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Cardiovascular patients with covid-19 in intensive care: a systematic review

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ABSTRACT

OBJECTIVE

Analyse in the literature, the prevalence of cardiovascular diseases (CVD) and the development of cardiac or vascular dysfunctions, in individuals hospitalized in intensive care units (ICU), due to Covid-19.

METHODS

Integrative literature review, carried out in the databases: BVS: BDENF and LILACS; PuBMED: MEDLINE; Web of Science and CINAHL. Inclusion criteria, full-text articles, in Portuguese, English or Spanish, published from 2019 onwards.

RESULTS

Six articles were selected, and three central themes listed: patients with previous CVD; patients who developed heart or vascular diseases during hospitalization; and patients who presented alterations in biomarkers of cardiac injury and fibrin degradation. A prevalence of CVD between 0 and 29% of the studies was observed, as coronary diseases, arrhythmias, valvular and ventricular dysfunctions, and the incidence of CVD between 2.6 and 59%, presenting electrical, functional, structural alterations and cardiogenic shock.

CONCLUSIONS

An important percentage of patients with Covid-19, admitted to the ICU, who had previous CVD and who developed CVD were identified. However, until the end of this study, there weren't studies in which 100% of the sample had previous CVD, which would be important for understanding the possible impairments under it. Even as, research that specified the types of involvement developed, named only as "cardiac injuries" or biomarkers increased. As limitations of this study, we emphasize that new research was carried out after its conclusion, which will certainly add better knowledge. This way, the concern about the severity in which Covid-19 can affect people with previous CVD and its cardiovascular manifestations remains.

DESCRIPTORS

Coronavirus Infections, Cardiovascular Diseases, Intensive Care Units.

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INTRODUCTION

Coronavirus disease (Covid-19) is a disease caused by a virus from the *Coronaviridae* family[1]. The first description of a virus from this family was in 1937, but only in 1965 was it named as a "coronavirus", because of its microscopic appearance like a crown[2]. Two variations of this virus have already been reported as epidemics: the Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1), from 2002 to 2004, which caused 774 deaths, and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), from 2012, with 858 deaths[3].

The disease was considered a pandemic in March 2020[4], with approximately 233,150,000 confirmed cases of Covid-19 and 4,770,000 deaths worldwide by September 2021. In Brazil alone, there were approximately 21,380,000 confirmed cases and 595,000 deaths, ranking Brazil third in the number of cases and second in the number of deaths[5].

As for the behavior of the virus in the human body, its incubation period is usually five to six days, but it can vary from one to 14 days, and its transmissibility occurs through droplets, aerosols, contact with surfaces, objects, or body fluids from infected patients[4]. It is known that the virus is inoculated in mucous membranes such as eyes, nose, and mouth[2].

Initially characterized as a flu-like syndrome, in which the main signs and symptoms were headache, fever, coryza, dry or secretive cough, sore throat, fatigue on exertion, and myalgia. Later, patients affected by the disease presented other signs and symptoms, such as anosmia, ageusia, nausea, emesis, diarrhea, and coagulation alterations[1]. It is now characterized as a systemic dysfunction, with changes in cellular composition and blood biochemistry, caused by inflammatory response[6].

The virus has a higher affinity for angiotensin-II converting enzyme receptors (ACE2), and the excessive, toxic accumulation of angiotensin-II in plasma can induce SARS and fulminant myocarditis[7]. Dysfunctions in other organs, such as the lungs, heart, gastrointestinal tract, liver, and kidneys, in addition to acid-base changes, have been proven to lead to multiple organ failure and death[6]. Due to changes in the coagulation cascade, there is also hypercoagulability and increased risk of thromboembolic events, with the occurrence of Disseminated Intravascular Coagulation (DIC)[8]. Thus, it can be inferred that the systemic immune response and coagulation disorders are directly linked to disease severity[6].

Due to this affinity of the virus for ACE2 receptors and the human cardiomyocytes express this enzyme, the Covid-19 virus can infect these cells and adjacent tissues directly, and replicate. Thus, the death of cardiomyocytes, the development of inflammatory myocarditis, contractile dysfunction of the cardiac muscles, segmental abnormalities, and pericardial effusion have a high occurrence[9].

Not infrequently, patients with Covid-19, in severe presentations of the disease, need to be referred to Intensive Care Units (ICU) during the period of their contamination. This situation occurs due to the need for intensive health care, which ranges from hemodynamic decompensation requiring the use of vasoactive drugs (VAD), ventilatory devices such as NIV (non-invasive ventilation) and high-flow nasal catheter (HFNC), to the use of mechanical ventilation (MV)[10].

It is noteworthy that hemostasis is intrinsically linked to inflammatory and immune responses. This shows that the disease has a systemic character, because it presents a progressive hyperinflammation caused by diffuse endothelial lesions. That is, due to the human body's immune response to develop an inflammatory response focused on fighting the virus, a systemic microangiopathy occurs[11]. Converging to the triggering of severe systemic dysfunctions and later to "acute deterioration of the function of two or more organs", which can cause a Multiple Organ Dysfunction Syndrome (MODS)[12].

The search for new evidence on Covid-19 is justified because it is a new pandemic disease with specific involvement in the cardiovascular system, to guide the best management and care provided by health professionals focusing on early identification and prevention of diseases in this system.

Given this, this study aims to analyze the literature, the prevalence of cardiovascular disease (CVD) and the development of cardiac or vascular dysfunction in individuals admitted to the ICU due to Covid-19.

METHODS

This is an integrative literature review, the broadest methodological approach, which aims to gather and synthesize research results in an orderly and systematic way, which provides the visualization of knowledge gaps in the literature that require new studies[13].

This methodology can be performed after delimiting a clinical problem by determining the information needed, searching the literature, selecting pertinent studies, and applicability in the desired scenario[14].

The integrative review is composed of six steps: 1) Definition of the subject and guiding question; 2) Literature search using descriptors in databases, establishment of inclusion and exclusion criteria; 3) Categorization of data; 4) Critical analysis of included studies; 5) Interpretation and synthesis of results and 6) Presentation of the integrative review[13].

For the development of the research, it was possible to develop the guiding question by using the PICo[15] strategy (Population, Interest, Context), Population: patients with cardiovascular disease affected by Covid-19, Interest: cardiovascular dysfunction, Context: ICU admissions.

Thus, the following guiding question was formulated: "Individuals affected by Covid-19 and admitted to an Intensive Care Unit, with pre-existing cardiovascular diseases will present what possible cardiovascular manifestations during hospitalization?"

The search was performed from the combination of keywords that addressed the research question, considering the descriptors in DeCS (Descriptors in Health Sciences) and MeSH (Medical Subject Headings): Coronavirus Infections, Cardiovascular Diseases and Intensive Care Units, through the use of the Boolean operator AND.

We used the publications indexed in electronic databases, through the Virtual Health Library (VHL): Nursing Database (BDENF) and Latin American and Caribbean Literature on Health Sciences (LILACS), in the portal of Bibliographical Database in Medicine (PuBMED): Medical Literature Analysis and Retrieval System Online (MEDLINE), as well as the Web of Science and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Cross-referencing with descriptors, words from the title, abstract and subject were carried out by truncating the descriptors.

Inclusion criteria were free articles available in full in Portuguese, English, and Spanish. They should be published from 2019, with a sample of individuals affected by Covid-19 and fully admitted to the ICU or partially (case-control studies, among others), but with a specific description of its population in the ICU. Exclusion criteria were studies that did not address the proposed topic.

All articles were exported to EndNote Online® for compilation and selection of relevant articles for the study. For data extraction the URSI[16], Melnyk and Fineout-Overholt[17] instruments were used, both adapted, collecting the following data: articles identification (country and year of pub-

lication, authors, and title), type of research and level of evidence, sample (# patients, % ICU admission, mean age in years and % men) and results found (% CVD prevalence, % CVD incidence and % mortality).

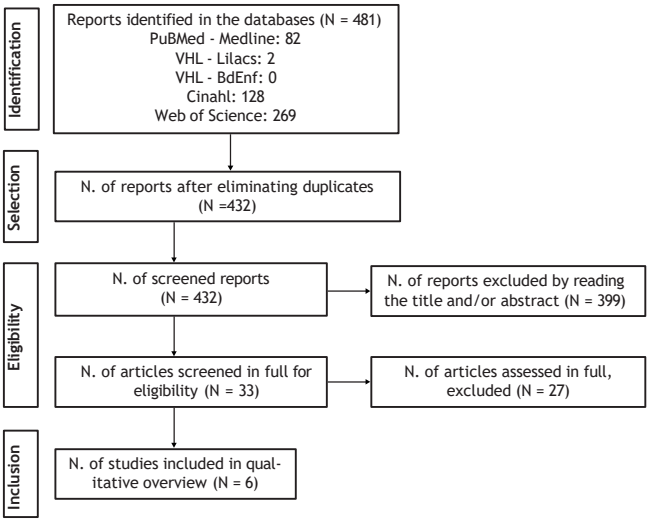
The format with the Main Items for Reporting Systematic Reviews and Meta-analyses (PRISMA) widely used in systematic reviews and meta-analyses helped to organize the article selection process[18].

To evaluate the different types of methods, we used the hierarchy of evidence classification that corresponds to the evaluation of different studies from levels, as follows: I - meta-analysis of systematic reviews or multiple clinical trials; II - evidence from at least one well-designed randomized controlled clinical trial; III - well-designed clinical trial without randomization; IV - well-designed cohort and case-control studies; V - systematic review; VI - evidence from at least one of the qualitative or descriptive studies; VII - opinions of authorities or expert committees[17].

RESULTS

After searching the databases on August 9, 2021, the article selection process, using the PRISMA flowchart, was performed as shown in Figure 1.

Figure 1. Flowchart of article selection, PRISMA format.



After selecting the articles by using the adapted URSI12, Melnyk, and Fineout-Overholt[13] instruments, some important items were listed for analysis, as shown in chart 1.

Chart 1. Selected articles, according to: Authors, Type of study, Nº patients, % ICU admission, Mean age (years), % Men, % CVD prevalence, % CVD incidence, and % Mortality.

Nº	Study	Type of study	Patients (Nº)	ICU admission (%)	Average age (years)	Men (%)	CVD prevalence (%)	CVD incidence (%)	Mortality (%)
A1	Alkindi F, Alhashmi K, Nadar S, Alharthi S, Alsaidi K, Alrashdi T, et al[19].	IV - Cohort study	541	100	50,57	74,1	17,5	34.2, being: 4.3% VT/VF, 2.6% AMI, 0.9% drop of >20% of LVEF, 0.6% myocarditis and 0.6% AF. Elevation of biomarker: 31.6% troponin.	16.4 (total), of which 41.6 (cardiovascular).
A2	El Rhalete A, Rhazi I, Bensaid A, Zaid I, Bkiyer H, Ismaili N, et al[20].	VI - Descriptive study	84	100	65	71,42	14.28, of which 25% were PCI with stents, 8.3% CABG, and 66.6% clinical treatment.	59.52% PE, 14.28% AMI, 11.9% pericarditis and 3.57% myocarditis, 7.14% limb ischemia, 2.38% AVEI and 1.19% HF. Clinical signs of: Left HF (22.1%), 14.28% Right HF, 2.38% pericardial friction. ECG changes: 21.42% isolated tachycardia, 11.9% ST segment elevation, 10.71% tachycardia with inverted T wave, 4.76% AF, 3.57% STEMI, 1.19% tachycardia with ST elevation. LVEF drop: 26.19% (≤60% and 50% or ≤50% and 40%), 14.28% (≤40% and 30%) and 9.52% (≤30%). Elevation of biomarkers: 16.66% troponin and 80.95% D-dimer.	40,47
A3	Hasan SS, Radford S, Kow CS, Zaidi STR[21].	I - Meta-Analysis of Systematic Reviews	903 (12 studies)	100	63,25	73,7	0 to 10% VTE (7 studies).	VTE 31% (patients on prophylactic or therapeutic anticoagulation), 38% (prophylactic anticoagulation alone), and 27% (mixed therapeutic and prophylactic anticoagulation).	No data
A4	Jain R, Salinas PD, Kroboth S, Kaminski A, Roemer S, Perez Moreno AC, et al[22].	IV - Cohort study	52	100	59,9	60	12% AF/atrial flutter, 11% HF, 29% heart disease: 8% (LV) systolic dysfunction, 4% RV dysfunction, 17% CAD, 4% TxC, 2% severe MI regurgitation and 2% moderate AoS.	56: 40% acute ventricular dysfunction, 11.5% recent onset AF, 2% VT and 2% IAMS-SST. 21% LV dysfunction (new or worsening), 17% abnormal LVEF (<50%), 38% RV enlargement. 35% worsening or new RV dysfunction, of these 15% biventricular dysfunction. 65% some measure of abnormal RV function.	57,69
A5	Jenner WJ, Kanji R, Mirsadraee S, Gue YX, Price S, Prasad S, et al[23].	V - Systematic Review	2.928 (29 studies)	100% (22 studies) and mixed population (6 studies)	45 to 70 (23 studies)	69 (24 estudos)	20% CVD (15 studies), 7% AF (3 studies).	16.1% DVT (24 studies) and 2.6% PE (22 studies). 12% arterial thrombosis (9 studies), of which: 3% CVAI, 8% AMI, 2.5% limb or mesenteric ischemia.	9 to 54 (20 studies)
A6	Qian H, Gao P, Tian R, Yang X, Guo F, Li T, et al[24].	VI - Descriptive study	77	100	65,5	68,8	23.4% (one or more CVD), of which 11.7% CAD, 0.6% AMI, 2.6% HF.	Two groups: group with LM (53.2%) and group without LM (46.8%). In the group with LM: 41.5%, 34.1% arrhythmias and 7.3% cardiogenic shock. Elevation of biomarkers: cTn-US, NT-proBNP and D-dimer.	75.3 (total), of which 7.8 (cardiovascular).

Legenda: AVEI - Ischemic stroke, CABG - Coronary artery bypass graft surgery, cTn-Us - Ultrasensitive Troponin I, AoS - Aortic stenosis, ECG - Electrocardiogram, PE - Pulmonary embolism, AF - Atrial Fibrillation, LVEF - Left Ventricular Ejection Fraction, VF - Ventricular Fibrillation, AMI - Acute Myocardial Infarction, STEMI - Acute Myocardial Infarction without ST Supra, IC - Heart Failure, PCI - Percutaneous Coronary Intervention, ISST - ST-segment elevation, LM - Myocardial Injury, Mi - Mitral valve, NT-proBNP - N-terminal pro-b-type natriuretic peptide, VTE - Venous thromboembolism, VT - Ventricular Tachycardia, DVT - Deep Vein Thrombosis, TxC - Heart Transplant, RV - Right Ventricle, LV - Left Ventricle.

Among the articles with primary data, the countries in which they were conducted are Oman[19], Morocco[20], United States of America[22] and China[24]. The review articles did not specify where the research was carried out, but in one article we have authors from the United Kingdom, Australia and Malaysia[21], and in other authors only from the United Kingdom[23].

The total number of patients was 4,585, the mean age of patients was 60.8 years (in five studies)[19-22,24], one study only cited a mean age between 45 and 70 years[23]. Men made up approximately 69.5% of the sample of articles.

A5[23] reports that of the patients who used Extracorporeal Membrane Oxygenation (ECMO), 9 studies with 13% of the pa-

tients, and Renal Replacement Therapy (RRT), 8 studies with 18% of the patients, system thrombosis occurred in 27.1% and 96.6% of them, respectively.

A6[24] does not report the percentage of patients who had biomarker changes, but reports that the mean serum values were 312.8 ng/L (cTn-US), 2,251 ng/L (NT-proBNP) and 21 mg/dL (D-dimer).

Subsequently, three central themes were identified for compilation of the results, namely: patients with prior CVD; patients who developed cardiac or vascular diseases during hospitalization; patients who developed alterations in biomarkers of cardiac injury and fibrin degradation, as shown in charts 2, 3, and 4:

Table 2. Patients with previous CVD.

Articles	Evidence
A1, A5	Previous presence of unspecified CVD.
A4, A6	Prior presence of structural diseases: CAD, AoS.
A4, A6	Prior presence of functional diseases: AMI, HF, MI regurgitation, LV and/or RV dysfunction.
A4, A5	Prior presence of electrical diseases: AF / atrial flutter
A2, A4	Prior presence of structural or functional diseases (not specified): patients who underwent PCI with stenting, CABG, TxC.

Legenda: CABG - Myocardial Revascularization Surgery, AoS - Aortic Stenosis, AF - Atrial Fibrillation, AMI - Acute Myocardial Infarction, PCI - Percutaneous Coronary Intervention, MI - Mitral, TxC - Heart Transplantation, RV - Right Ventricle, LV - Left Ventricle.

Table 3. Patients who developed cardiac or vascular diseases during hospitalization.

Articles	Evidence
A1, A2, A4, A6	Electrical changes, involving: VT/VF, AF, isolated tachycardia, ST-segment elevation with or without tachycardia, ST-segment depression, tachycardia with inverted T-wave.
A1, A2, A4	Structural alterations: myocarditis, pericarditis, RV enlargement.
A1, A2, A4, A5	Functional changes: AMI, HF, LVEF drop, new or worsening LV and/or RV dysfunction.
A2	Changes related to clinical signs and symptoms: of left HF (not specified), right HF (not specified), pericardial friction.
A1, A6	Cardiogenic shock.
A2, A5	Development of LVA.
A2, A5	Development of PE.
A3	Development of VTE.
A5	Development of DVT .
A2, A5	Development of limb or mesenteric ischemia .

Legenda: AVEI - Ischemic stroke, PE - Pulmonary Embolism, AF - Atrial Fibrillation, LVEF - Left Ventricular Ejection Fraction, VF - Ventricular Fibrillation, AMI - Acute Myocardial Infarction, HF - Heart Failure, VTE - Venous Thrombo Embolism, VT - Ventricular Tachycardia, DVT - Deep Vein Thrombosis, RV - Right Ventricle, LV - Left Ventricle.

Chart 4. Patients who developed alterations in biomarkers of cardiac lesion and fibrin degradation

Articles	Evidence
A1, A2, A6	Serum Troponin changes (above the 99th percentile or cTn-US).
A6	Serum alterations of NT-proBNP.
A2	Serum D-dimer alterations.

Legenda: cTn-Us - Ultrasensitive Troponin I, NT-proBNP - N-terminal pro-b-type natriuretic peptide.

DISCUSSION

Patients with Covid-19 and admitted to the ICU, may present prevalence of cardiovascular diseases. The results obtained in this review converge with those of other studies, such as the prevalence of CAD in 44% of patients, 16% had PCI with stenting, 6% had a history of CABG, and 40% had HF[25], besides finding previous arrhythmias in 6.9% of patients[26].

The susceptibility of patients with Covid-19, especially those with severe forms of the virus, to develop cardiac involvement during their hospitalization is also since the virus has a high affinity for ACE receptors[27], causing direct impact on the cardiovascular system. The literature shows structural changes, such as enlargement of the cardiac chambers, as found in this review, such as severe RV dilatation in 2.4% of patients[27]. Electrical changes, leading to atrial or ventricular arrhythmias are also found in 39.1% of patients and segmental unevenness in 65.2%[28].

Similarly, new functional modifications or worsening of existing ones can occur due to the overload of the organ, such as, for example, decrease in LVEF in 12.9% of patients, from mild, moderate, or severe intensity[27]. Finally, depending on the severity of the patient's involvement, all these changes caused by the virus can also lead to cardiogenic shock, as observed in 4.3% of patients[27].

The vascular involvement can occur due to the state of progressive hyperinflammation that the virus causes, causing endothelial lesions and leading to venous and/or arterial microangiopathies, thus increasing the risk of thrombotic events[11]. A study cites that the weighted average prevalence of patients with VTE was 32.7%, DVT 17.9%, and PE 16.1%[29]. In addition, cases of VTE were reported in 1.63% of patients in a Dutch study[30].

The cellular changes, structural and/or functional modifications, that the virus triggers in the human body can be monitored through the expression of biomarkers of cardiac injury and fibrin degradation. According to a study of 100 critically ill patients, 9% had an increase in serum cTn-US and 22% of NT-proBNP[31]. Moreover, another study cited elevated levels of D-dimer in 87,36% of patients[32].

CONCLUSION

It is noteworthy the importance of the continuous search for understanding about Covid-19, through evidence that supports the management and care provided by health professionals, especially to individuals in the ICU, with pre-existing CVD, focusing on the prevention of injuries.

In view of the studies analyzed, it was possible to identify that a significant percentage of patients with Covid-19 and admitted to the ICU had pre-existing cardiovascular diseases, such as CAD, previous AMI with PCI with stents or CABG, arrhythmias, ventricular dysfunction, valve changes, among others. Moreover, it was possible to observe that this study population also develops cardiovascular complications during hospitalization, such as arrhythmias, myocarditis, cardiac lesions with decreased LVEF, HF, and cardiogenic shock.

Although it is already known and evidenced that people with pre-existing CVD are more likely to develop severe forms of Covid-19, requiring ICU admission, according to the results found and compared to those already available in the literature until the completion of this study, it was observed that it would be interesting and important to carry out studies in which 100% of the sample had some kind of prior CVD, in order to understand the possible complications that this population could develop during hospitalization.

Likewise, studies that specify the types of cardiovascular events that occurred in this population with Covid-19 and admitted to the ICU, because some studies only mention that the study sample developed "cardiac lesions" or that there was an increase in cardiac biomarkers. As limitations of the present study, we point out that further research has been conducted after its completion, which will certainly add better knowledge, regarding the aggravations of Covid-19, in individuals with CVD.

Thus, we remain concerned about the severity in which Covid-19 can affect people with pre-existing CVD, often leading to critical states, with the need for ICU admissions, use of drugs for hemodynamic stabilization and/or life support equipment and worsening or onset of new cardiovascular conditions.

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