

REVIEW ARTICLE

IMPACT OF ACUTE COVID-19 ON CARDIAC FUNCTION IN THE LONG TERM: A Systematic Review

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Highlights:

- (1) Uncertainties regarding the prediction of permanent damage based on biomarkers.
- (2) Routine measurements are only justified in patients with high cardiovascular risk.
- (3) Low prevalence of significant results regarding the use of echocardiography.

ABSTRACT

The present study aimed to evaluate the relationship between elevated biomarkers due to Covid-19 infection and possible permanent damage to the heart muscle. This is a systematic review including studies with eligible randomized clinical trials and case-control studies. Papers' eligibility criteria were adults diagnosed and treated for Covid-19 and assessment of cardiac biomarkers during the acute phase of Covid-19 infection, with symptoms or not, without previous structural or functional changes related to the cardiovascular system and who, after a minimum of after 30 days, cardiac structural assessment was obtained through imaging tests, either echocardiogram or cardiac magnetic resonance. The findings were not robust when analyzing the association between the elevation of secondary cardiac biomarkers to Covid-19 and the presence of late cardiac sequelae. Based on the cost-effectiveness ratio for adopting such strategy, it becomes unjustifiable to perform it routinely in the Brazilian Unified Health System. It is more appropriate and less costly to adopt health promotion strategies, individualized attention, multidisciplinary therapeutic approach, frequent clinical surveillance and specialized assessment when affected by Covid-19, reducing damage caused to the cardiocirculatory system, minimizing spending on public health exams and better effectiveness in collective health with care practices.

Keyword: biomarkers; troponin; natriuretic peptide; brain; myocardium; Covid-19.

IMPACTO DA COVID-19 AGUDA NA FUNÇÃO CARDÍACA A LONGO PRAZO: UMA REVISÃO SISTEMÁTICA

RESUMO

O presente estudo teve como objetivo avaliar a relação entre a elevação de biomarcadores devido à infecção por Covid-19 e possíveis danos permanentes ao músculo cardíaco. Trata-se de uma revisão sistemática que incluiu estudos com ensaios clínicos randomizados elegíveis e estudos de caso-controle. Os critérios de elegibilidade dos artigos foram: adultos diagnosticados e tratados para Covid-19 com avaliação de biomarcadores cardíacos durante a fase aguda da infecção pelo coronavírus, sintomáticos ou não, sem alterações estruturais ou funcionais prévias relacionadas ao sistema cardiovascular e que, após um mínimo de 30 dias, realizaram avaliação estrutural cardíaca por meio de exames de imagem, como ecocardiograma ou ressonância magnética cardíaca. Os achados não foram robustos ao analisar a associação entre a elevação de biomarcadores cardíacos secundários à Covid-19 e a presença de sequelas cardíacas tardias. Com base na relação custo-efetividade da adoção de tal estratégia, torna-se injustificável sua realização rotineira no Sistema Único de Saúde. É mais apropriado e menos dispendioso adotar estratégias de promoção da saúde, atenção individualizada, abordagem terapêutica multidisciplinar, vigilância clínica frequente e avaliação especializada quando acometido pela Covid-19, reduzindo os danos causados ao sistema cardiocirculatório, minimizando os gastos com exames em saúde pública e obtendo melhor efetividade em saúde coletiva com práticas assistenciais.

Palavras-chave: biomarcadores; troponina; peptídeo natriurético cerebral; miocárdio; Covid-19.

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INTRODUCTION

Due to the Covid-19 (Sars-CoV-2) pandemic, the infected population began to show severe symptoms of acute respiratory dysfunction syndrome (Ards)^{1,2}. Although the virus mainly affects the respiratory system, cardiovascular complications are also common³.

Myocardial injury, reflected in high concentrations of biomarkers, such as Troponin, BNP and NT-pro BNP, are widely described in the acute stages of Sars-cov-2 infection⁴. The increase in the levels of cardiac biomarkers (BNP, NT pro-BNP and Troponin) reflects an excessive amount of inflammation, viral load, cytokine storm and atherothrombotic processes, which can cause direct and indirect cardiac damage. This demonstrates the relevance of these parameters with important information not only in the acute phase, but also in quantifying the risk of long-term mortality after Covid-19 infection⁵. Furthermore, dilations and other structural changes were identified in echocardiogram and cardiac resonance examinations in patients acutely affected by the disease⁶.

Currently, the most plausible cause of myocardial injury found in Covid-19 is the presence of ACE2 receptors in the myocardium. These receptors allow the binding of the Sarscov2 structural protein, leading to a direct viral infection of the heart. Furthermore, Covid-19 infection-mediated vasculitis may also contribute to causing direct myocardial injury because of ACE2 receptor expressions on arterial and venous endothelial cells⁷.

A meta-analysis showed that the high level of NT-pro BNP was associated with increased mortality in Covid-19 pneumonia with satisfactory AUC and specificities, and the possibility that NT-pro BNP was independently associated with mortality after adjustments in myocardial troponin and creatine kinase band⁸.

Considering that the majority of patients recover from the disease, understanding the late consequences on the heart muscle is still uncertain, but extremely relevant. Therefore, the present study aims to verify whether there is evidence relating the detection and/or elevation of Troponin and Brain Natriuretic Peptides (BNP; NT-Pro BNP) in the acute phase of Sars-Cov-2 infection and the presence of permanent cardiovascular damage or possible long-term sequelae.

METHODS

The systematic review was carried out based on studies of case-control, prospective and cohort studies that aimed to verify the causal relationship between troponin and brain natriuretic peptides and the long-term impact on cardiac function of patients affected by Covid 19.

The search for articles was conducted in the Cochrane Library, Medline, Embase e Lilacs databases and the following search strategy was designed, developed with Boolean operators, and matched to accessible and available databases: “((“Brain natriuretic peptide”) OR (“Troponin” OR “Troponin T” OR “Troponin I” OR “Troponin C”)) AND (“Covid-19” OR “Sars-CoV-2”)). The search was conducted on October/2023 and the articles included were from 2020 to the date of the collection. The articles found in the databases were exported and combined in the Rayyan reference manager software.

The Pico strategy was applied by the author to determine the inclusion and exclusion criteria for this systematic review. Summarily, the population included patients diagnosed with Covid-19 confirmed by nasal swab and antigen test and/or PCR test. Based on this population, those who had their cardiac biomarkers measured within 7 days of the primary diagnosis were included. Carrying out cardiac imaging tests (echocardiogram and/or magnetic resonance imaging) after a minimum of 30 days of the disease recrudescence period and evaluating the outcomes related to cardiac function and structure found.

Studies that included a population aged between 18 and 64 years old, infected by Covid 19, were considered for reading and inclusion in the review, in which cardiac biomarkers were measured – especially BNP, NT pro-BNP and Troponin – during the acute infection and who, at least 30 days after the resurgence of the disease, presented or not, some type of structural evidence of damage to the myocardium, assessed through imaging tests such as Echocardiography and/or Magnetic Resonance. The inclusion criteria for titles and abstracts were established for all articles that allow quantifying or qualifying data that establish a relationship between acute Covid 19 infection, the detection of cardiac biomarkers and the presence of late or long-term myocardial damage (greater than 30 days after primary infection).

Articles carried out through case-control, prospective and cohort studies, which showed an increase in cardiac biomarkers related to the acute phase of Covid-19 infection with symptoms and structural or functional changes related to the cardiovascular system, were considered eligible. Patients who present an increase in cardiac biomarkers related to the acute phase of Covid-19 infection and who, after 30 days, still present symptoms, structural or functional changes related to the cardiovascular system. Studies that highlighted the treatments used during the acute phase of the disease and assessed the presence of comorbidities as risk factors for cardiovascular diseases (SAH, DM2, dyslipidemia and smoking).

The first step for screening the data was excluding the duplicated articles pointed out by the Rayyan software. After that, the authors started reading the title and abstracts based on the inclusion and exclusion criteria. Finalized this step and the authors in accordance with the articles included and excluded, started the step of reading the whole paper.

Two independent authors assessed the risk of bias in each included study, as follows: sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The risk of bias of primary studies was assessed using the Risk of Bias 1.0 (RoB 1.0, Cochrane Collaboration) tool. This process was performed in duplicate (LGM and JMF) and only the final decision was verified (i.e., “potentially yes” and “yes” decisions that do not change the direction of the algorithm will be considered the same). In case of discordance, a third researcher was invited to take the decision.

Based on the articles included in the review, we qualitatively grouped the data to present results in a systematic way. Narrative synthesis of the studies, including information about the method and main results as well as quantitative information about the results were analyzed (e.g., means, standard deviations, significance levels, confidence intervals, effect sizes) and presented.

RESULTS

Based on the search strategy (Figure 1), 1,213 papers were identified from Embase, 439 from Medline and 5 from Cochrane. No study was identified in Lilacs database. After excluding the duplicated studies (n = 147), a total of 1,510 papers were identified. After initial screening on titles and abstract, 107 articles were considered suitable for full-text screening. Lastly, only 12 articles met the eligibility.

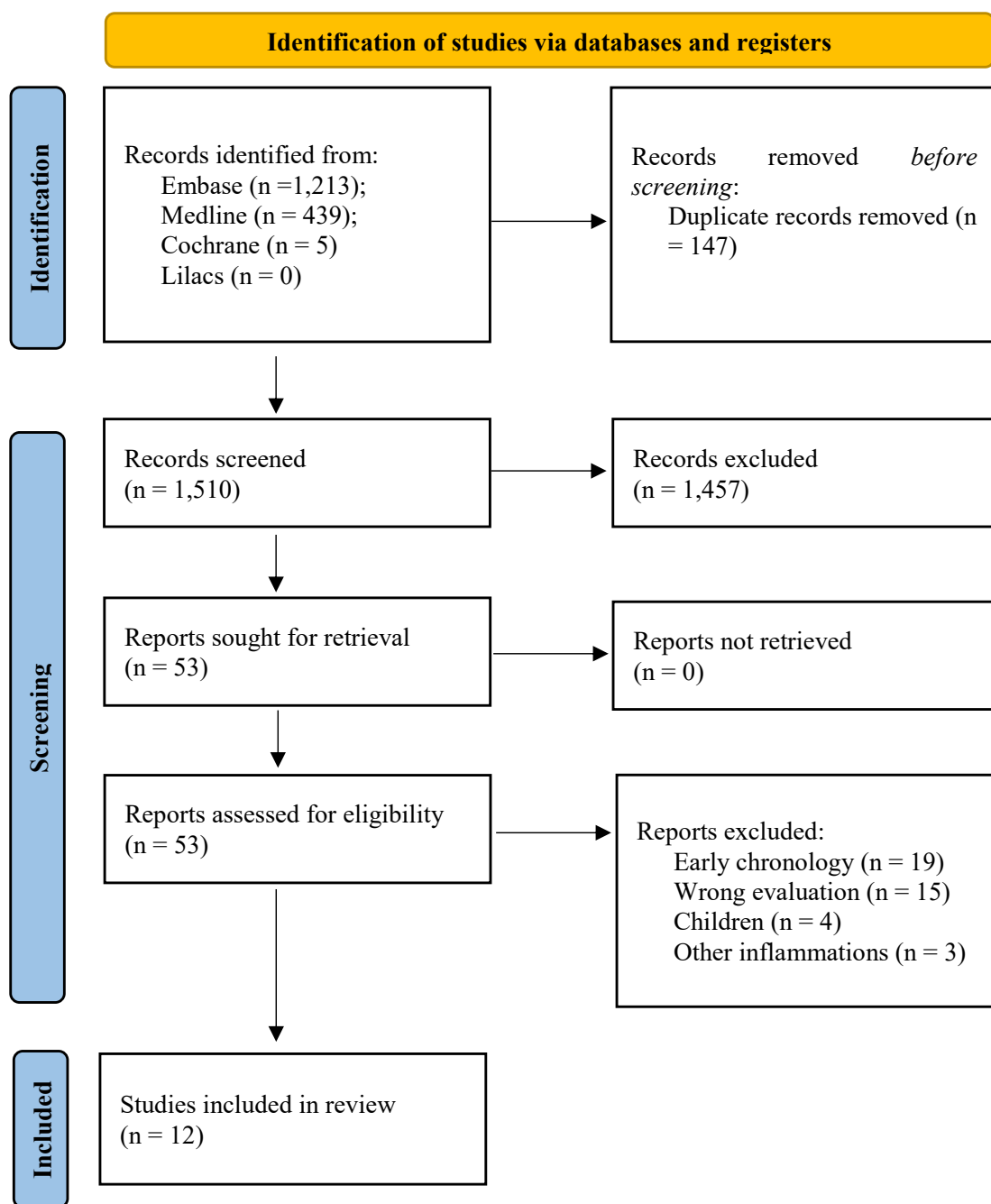


Figure 1 – Prisma flowchart.

Table 1 presents the detailed characteristics of the papers included in the review. Age is one of the major associated risk factors. Several studies were carried out with populations considered to be young (under 60 years old), which can substantially interfere with the results achieved. The study evaluation period was very short (average of 4.4 months), considering that the pandemic lasted for more than 2 years. Furthermore, numerous different virus strains were identified in the meantime, which may have overlooked a considerable number of the affected population and, consequently, information that could reveal results different from those obtained in this study.

Table 1 – Detailed characteristics of included studies

1º Author	Journal	Study design	Country	Evaluation time after COVID-19 ("follow up")	Study period	N / population, sex and age
Myhre et al	Frontiers in Cardiovascular Medicine, American Heart Journal	Prospective observational	Norway	Mean: 175 days (105-217 days)	March 18 th , 2020 – May 4, 2020	N= 58; (30M – 28F); Mean age: 56 (50-70)
Italia et al	Ecocardiography	Case control, Prospective observational	Italy	Mean: 85 days (70 – 103 days)	March 3 rd , 2020 and May 13 th , 2020	N = 123 (84M- 39F); Mean age: 62,1anos (+/-12,9) Control = 77 patients
Huang et al	JACC Cardiovascular imaging	Retrospective observational	China	Mean: 47 days (36-58 days)	March – April, 2020	N= 26 (10M-16F); Mean age: 38 (32-45) Control = 20 patients
Rodenás -Alesina et al	International Journal of Cardiology	Case control, Prospective observational	Spain	Mean: 210 days (198 – 225 days)	March 1 st – May 25 th , 2020	N=61 w/ positive biomarkers (40M – 21F); Mean age: 62.7 (53.2 – 72.1) Control = 29 patients
Gul et al	Journal of Physiology and Pharmacology	Observational cohort	Türkiye	Mean: 58,4 days (10-180 days)	November, 2020 – July, 2021	N = 126 w/ positive biomarkers (64M – 62F), Mean age: 43.4 (± 11.9) Control: 98 patients
Lassen et al	European Journal of Heart Failure	Longitudinal cohort, prospective observational	Denmark	Mean: 77 days (72-92 days)	March 30 th – June 3 rd , 2020	N = 91 (54M – 37F), Mean age: 63 (±12) Control = 91 patients
Van den Heuvel et al	The International Journal of Cardiovascular Imaging	Prospective cohort	Netherlands	Mean: 131 days (116 – 136 days)	April 1 st – May 12 th , 2020	N = 40 (31M – 9F), Mean age: 62,5 (53.5 – 68)
Kotecha et al	European heart Journal	Prospective cohort	United Kingdom	Mean: 56 days (30– 88 days)	January, 2020 – June, 2020	N=148 (144M – 44F), Mean age: 64 (52-76)
Puntmann et al	Nature Medicine	Prospective observational cohort	Germany	Mean: 109 days (77–177 days)	19/April/2020 – October/2021	N = 346 (165M – 181F), Mean age: 43.3 (± 12.1)
Joy et al	JACC Cardiovascular Imaging	Longitudinal prospective control case	United Kingdom	Mean: 189 days (176 – 200 days)	September 3 rd , 2020 – November 7 th , 2020	N = 74 (38M – 46F) Mean age: 39 (30 – 48)
Breitbart et al	Clinical Research in Cardiology: Journal of the German Cardiac Society	Longitudinal prospective control case	Germany	Mean: 70,7 days ± 65,9 days	November, 2020 and March, 2021	N = 56 (26M – 30F), Mean age: 45,7 (±12.2)
Puntmann et al	Jama Cardiology	Prospective observational cohort	Germany	Mean: 71 days (64-92 days)	April, 2020 – June, 2020	N = 100 (53M – 47F), Mean age: 49 (±14) Control = 50 patients

M= male; F= female

The studies included in the review did not have standardized assessment protocols (Table 2), as each study adopted a different strategy for evaluating cardiac morphological parameters. A significant number of studies were unable to perform cardiac structural assessments at the time of Covid-19 diagnosis and concomitantly with biomarker measurement, leaving structural assessment only through imaging, after the period of recrudescence. Therefore, by not knowing the previous condition of the heart of the individuals evaluated, the accuracy and power of comparison of the data collected are reduced

Table 2 – Measured values of the cardiac structure including function, volumes, presence of late enhancement and global longitudinal strain of the left ventricle, in addition to the presence of other findings unrelated to cardiac sequelae

1º Author	Ejection fraction (%) / <i>p-value</i>	Indexed left diastolic volume (ml/m ²) or measured in ml / <i>p-value</i>	Indexed right diastolic volume (ml/m ²) or measured in ml / <i>p-value</i>	Strain (%GLS) in the Echo or late enhancement in NMRI	Patients with image exam alterations (effusion, inflammation, edema)
Myhre et al	59% (±7.8) / <i>p</i> = 0.58	74.6ml (±13.7) / <i>p</i> = 0.26	72.9ml (±13.1) / <i>p</i> = 0.15	GLS: -19.1% (± 1.8) / <i>p</i> = 0.69	N = 12
Italia et al	BM+: 59% (± 1) BM -: 59% (±1) / <i>p</i> = 0.69	BM+: 103ml (± 3) BM -: 102ml (±4) / <i>p</i> = 0.89	BM+: 82ml (±5); BM -: 80ml (± 4) / <i>p</i> = 0.76	BM+: GLS: - 15% (±0.7) BM -: GLS: -18.1% (± 0.3) / <i>p</i> < 0.001	N = 13
Huang et al	Experimental: 60.7% (± 6.4) Control: 63% (± 8.9) / <i>p</i> = 0.40	Experimental: 43.9 ml/m ² (± 10.7) Control: 47.3ml/m ² (± 10.1) / <i>p</i> = 0.49	Experimental: 44.1ml/m ² (±10.2) Control: 44.1ml/m ² (±10.2) / <i>p</i> = 0.62	Positive delayed enhancement in 15 patients	N = 15
Rodenás -Alesina et al	Experimental: 59% (58 – 63) Control: 60% (58 – 64) / <i>p</i> = 0.764	Experimental: 51.5ml/m ² (45.5 – 60.4) Control: 48ml/m ² (40.7 – 62.9) / <i>p</i> = 0.767	Experimental: 49.7ml/m ² (42.1 – 59.9) Control: 50.1 ml/m ² (43.7 – 60.3) / <i>p</i> = 0.652	Experimental: GLS: – 20.3% (-18.2 – 21.4) Control: GLS: – 21.1% (-19.9 – 22.5) / <i>p</i> = 0.151	N=5
Gul et al	Experimental: 60% (55-67) Control 64% (55-68) / <i>p</i> 0.006	Experimental: 46ml/m ² (36-56) Control: 45ml/m ² (34-52) / <i>p</i> 0.048	NR	NR	N=5
Lassen et al	Baseline: 59% (±6.2) Follow up 57.1% (±7.4) / <i>p</i> 0.55	Baseline: 98 ml (± 32) Follow up: 99ml (±30) / <i>p</i> 0.02	84 ± 30ml / <i>p</i> 0.04	Baseline: GLS: -17.6% (± 3.3) Follow up: GLS: -17.4% (±2.9) / <i>p</i> 0.004	NR
van den Heuvel et al	Baseline: 60% (56-60) Follow up :58% (54.3 – 60.4) / <i>p</i> 0.544	Baseline: 83ml (68-92ml) Follow up: 81ml (67 –93) / <i>p</i> 0.036	NR	Baseline: GLS: -18.5% (-19.5 – 17) Follow up: GLS: -19.1% (- 20.8 – 18.2) / <i>p</i> 0.067	NR

Kotecha et al	BM+: 67% (± 8) Control: 67% (± 9) / p 0.55	BM+: 67ml/m ² (± 15) Control: 60ml/m ² (± 13) / p < 0.001	BM+: 70ml/m ² (± 12) Control: 65ml/m ² (± 13) / p < 0.025	BM+: 49% with Positive delayed enhancement Control: 45% with Positive delayed enhancement / p 0.8	54% dos patients; N = 80
Puntmann et al	Baseline: 56.6% (± 4.6) Follow up: 56.9% (± 4.8) / p 0.318	Baseline: 86.3ml (± 13.8) Follow up: 85.2 ml (± 13.9) / p 0.315	NR	Baseline: GLS: -19.4% (± 3.1) Follow up: GLS: -18.7% (± 3.2) / p 0.070 Positive delayed enhancement 135 (39%) / p < 0.001	NR
Joy et al	Experimental: 67.5% (64.4 – 70.2) Control: 66.8% (62.8–70.1) / p = 0.28	Experimental: 78.1ml (69.7 – 90.3) Control: 80.0 ml (71.3 – 94.9) / p = 0.37	Experimental: 85.5 ml (76.9 – 100.8) Control: 79.1ml (74.9 – 100.2) / p = 0.25	Experimental: 0.27 – 0.78 Control: 0.32 – 0.93 / p = 0.72 ----- SGL: Experimental: GLS: -17.5% (± 1.8) Control: GLS: -17.3% (± 2.4) / p = 0.62	NR
Breibart et al	62.3% (± 5) / p = 0.89	76.4ml (± 13.8) / p = 0.65	NR	Delayed enhancement: 7 patients (12.5%)	N=14
Puntmann et al	Experimental: 57% (± 6) Control: 62% (± 8) / p < 0.01	Experimental: 86 ml/m ² (± 13 ml/m ²) Control: 76ml/m ² (± 14) / p < 0.001	NR	Delayed enhancement: Experimental: 32% Control 17% / p < 0.01	N = 78

GLS = Global longitudinal strain (Normal value < -16%); Fraction inflection normal value > 55%; Left ventricle diastolic volume: normal value = 70-120ml. Indexed left ventricle diastolic volume: normal value = 20-60ml/m²; NMR = Nuclear magnetic resonance; BM+ = Positive biomarkers; BM- = Negative biomarkers; NR = not reported.

Another relevant observation is that some studies failed to include the dosage of biomarkers in the “follow-up” period (Table 3), or when imaging exams were performed. It would be important for such a measurement to have been made and presented, as it would allow for greater comparison capacity and greater robustness in quantifying such information.

Table 3 – Measurements of cardiac biomarkers at baseline (in the presence of infection) and at follow-up (period of imaging tests)

1º Author	BNP or NT-Pro BNP value (peak g/ml) at baseline	BNP or NT-Pro BNP value (peak g/ml) at “follow up”	Troponin value (nano g/L) at baseline	Troponin value (nano g/L) at “follow up”
Myhre et al	Mean = 97peak g/ml (35-195) (NT pró-BNP) – Higher in 35% patients	NR	Mean =8ng/L (4-19) * Higher in 28% patients	NR
Italia et al	Mean = 164.5peak g/ml (59.2 – 465.8) (NT pro-BNP) Positives: 425 peak g/ml (169-1142) Negatives: 94peak g/ml (44.7 -193) / p <0.001	NR	Mean = 12.2ng/L (5.8 – 17.9) Positives: 14.2 (6.6 -18.2) Negatives: 7.2 (5 – 9.2) / p = 0.004	33 “normalized troponin”; 13 still with high values
Huang et al	Mean = 280 peak g/ ml (110-360)	NR	Mean = 2ng/L (1.9 – 2.2)	NR
Rodenás -Alesina et al	33 patients > 300 peak g/mL Mean = 735 peak g/ ml (534 – 1848)	NR	28 patients > 45 ng/L Mean = 176 ng/L (73 – 762)	NR
Gul et al	Experimental: Mean: 43 peak g/ml (10-505) Control: Mean 37.7 peak g/ml (4.2 – 135) / p 0.049	NR	Experimental: Mean :3.8 ng/L (3-18) Control: Mean 3.7ng/L (2-12.6) / p 0.005	NR
Lassen et al	Mean = 177.6 peak g/ml (80.3 – 408)	Mean 11.7 peak g/ml (5.7 – 24) / p< 0.001	High values (> 14ng/l) in 27% of experimental group	Mean = 4ng/L (3-7) 0% of the patients from experimental group
van den Heuvel et al	Mean = 315 peak g/ml (94 – 695)	Higher than 300 peak g/ml = 19 patients	Mean = 12ng/L (8-19)	Higher than 14ng/L = 19 patients
Kotecha et al	Mean = 231 peak g/ml (72–878)	NR	Mean = 39 ng/L (21–82)	Mean = 33ng/L (19 – 82)
Puntmann et al	Mean = 43.5 peak g/ml (26 – 78.6)	NR	Mean = 4.1 ng/L (3.0-5.8)	NR
Joy et al	Experimental: 36 peak g/ml (18–53) Control: 28 peak g/ml (17–56) / p = 0.24	NR	Experimental: 4ng/L (3–7) Control:4 ng/L (3–7) / p = 0.57	NR

Breibart et al	Mean 34.5 peak g/ml (23 – 68.5)	NR	Mean = 4.3 ng/L (± 1.9)	NR
Puntmann et al	Experimental: 51 peak g/ml (31-96) Control: 59 peak g/ml (35-76) / p = 0.26	NR	Experimental: 4.9 ng/L (3-6.9) Control: 3.2 ng/L (3 -4.5) / p < 0.019	NR

Normal Troponin Values < 14ng/mL; Normal BNP Values < 400 peak g/ml; Normal NT pro-BNP values < 100 peak g/ml; NR = not reported

The results demonstrate the presence of symptoms at the time of imaging exams in the majority of individuals evaluated (Table 4). However, none of the studies demonstrated relevant sequelae of the heart muscle, indicating that such complaints may be due to other causes, such as residual lung damage, metabolic changes, anemia or emotional factors, for example. Table 4 also presents information on the comorbidities of the individuals evaluated, with a low prevalence of major risk factors for diseases of the cardiovascular system, especially diabetes, hypertension, cholesterol and smoking. This may have greatly contributed to the incidence of cardiac sequelae that we found, as this population is less vulnerable to such damage.

Table 4 – Data on the presence of symptoms during imaging tests, comorbidities, treatment used and imaging method used for cardiac structural analysis

1º Author	Presence of Symptoms during imaging exams	Other pre-existing illnesses	Treatment used	Type of measure for diagnosis
Myhre et al	NR	DM2 (11%), SAH (21%), CKF (4%), CAD (9%)	Hydroxychloroquine 40%	Cardiac Magnetic Resonance Imaging
Italia et al	Nos BM +: 33 with mild/moderate symptoms; Nos BM -: 19 with mild/moderate symptoms	HAS (35%), DAC 8%, DM2 (2%)	Hydroxychloroquine (57%); antivirals (51%), Tocilizumab (4%), Antibiotics (56%)	Transthoracic Echocardiogram
Huang et al	Varied symptoms: palpitations, atypical pain and stuffiness (88%)	SAH (8%), DM2 (0%),	Antibiotics (100%), antivirals (100%) e oxygen (81%).	Cardiac Magnetic Resonance Imaging
Rodenás-Alesina et al	NR	HAS (39%), Smoker (28%), Diabetes (29%), Dyslipidemia (22%)	NR	Transthoracic Echocardiogram
Gul et al	NR	Smoker (30,2%), HAS (18,3%)	NR	Transthoracic Echocardiogram
Lassen et al	NR	Smoker (51%), HAS (48%), CAD (8%), Dyslipidemia (36%), DM2 (20%)	NR	Transthoracic Echocardiogram
Va den Heuvel et al	N= 14 (dyspnea, chest pain, palpitations, fatigue)	CAD (12,5%), HAS (40%), DM2 (17,5%), Smoker (7,5%)	Immunosuppressants (25%), O2 mask (92,5%)	Transthoracic Echocardiogram
Kotecha et al	NR	SAH (57%), DM2 (34%), Dyslipidemia (46%), Smoker (24%)	NR	Cardiac Magnetic Resonance Imaging

Puntmann et al	Dyspnea (62%), Palpitations (28%), atypical chest pain (27%) syncope (3%)	SAH (14%), DM2 (3,5%), Dyslipidemia (12%), Smoker (7,2%).	NR	Cardiac Magnetic Resonance Imaging
Joy et al	NR	Smoker (14%), HAS (14%), Dyslipidemia (5%), Diabetes (3%).	NR	Cardiac Magnetic Resonance Imaging
Breibart et al	Fatigue (75%), Dyspnea (66%), Palpitations (7%), Headache (5%)	SAH (28%), DM2 (16%), Dyslipidemia (13%), Smoker (8%)	NR	Cardiac Magnetic Resonance Imaging
Puntmann et al	NR	SAH (22%), DM2 (18%), Dyslipidemia (22%), Smoker (22%), CAD (13%)	Oxygen (28%), Antibiotics (15%), Corticosteroids (8%)	Cardiac Magnetic Resonance Imaging

BM+: Positive biomarkers; BM-: Negative biomarkers, SAH: Systemic arterial hypertension; DM2: Diabetes Mellitus type 2; CKF = Chronic kidney failure; CAD = Coronary artery disease.

DISCUSSION

This systematic review reveals conflicting data regarding the relationship between the elevation of biomarkers secondary to Covid-19 and the presence of long-term cardiac sequelae. Studies identified showed both abnormal and normal findings in the structure and function of the myocardium after imaging tests, whether echocardiography or magnetic resonance imaging.

In studies in which cardiac resonance was used as a structural assessment method, we found an increase in non-permanent findings, such as effusions, edema and inflammation. Puntman et al⁹ and Kotecha et al¹⁰, for example, found such findings in more than 50% of the individuals evaluated. This is due to the method's greater sensitivity, detection capacity and detailing of such changes. However, such changes did not translate, statistically, into permanent structural changes or sequelae to myocardial function.

In studies by Heuel et al¹¹, Joy et al¹² and Myhre et al¹³, there was no association between the elevation of cardiac biomarkers (especially troponin and NT pro-BNP) during infection and myocardial function in late follow-up, and no association was found between the presence of symptoms and sequelae parameters. However, Huang et al¹⁴, Puntmann et al¹⁵ and Italia et al¹⁶, suggest that in patients with elevated cardiac biomarkers in the acute phase there is a tendency to develop cardiac muscle dysfunction, detected by echocardiogram or cardiac magnetic resonance. However, the data did not present statistical significance.

Puntmann et al¹⁵, found that even though there were no differences in biomarker levels between the patients evaluated (sick x non-sick), data showed a statistically significant difference in lower ejection fractions, greater left ventricular dilations and greater occurrences of late enhancement in patients recovered from Covid-19. The authors suggest that the disease, even though it is not capable of altering troponin and BNP levels, is still capable of causing permanent sequelae in the myocardium. Gui et al¹⁷ suggest an increase in cardiac inflammatory markers during the acute phase of Covid-19 infection and that they are related to a greater presence of effusions or myocardial edema. However, these findings did not correlate with cardiac structural dysfunction and changes. Consequently, they have no impact on cardiac function.

The studies evaluated indicate that there is no robust evidence regarding the findings that normal cardiac enzymes indicate the absence of scars or sequelae in the heart. It is suggested, however, that patients who had cardiac enzymes at normal levels showed a tendency for smaller abnormalities on MRI scans. However, major works such as The Covid-Heart¹⁸ are emphatic in mentioning serious

long-term consequences related to Covid-19. According to the authors, most of these impacts will last for life and may impact the quality of life of affected citizens, in addition to other health-related issues. Given the magnitude of the number of infections caused by the disease globally, such risks cannot be neglected. Huang et al¹⁴ suggest, for these reasons, that the cardiac status of patients recovered from Covid-19 should be closely monitored.

CONCLUSION

In conclusion, we identified conflicting and unconvincing results related to the ability of biomarkers to predict permanent damage to the heart of individuals affected by Covid-19. It is unjustifiable to perform routine dosages during the acute infection of the disease, and such a strategy should be reserved only for those individuals at high cardiovascular risk, immunocompromised or who have a high probability of developing myocardial damage. Therefore, it does not justify carrying out cardiac imaging exams, especially echocardiography and magnetic resonance imaging, for the purpose of functional and structural assessment of the organ, given the low prevalence of significant findings as well as the low robustness of results in studies evaluated.

Although the results of the studies are limited, it is necessary to understand disease screening and its impacts in the context of collective health, the cost-effectiveness relationship as well as the pre-test probability to institute such a measure. Even with high sensitivity and specificity tests, a rare or low prevalence disease does not justify screening due to the high probability of false positive and false negative results being found. These burdens the organic, mental and financial health of the individual assessed and the health system itself, which lacks of abundant financial resources.

We considered limitations as the studies depended on participants' acceptance for interrogation purposes. It is possible that only individuals with better health conditions were evaluated when compared to those who did not change the outcomes. The presence of symptoms reported during the period in which the follow-up exams were carried out. None of the studies presented information about the cardiac conditions of the individuals evaluated in pre-covid moments and the studies presented heterogeneous protocols to evaluate the patients. The broad base of the studies evaluated was between the years 2020 and 2021, therefore there is an important gap in analyzes that encompass the entire duration of the pandemic.

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