health Library (VHL). Health Science Descriptors and the boolean operator “AND” were used to restrict the scope of the search for articles. The combination of descriptors used, as well as their alternative terms, consisted of: (*Sequelas AND COVID-19 AND miocardite*); (*Miocardite AND COVID*) and (*Ecocardiograma AND COVID*).



Inclusion criteria were articles in Portuguese, Spanish or English; original articles, available and free, with at least one descriptor and those that dealt with the desired theme. Studies outside the thematic scope, case reports and case series, literature reviews and studies with publication of *Qualis C* or less or absent were excluded. Figure 1 shows the flowchart of identification and selection of articles. The results were summarized in Table 1 with the following information: authors, year, study design, where the study was carried out, level of evidence, impact factor and *Qualis* of the journal.

RESULTS

In most of the studies presented, major changes were found in the titer of inflammatory markers such as D-dimer, brain natriuretic peptide (BNP), troponin and cytokines (e.g., interleukin 6 - IL-6). Such changes were more evident in patients admitted to an intensive care unit (ICU), who presented more severe symptoms of COVID-19 and/or who died (Bears et al., 2021; Krishna et al., 2021; Zeng et al., 2020). The increase in D-dimer and troponin markers was associated with adverse events at 30 days, such as prolonged hospitalization, myocardial injury and death (Krishna et al., 2021). In addition, echocardiographic findings showed greater disease severity when there was an increase in troponin associated with an increase in NT-proBNP (Yuan et al., 2021).

According to Yuan et al. (2021), this troponin and BNP association together have a negative predictive value of 95% to exclude echocardiographic findings indicative of severity, when those were within normal values. In another study, conducted by Karagodin et al. (2021), there was no association between troponin elevation and mortality. In this study, the authors concluded that, although the elevation of this biomarker indicates severity of the disease, it did not cause direct myocardial injury. Conclusion supported by weak correlation between troponin and longitudinal strain (degree of deformation of myocardial tissue seen by echocardiogram) of the left ventricle. Regarding echocardiographic findings, the influence of COVID-19 on the right heart was highlighted. In the study by Zeng et al. (2020), 10% of patients in ICU had increased right ventricular volume, decreased systolic function and pericarditis. Such changes, when present, indicated worsening of lung injury, expressed mainly by pulmonary arterial hypertension.

For Stöbe et al. (2020), the only change found was the free wall of the right ventricle. There was a reduction of about -17 and -23% in the longitudinal global strain of the right ventricle in 4 patients with severe symptoms in mechanical ventilation, and a reduction of -22 and -23% in 2 patients with mild symptoms. According to Karagodin et al. (2021), alterations in the strain of the right ventricle were considered independent markers for mortality. For Silverio et al. (2021), the reduction of the systolic excursion of the tricuspid ring plane (TAPSE) in patients with COVID-19 was associated with a higher in-hospital mortality rate. Moreover, the left ventricle was also affected in COVID-19 due to ischemia, myocarditis and stress cardiomyopathy (Takotsubo syndrome). The left ventricular ejection fraction (LVEF) was reduced (Krishna et al., 2021; Zeng et al., 2020). The reduction rates were higher in severe patients (Zeng et al., 2020, Karagodin et al., 2021) or who died (Silverio et al., 2021).

In patients with severe symptoms, the E/e' ratio obtained by echocardiography was significantly higher compared to those with mild to moderate symptoms (Karagodin et al., 2021). In agreement with this finding, Karagodin et al. (2021) also demonstrated that, in patients in ICU, changes in the longitudinal strain of the left ventricle were more frequent. Both the strain of the left ventricle and the longitudinal strain of the right ventricle free wall have in-hospital mortality rates independently. The autopsies performed by Bears et al. (2021) demonstrated that, in the 4 patients with myocarditis, none presented reduction of left ventricular function. Stöbe et al. (2020), when using the STE ($n=14$), also observed that, despite normal LVEF, most patients presented abnormal deformation of the left ventricle. In addition, changes in the basal segment were the most common, even in patients with mild to moderate symptoms. It was also concluded that the myocardial involvement of the basal circumference of the circumferential left ventricle was usually transmural. In contrast, Van Den Heuvel et al. (2021) demonstrated in their prospective cohort study that, when comparing echocardiographic parameters during hospitalization for COVID-19 and 4 months after discharge, the most significant difference found was the slight improvement of the longitudinal global strain.

Table 1. Characteristics of the studies included

Authors	Design	Setting	Sample Size	Loe/If/Qualis
Van Den Heuvel et al., 2021	Prospectivecohort	Radboudumc, Nijmegen, The Netherlands	51	3B // 2.00 // A3
Yuan et al., 2021	Retrospectivecohort	Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, USA	434	3B // 5.251 // A1
Silverio et al., 2021	Multicenterretrospectiv ecohort	Eboli Hospital and San Giovanni di Dio e Ruggi d'Aragona University Hospital in Salerno; Monaldi and Cotugno Hospital and San Giuliano Hospital in Naples, Villa dei Fiori Hospital in Acerra; University Hospital of Sassari in Sassari; "Umberto I" Hospital in Nocera Inferiore; Italy	226	3B // 4.686 // A2
Zeng et al., 2020	Retrospectivecohort	Third People's Hospital, Shenzhen, China	416	3B // 3.342 // A4
Stobe et al., 2020	Case-control	Leipzig University Hospital and the Community Hospital Halle (Saale), Germany	18	3B // 3.66 // A2
Karagodin et al., 2020	Multicenterretrospectiv ecohort	13 medical centers in Asia, USA, Europe and Latin America	870	3B // 5.251 // A1
Sheehan et al., 2021	Prospectivecohort	Cleveland Clinic Main Campus Hospital, Cleveland, USA	79	3B // 2.45 // A2
Bearse et al., 2021	Retrospectivecohort	Massachusetts General Hospital, Boston, USA	41 (postmortem)	3B // 49.962 // A1
Weckbach et al., 2020	Prospectivecohort	Ludwig-Maximilians-University Hospital, Munich, Germany	18	3B // 2.56 // A1
Krishna et al., 2021	Retrospectivecohort	Mayo Clinic Health System, New York and Arizona, USA	179	3B // 7.616 // A1

Table 2. Main echocardiographic and myocardial injury biomarkers findings of the selected studies

Authors	Biomarkers	Echocardiography
Van Den Heuvel et al., 2021	Higher titers of D-dimer, NT-proBNP, troponin and/or cytokines in patients with COVID-19	Comparing patients during and after hospitalization for COVID-10, there was no difference for LVEF, LV diastolic function, global longitudinal deformation (GLS) and TAPSE. The most significant difference found was the slight improvement in GLS after discharge.
Yuan et al., 2021	Higher titers of D-dimer, NT-proBNP, troponin and/or cytokines in patients with COVID-19. Elevated troponin and NT-proBNP associated with urgent echocardiographic findings	Urgent echocardiographic findings were not present in 94% of patients who underwent the examination before hospitalization due to COVID-19.
Silverio et al., 2021	-	The reduction in TAPSE was associated with in-hospital mortality. The LVEF was reduced, with higher rates of reduction in patients who died.
Zeng et al., 2020	Higher titers of D-dimer, NT-proBNP, troponin and/or cytokines in patients with COVID-19	10% of patients in the ICU had increased right ventricular volume, decreased systolic function and pericarditis. The LVEF was reduced, with higher rates of reduction in critically ill patients.
Stobe et al., 2020	Higher titers of D-dimer, NT-proBNP, troponin and/or cytokines in patients with COVID-19.	The only alteration found was in the GLS of the RV free wall, a parameter obtained from the STE. RV GLS was slightly reduced (between -17 and -23%) in 4 patients with severe symptoms on mechanical ventilation and in 2 patients with mild symptoms (between -22 and -23%). Among the patients who underwent STE (n=14), they also observed that, despite a normal LVEF, most of them had abnormal LV deformation, with changes mainly in the basal LV segments, even when they had mild to moderate symptoms.
Karagodin et al., 2020	It did not identify an association between troponin elevation and mortality.	Changes in right ventricular strain were independent markers for mortality The LVEF was reduced, with higher rates of reduction in critically ill patients. Changes in LVLS were more frequent in ICU patients. Both LVSL and RVFWS were independently associated with in-hospital mortality in this study.
Sheehan et al., 2021	Lower values of Troponin T and ultrasensitive troponin on admission compared to those with non-reactive test for SARS-CoV-2.	Those who died more often had elevated right ventricular systolic pressures (RVSP), but other parameters were similar between groups, including normal LVEF and RV systolic function.
Bearse et al., 2021	Higher titers of D-dimer, NT-proBNP, troponin and/or cytokines in patients who died from COVID-19.	-
Weckbach et al., 2020		At STE, deteriorated cardiac function was observed in patients with normal LVEF on cardiac magnetic resonance.
Krishna et al., 2021	Higher titers of D-dimer, NT-proBNP, troponin and/or cytokines in patients with COVID-19. Elevation of troponin and D-dimer was associated with adverse events at 30 days	Elevation of RVSParterial was related to adverse events at 30 days. The LVEF was reduced. Only 20% of the patients had previous echocardiographic data. Among these, there was a high prevalence of pre-COVID-19 abnormalities (78%). Of the 29 patients with LVEF<50%, 4 of the 7 patients with a previous echo already had reduced ejection fraction. Of the 26 patients with regional wall motion abnormalities, 12 had previously undergone ECOTT; 7 of these had new or worsened regional wall movement abnormalities and in the remaining 5, there was no change.

Despite a higher percentage of impairments such as troponin elevation, acute myocardial injury, arrhythmias and acute myocardial infarction in patients with heart disease, there was no statistically significant difference for echocardiographic measurements in both groups. In the study by Silverio *et al.* (2021), the rate of cardiovascular complications, including myocardial injury, myocardial infarction, pulmonary embolism and acute heart failure, was significantly higher in patients who died, compared to those who recovered from the disease. Most of these studies did not consider echocardiographic findings prior to virus infection. Krishna *et al.* (2021) demonstrated that, in the 20% (n=36) of patients with such previous echocardiographic data, there was a high prevalence of abnormalities prior to COVID-19 (78%; n=28). Of the 29 patients with LVEF<50%, 4 of the 7 patients with previous echo already presented reduced ejection fraction. Of the 26 patients with regional wall movement abnormalities, 12 had previously undergone transthoracic echocardiography (ECOTT); 7 of these had new or worsened regional wall movement abnormalities and, in the remaining 5, there was no change. In the cohort analyzed by Yuan *et al.* (2021), 99 out of 105 patients did not show TTECH changes before hospitalization due to COVID-19.

DISCUSSION

The cause of acute cardiac involvement associated with COVID-19 is still uncertain. This condition has been associated with both a primary involvement caused by SARS-CoV-2, and a multifactorial cardiac involvement due to severe systemic infection (Li *et al.*, 2021). Regarding primary involvement, it has been proposed that cardiac injury comes from multiple mechanisms. This includes the direct viral invasion of myocardial cells, which is corroborated by the finding of viral particles in cardiomyocytes (Tavazzi *et al.*, 2020). On the other hand, changes in cardiac biomarker levels associated with the absence of typical echocardiographic and electrocardiographic signs in patients suggest that myocardial involvement is more likely related to the systemic effects of the virus (Deng *et al.*, 2020). Therefore, it is proposed that infection by SARS-CoV-2 can either induce new cardiac involvement, or precipitate a worsening in underlying cardiovascular diseases and even death (Martins-Filho, Barreto-Filho, and Santos, 2020). It is worth mentioning that only hospitalized patients due to COVID-19 were evaluated in all review studies. Most of these patients were part of a cohort with previous comorbidities such as hypertension, diabetes mellitus, cardiovascular disease, arrhythmias, obesity and smoking history.

Regarding the biomarkers of myocardial injury, especially Troponin Ultrasensitive (Tn -US) and NT-proBNP, were considered as acute injury when the levels of Tn - US were above the 99th percentile reference upper limit and as heart failure when there was an increase in serum level of NT-proBNP beyond the normal value associated with symptoms such as dyspnea, orthopnea and edema of the lower limbs (Martins-Filho, Barreto-Filho, and Santos, 2020). The literature suggests that elevated cardiac markers may be a sign of worse prognosis and important predictors of mortality from the virus (Deng *et al.*, 2020; Martins-Filho, Barreto-Filho and Santos, 2020; Shi, Qin, and Shen, 2020; Shi *et al.*, 2020) regardless of previous history of cardiovascular disease (Chen *et al.*, 2020).

In addition, both biomarkers showed excellent performance when identifying patients without echocardiographic abnormalities. According to the pathophysiology of the disease, the lungs are the main targets of SARS-CoV-2 and, due to the high prevalence of acute respiratory distress syndrome in critical patients, the right ventricle is particularly susceptible to dysfunction due to COVID-19 (Karagodin *et al.*, 2021). In this sense, the right ventricle is essential to maintain clinical balance, and its evaluation during the progression of infection may be crucial to determine patient risk (D'Andrea *et al.*, 2020; Rath *et al.*, 2020). Given the knowledge of the relationship between COVID-19 and cardiovascular disease, the identification of underlying cardiac abnormalities in patients with myocardial infection and injury using available imaging modalities is critically important (Karagodin *et al.*, 2021). Cardiac involvement assessed from echocardiography has been performed in other systemic viral infections, such as in the SARS-CoV outbreak from 2002 to 2003 (Li *et al.*, 2003). In this context, the use of echocardiography proved to be extremely important for risk stratification in patients with COVID-19.

An accurate evaluation of left and right ventricular functions by echocardiography should be strongly considered in this scenario, especially in more critical and severe cases (Zhang *et al.*, 2020). Considering the need for isolation and care in examining critically ill patients, transesophageal echocardiography is the main means for observation and monitoring of structural and functional heart abnormalities in patients with COVID-19 (Zeng *et al.*, 2020). Moreover, as verified by Karagodin *et al.* (2021), when using the composite ROC model, the sensitivity of the model for association with mortality is improved when echocardiographic parameters with strain are added to clinical parameters. Thus, the use of STE allows a more complete risk assessment for infected patients. In this context, LVEF is well established as a risk stratification parameter even in patients not admitted to the ICU and still represents the most used parameter for the evaluation of left ventricular systolic function (Lang *et al.*, 2015). In patients with reduced LVEF, COVID-19 could act as a precipitating factor and quickly deteriorate the clinical status of patients. In addition, previous studies have demonstrated the association of concomitant heart disease with negative outcome in patients infected with SARS-Cov-2 (Inciardi *et al.*, 2020).

Regardless of the period of installation of left ventricular dysfunction, the ejection fraction at admission may be very useful to identify patients with a higher probability of fatal outcome. However, normal LVEF does not exclude underlying cardiac abnormalities. In the meantime, STE may show a deteriorated cardiac function even in the presence of preserved LVEF and normal levels of troponin and/or BNP (Weckbach *et al.*, 2021, Li *et al.*, 2021). Due to the multicenter and intercontinental character of the WASE COVID-19 study, Karagodin *et al.* (2021) also showed a significant diversity in cardiac phenotype and echocardiographic use between different global regions. These regional differences observed in the study may partially reflect the different echocardiographic application criteria used, including strain parameters. It is worth mentioning that, as postulated by Sheehan *et al.* (2021), echocardiography should be used only if there is an expected benefit in patient management. The risk to health professionals and the patient should also be carefully considered.

However, as already explained, the American Society of Echocardiography recommends clinical categorization for the indication of elective and non-elective examination, and, in this case, the titration of myocardial biomarkers may be used as a screening method. In this context, Yuan *et al.* (2021) demonstrated in their study that, despite almost 25% of severe echocardiographic changes in all patients with COVID-19, in those with normal levels of these biomarkers, about 95% had no abnormal findings on imaging. Thus, it is suggested a better indication for the use of the test so that there is less cost for unnecessary ECOTT and less risk of exposure to the virus. Among the limitations found in the studies evaluated, most of the data were collected retrospectively, obtained through analysis of electronic medical records and/or with small sample size. Therefore, they were subject to notification bias, investigation and generalization of data. Moreover, the selection of which patients would be submitted to echocardiography and measurement of laboratory markers was mostly based on clinical judgment and not on a systematic method. This may have generated an overestimation of the frequency of cardiovascular abnormalities and laboratory changes, in addition to hindering the generalization of the findings. There is also the fact that there may not be uniformity in the evaluation of echocardiographic and laboratory parameters due to differences intrinsic to the devices and approaches in various parts of the world. Furthermore, STE, important for assessing subclinical abnormalities, was not widely used in the studies evaluated, possibly due to the approach based on parameters that are easy to access at the bedside in the pandemic context. In short, most studies did not take into account or did not have access to echocardiography data prior to hospitalization for COVID-19, which may have influenced the analysis about the appearance of abnormalities, either prior to or due to COVID-19. There was no association between increased biomarkers during hospitalization and myocardial function at follow-up, nor between symptomatology and echocardiographic functional parameters at follow-up. In patients recently infected with COVID-19, the benefits of performing echocardiography should be evaluated in relation to the risks of exposure and transmission of the coronavirus. In critical patients, echocardiographic imaging, especially speckle tracking, allows accurate assessment of cardiac abnormalities and risk of fatal outcome. After evaluation of several comorbidities and several biomarkers, troponin and BNP were highly sensitive for echocardiographic abnormalities. Thus, we propose that troponin and BNP can be used as part of a simple screening tool to determine in whom TTECH can be safely delayed until its peak infectious window has passed.

Conflicts of interest: The authors declare that they have no conflict of interests.

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