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Laboratory biochemical markers of cardiac injury by COVID-19: an integrative review.

Marcadores bioquímicos laboratoriais de lesão cardíaca por COVID-19: uma revisão integrativa.

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ABSTRACT

The damaging effects of Sars-CoV-2 on cardiac tissue may be intensified with the presence of cardiocirculatory pathologies. The use of clinical biomarkers has grown, in order to monitor this cardiotoxicity early. In this sense, this study aimed to investigate, through an integrative review, the main biomarkers of cardiac injury associated with comorbidities in patients with COVID-19. A systematic bibliographic search was conducted on July 26, 2020, in the Scopus database. Of the total of 669 publications purchased, only 40 articles were eligible for this review. From the content of these publications, 16 systemic cardiac and inflammatory biomarkers that are part of the clinical findings of critically ill patients with COVID-19 were identified. Most of these patients were male, had a mean age of 63 years, and pre-existing comorbidities, such as were hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, and chronic obstructive pulmonary disease. Cardiac injuries in patients infected with COVID-19 are related to the increase in cardiac and systemic biomarkers observed in most of these individuals. Finally, it is expected to increase physicians' awareness of biochemical markers of non-invasive cardiac injury, for diagnosis and prognosis, of unusual extrapulmonary pathophysiological presentations during infection by COVID-19.

KEYWORDS: Biomarkers; Cardiac tissue; Comorbidities; COVID-19; Myocardial injury; SARS-CoV-2.

RESUMO

Os efeitos nocivos do Sars-CoV-2 no tecido cardíaco podem ser intensificados com a presença de patologias cardiocirculatórias. O uso de biomarcadores clínicos tem crescido, a fim de monitorar essa cardiotoxicidade precocemente. Nesse sentido, este estudo teve como objetivo investigar, por meio de revisão integrativa, os principais biomarcadores de lesão cardíaca associados a comorbidades em pacientes com COVID-19. Uma pesquisa bibliográfica sistemática foi realizada em 26 de julho de 2020, no banco de dados do Scopus. Do total de 669 publicações adquiridas, apenas 40 artigos foram elegíveis para esta revisão. A partir do conteúdo dessas publicações, foram identificados 16 biomarcadores cardíacos e inflamatórios sistêmicos que fazem parte dos achados clínicos de pacientes gravemente doentes com COVID-19. A maioria desses pacientes era do sexo masculino, tinha idade média de 63 anos, e comorbidades pré-existentes, como hipertensão arterial, diabetes mellitus, doença arterial coronariana, doença cerebrovascular e doença pulmonar obstrutiva crônica. Lesões cardíacas em pacientes infectados com COVID-19 estão relacionadas ao aumento de biomarcadores cardíacos e sistêmicos observados na maioria desses indivíduos. Finalmente, espera-se aumentar a conscientização dos médicos sobre marcadores bioquímicos de lesão cardíaca não invasiva, para diagnóstico e prognóstico, de apresentações fisiopatológicas extrapulmonares incomuns durante a infecção pelo COVID-19.

PALAVRAS-CHAVE: Biomarcadores; Tecido cardíaco; Comorbidades; COVID-19; Lesão miocárdica; SARS-CoV-2.

INTRODUCTION

COVID-19 is a rapidly spreading infectious-contagious disease, with a direct impact on worldwide public health[1]. In parallel with the increased morbi-mortality due to this pandemic situation, an unprecedented race was carried out in several fields of research to search for new alternatives for clinical diagnosis, as well as treatments with better cost-benefit-effectiveness for patients affected by this virus[2]. Previous studies described the general clinical characteristics, and epidemiological findings of patients with MERS and SARS-Cov showing that both are associated with myocardial injury, myocarditis, and heart failure[3-4]. Additionally, clinical evidence has shown that the condition of the patients with comorbidities such as diabetes and hypertension may be associated with an increased risk of death caused by COVID-19[5-6].

The increasing number of cases and the clinical experience acquired about the disease has evidenced that it can affect the pulmonary system, and inducing severe respiratory failure[7] accompanied by extrapulmonary clinical manifestations[8-9]. In these cases, cardiovascular changes have generated great concern and leading to a negative prognosis for patients in risk groups, in addition to possible morpho-functional impairment of the myocardium[10]. An increasing spectrum of cardiac complications includes myocarditis, heart failure, cardiac arrhythmias, and myocardial infarction have been described in clinical findings of hospitalized patients with COVID-19[7-11]. The acute cardiac injury (ACL), is one of the main complications, and it has been described in over 20% of patients, as well as seems to be related to an increased mortality[9-12]. Although the injury mechanism of ACL is not fully understood, its main forms of diagnosis involve clinical indicators, cardiac imaging and biomarkers of acute cardiac damage[13]. In addition, biochemical markers can be useful as non-invasive tools for the early diagnosis and prognosis of patients with severe COVID-19[14]. Give these findings, we conducted an integrative review study to investigate the main cardiac injury biomarkers, which are found in COVID-19 patients, as well as the associated comorbidities.

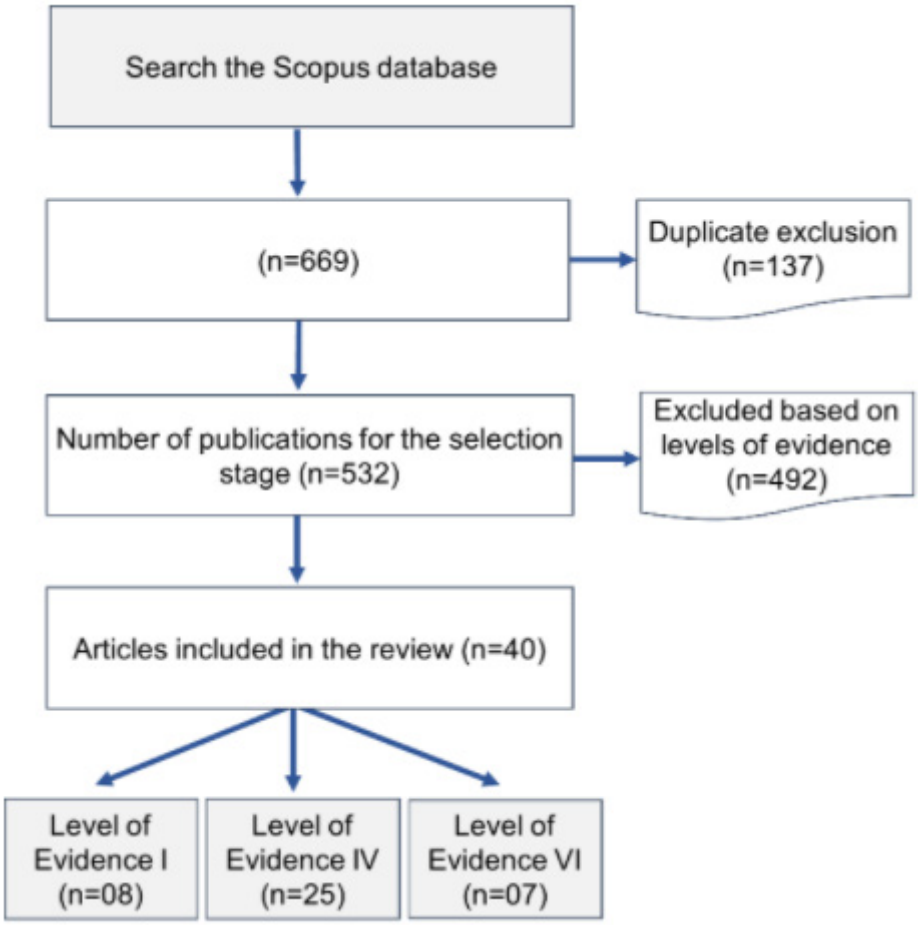
METHODS

This bibliographic review was carried out by searching with the following terms: “Covid-19”, “Sars-CoV-2”, “myocardial injuries“ “biomarkers“, “cardiac injuries“, “cardiac risks”, myocardium, “cardiac function”, “Troponin I”, “Ferritin“, “Transaminases“ and “creatine kinase” and Boolean operators (“ OR ”and“ AND ”) using the Scopus Database, on July 26, 2020. The returned publications were imported in BIBTEX format with the software StArt (State of the Art through Systematic Review), and excluding duplicated records between different search strings.

The initial selection criteria were based on the article titles, and followed by abstracts and methodology. In addition, it was considered publications written in English only, and related to levels of evidence I through VI[15]. (Table 1 of supplementary material). Thus, we selected all publications, including their data such as study sample (n), objectives,

methodology, publication date, country where the research was conducted, main results, conclusions and related cardiac injury biomarkers. The selection process steps are described in Figure 1.

Figure 1: Detailed protocol for the identification, selection, exclusion and inclusion of publications included in this integrative review.



RESULTS

669 publications were obtained from the bibliographic search, and only 40 articles were eligible for this review after applying the exclusion and selection criteria. Within this set of publications, only three levels of evidence have been identified: I, IV, and VI. Thus, the included publications are corresponding to observational case studies (29), a meta-analysis (06), systematic reviews (03), and experimental studies (02) published in scientific journals that present impact factors ranging from 0.8 to 60.392.

From the studies included in this review, 16 systemic biomarkers were identified as part of the clinical findings of critically ill patients with COVID-19, which the most cited are Creatine Kinase-MB (CK-MB), High Sensitive Troponin I (hsTnI), N-terminal Pro-Hormone Brain Natriuretic Peptide (NT-proBNP), MYO (myoglobin), High Sensitive Troponin T (hs-TnT), CRP (C-Reactive Protein), Dimer D (D-dimer), LDH (Lactate Dehydrogenase), and SF (Serum Ferritin). On the

other hand, some studies have not specified the biomarkers which were part of the publications' content. In this sense, a total of nine biomarkers were not identified and discussed in this review (Table 1).

Table 1: Cardiac injury markers selected as the main biomarkers used in the diagnosis of cardiac function, its corresponding number of citations and the main system of the human body where biomarkers can be located.

Biochemical marker [1]	Citations[2]	Human body system[3]
Creatine Kinase-MB (CK-MB)	15	Cardiocirculatory system
High Sensitive Troponin I (hsTnI)	15	Cardiocirculatory system
N-Terminal Pro-Hormone Brain Natriuretic Peptide (NT-proBNP)	12	Circulatory system
Unspecified biomarker*	9	-
Myohemoglobin (MYO)	8	Muscle system
High Sensitive Troponin T (hs-TnT)	7	Cardiocirculatory system
C reactive protein (CRP)	6	Digestive system Circulatory system
D-dimer	6	Circulatory system
Lactate dehydrogenase (LDH)	6	Others systems
Serum ferritin (SF)	5	Hematological system
Interleukin-6 (IL-6)	4	Systemic inflammation
Transaminase enzyme (AST/ALT)	4	Enterohepatic system
B type natriuretic peptide (BNP)	3	Circulatory system
Procalcitonin (PCT)	3	Others systems
Aspartate aminotransferase (AspAT)	2	Enterohepatic system
Blood urea nitrogen (BUN)	2	Imune System
Interleukin-10 (IL-10)	1	Imune System

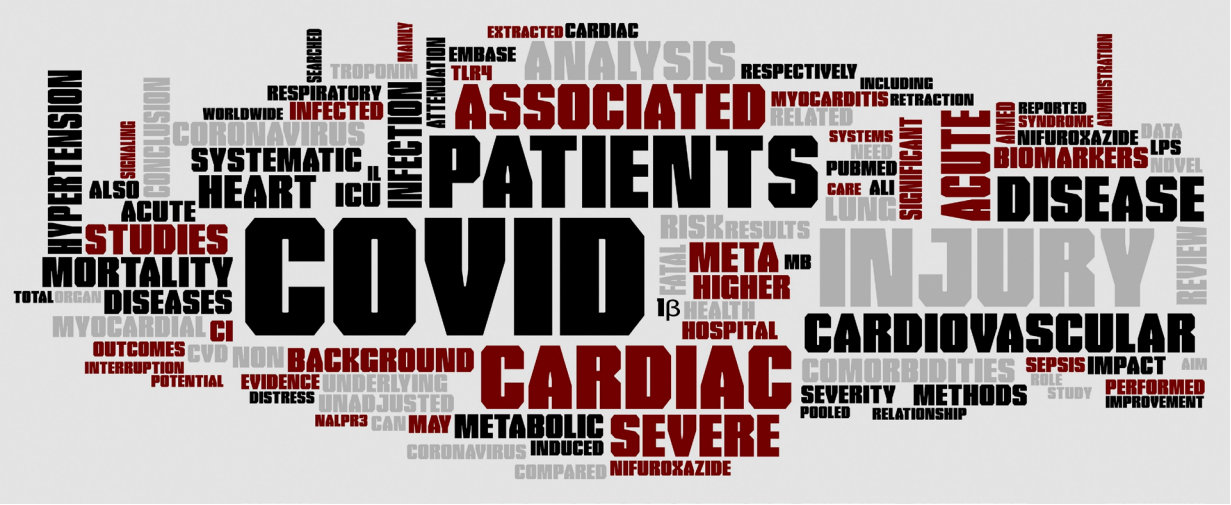
[1] Covid-19 associated cardiac injury biomarkers that were cited in publications included in this review.
[2] Number of publications that cited the biomarkers present in table 1.
[3] Human body systems where the biochemical marker can be located.
* Biomarkers not specified within the studies.

In summary, the studies addressed in this review report clinical analyzes performed with patients affected by COVID-19, mostly hospitalized. Among these patients, the most frequent were mean 63 years age male with pre-existing comorbidities, which were the most common: hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, and chronic obstructive pulmonary disease. Clinical findings revealed that several of these patients had a myocardial injury, defined by elevated cardiac biomarkers, which were the most reported: hsTnI, CK-MB and NT-proBNP.

Among the publications included in this review, there was greater representativeness of observational studies and meta-analyses. For these studies, the most addressed biomarkers were CK-MB (for observational studies only) and hsTnI (for both cases). Six Meta-analyses were identified with a higher prevalence of studies focusing on hsTnI, and only two experimental studies. Additionally, only one of these studies discussed a single biomarker, the BNP (Table II of Supplementary Material).

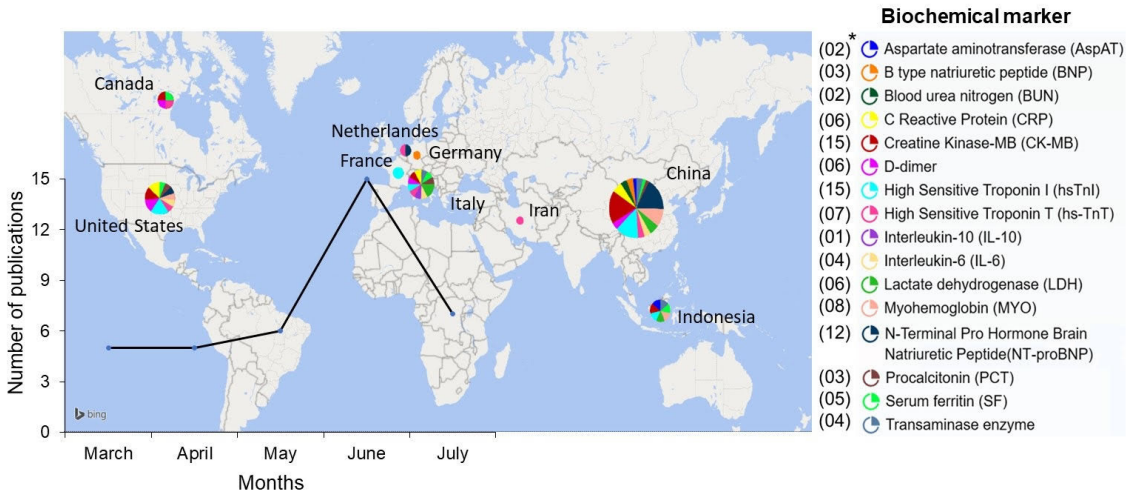
According to the global geographic distribution of research institutions that were involved with the selected studies on biomarkers of cardiac injuries associated with Covid-19, the publications were conducted in 12 countries, with China, Italy, and the United States as the most representative. The most frequent biomarkers among the studies, and with the greatest distribution among the countries were CK-MB, hsTnI, and NT-proBNP. Regarding the temporal analysis of the included studies, it was identified that they were published in the month of March more frequently, mainly in the months of June and July 2020 (Figure 2).

Figure 2: Geographical distribution of the studies included in this review. Map of biomarkers of cardiac injuries showing the locations where the studies were performed and the *number of biomarkers that were included in each study. Number of articles published between the months of 2020.



Based on the titles and abstracts of all publications included in this review, a word cloud was constructed to reflect the fifty most cited terms. The most prominent words are COVID-19, Patients, Coronavirus, Disease, Myocardial, Injury, Biomarkers, and Troponin. These data suggest that the research and selection strategy was efficient and consistent with the proposed objectives of this study (Figure 3).

Figure 3: Word map that reflects the most cited terms within the set of articles included in this review.



DISCUSSION

More recently, the interest in non-invasive biomarkers diagnoses has grown, in order to early predict and monitor the aggressive pathophysiological effects induced by COVID-19 on the patients' myocardium[16]. Using biomarkers are less costly than cardiac imaging techniques, as well as this is easily repeated without the irradiation effects to the patient. Thus, the main cardiac markers most cited in this study are described below.

High Sensitive Troponin I (hsTnI)

Troponin (cTn) is an extremely sensitive and specific clinical biomarker to assess myocardial injury[17]. Due to its importance, it has become a standardized marker for ischemic heart injury. Currently it has been associated with other diseases with cardiocirculatory repercussions such as left ventricular hypertrophy, congestive heart failure, pulmonary embolism, blunt trauma, sepsis, moderate renal failure, diabetes mellitus and cardiotoxicity associated with antitumor drugs[18]. This biomarker was found in patients with cardiac comorbidities hospitalized with COVID-19 in hospitals[19].

Patients admitted with COVID-19 are noteworthy due to a large number of clinical abnormalities, many of them associated with the increase or unevenness of cardiac and inflammatory biomarkers[19]. The hsTnI can be found in altered levels in a clinical condition of patients who have a basic epidemiological profile involved with cardiovascular disease, and including advanced age and male gender (between 50-80 years), with some of them progressing to the aggravation of the clinical condition[10-20]. In all situations analyzed the hsTnI was at altered levels, including after patients' death[7-21].

The HsTnI is considered the gold standard for assessing associated myocardial lesions, especially for pre-existing cardiac comorbidities[22]. In patients with COVID-19, its changes are also related to the elevated level of other biomarkers

such as BNP, CK-MB, CRP, neutrophilia, and urea[5-23]. The strong correlation between the risk of death from COVID-19 and underlying cardiovascular diseases further increases the importance of diagnosis using this biomarker[23]. In this way, monitoring its plasma concentrations could guide doctors in conducting a faster and more effective drug treatment, avoiding or minimizing bad prognosis.

Cerebral Natriuretic Peptide (NT-proBNP)

Cerebral Natriuretic Peptide is a potent hormone released by the heart into the systemic circulation, and this is used as a biomarker for assessing the risk of future cardiac events (prognosis)[24]. Furthermore, when this hormone is enzymatically cleaved it produces an active compound, the BNP, and one inactive, the NT-proBNP, and it has been related that both have their concentration elevated in cases of increased myocardial tension[25]. Patients with a severe COVID-19 clinical condition and cardiac injury have a higher level of NT-proBNP, and it have been shown a significantly increased rates in non-survivors when compared to the survivors[7,19]. Thus, the elevation of this biomarker, together with other risk variables, such as: age, female gender, hypertension and coronary heart disease, is related to heart complications and shorter patient survival time[26]. Therefore, monitoring is an important careful by using NT-proBNP profiles as a parameter with high sensitivity (100%) and relative specificity (66.67%) to predict hospital death in low doses (88.64 pg/mL), although it cannot be used to exclude or suggest cardiac dysfunction[27,28,29]. Therefore, in the current pandemic situation, where resources are scarce, this biomarker can be used for risk stratification in infected patients[24].

Creatine kinase (CK-MB)

CK-MB is found predominantly in the cardiac muscle, representing about 15% of the total CK in this tissue[30]. It is used as a biomarker of cardiac injury, as it is elevated in cases of ischemia and tissue hypoxia[31]. In large-scale infarctions, for example, this isoenzyme shows high correlation between the size of the cardiac damage and its global fraction ejection after myocardial injury[32]. Thus, CK-MB is an important marker for monitoring and identifying patients with COVID-19 who developed cardiac injury and predict clinical complications[19]. In addition, CK-MB has greater sensitivity and specificity for predicting mortality from cardiac damage in a hospital environment[25], such it was demonstrated in a study that included a total of 4,189 patients confirmed with COVID-19 which pointed out that CK-MB was among the cardiac injury biomarkers that increased above the normal range (0-5 ng/mL) at the midpoint of hospitalization and immediately before death[33]. Furthermore, these results demonstrated a remarkable value for the prognosis of cardiac injury.

Other Biomarkers

Serum Ferritin (FS), is an intracellular iron storage protein, and an important parameter for quantifying this metal

in the body. Its elevation is not specific, however it is related to inflammatory states34, such as those observed in severe cases of COVID-19[12, 34.]

C-reactive protein (CRP) is mainly produced in the liver and is traditionally associated with acute inflammation and cardiovascular events, as well as it is one of the markers involved in the "cytokine storm" once it seems to be associated with cardiac injury[35] and directly related to the increase in mortality, its values being higher in patients with this outcome than in survivors[36].

Lactate dehydrogenase (LDH) is an enzyme related to the use of intracellular glucose, released into the bloodstream as an effect of cell damage. Different organs have different types of the isoenzyme LDH allowing, therefore, the location of the cell lesion[37]. In this case, the enzyme blood concentration is high at the beginning of the inflammatory process and decreases as the inflammation progresses, being an important, highly sensitive, but not very specific instrument[38]. The increase of LDH rates in patients with COVID-19 is compatible with other cardiac markers (CRP, PCT, NT-proBNP and CK-MB), as those related for patients with a higher prevalence of pre-existing cardiovascular disease, advanced age, as well as cardiac comorbidities with progression to death[39-40].

D-Dimer is a biomarker derivative of the blood coagulation and decomposition process[41]. The persistent activation of the coagulation cascade can induce the disseminated intravascular coagulation (DIC) process, which is very common in patients with significantly high D-Dimer values[42] and mainly caused by infection, inflammation, and surgery[43]. The hypoxia commonly associated with DIC is considered to be one of the most related factors generated by COVID-19, which is related to ischemic damage to the myocardium[44]. It was observed that patients with severe COVID-19, presented ischemic changes in the fingers, which may develop DIC, elevated D-Dimer level, and prolonged prothrombin time, as well as suggesting an excessive activation of coagulation, leading to increased mortality[45]. In addition, coagulative abnormalities linked to the viral infectious inflammatory process are directly associated with cardiac injury[36].

The bibliographic material analyzed in this review related an increase in inflammatory markers and an evolution in the levels of cardiac markers, and it can be inferred that inflammation may be one of the main causes of complications in the clinical condition of patients with comorbidities, being a risk factor for death[46]. The other biomarkers associated with systemic changes caused by the "cytokine storm" may indirectly signal future damage to the myocardium. The increase of transaminase ratios (AST/ALT), as well as the C-reactive protein, suggests a possibility of liver dysfunction and acute inflammation[47], the latter being an important additional biomarker to assess the risk of future cardiac events.

The elevated serum levels of the interleukins IL-6, IL-10, IL-8, and interleukin-2 receptor, as well as plasma urea, were observed in non-surviving patients, which implies that "cytokine storm" is associated bad prognostics for COVID-19[23]. IL-1 and TNF-alpha are cytokines produced in the early response to viral infection, interleukin-1β in particular has its production reduced in a late inflammatory process[46]. The cytokines and chemokines produced by the infected cells

imply not only the extensive infiltration of neutrophils and macrophages, but it also leads to tissue damage, both locally and systemically[48]. Furthermore, when released in the hyperinflammatory response, they activate various organ systems and tissues that respond by producing other biomarkers such as procalcitonin, which is find elevated together with CRP, and it is strongly suggestive of secondary bacterial infection, observed in the weakened immune system of patients with severe COVID-19[23]. This biomarker is directly related to lower airway infections affected by SARS-CoV-2 and is also released with thyroid neuroendocrine cells, hepatocytes, renal cells, adipocytes, and myocytes[49].

Myoglobin (MYO) is the main intracellular oxygen transport protein in muscle tissues (skeletal and cardiac). This protein works as an indicator of myocardial injury risk, and it has been observed in high serum concentrations in patients with severe COVID-19[50, 39.] Additionally, in patients with cardiac comorbidities, it may be directly associated with the lethality rate of COVID-19[51]. However, in many cases the myoglobin does not appears altered, so its analysis is associated with other biomarkers such as troponin, CK-MB, and NT-proBNP, and it has become necessary for accurately identifying severe cases of myocardial injury as a secondary consequence of SARS-CoV-2[52].

FINAL CONSIDERATIONS

Patients infected with COVID-19 may have cardiac lesions. These changes are related to the increase in cardiac and systemic inflammatory biomarkers observed in most of these individuals. Thus, directly or indirectly, cardiomyocytes can be affected by SARS-CoV-2. Finally, it is expected to increase awareness among physicians about biochemical markers, mainly of cardiac injury, and about unusual extra-pulmonary pathophysiological presentations during infection.

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