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Prognostic biomarkers in patients with long COVID related myopericarditis

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Minas Gerais.**ADMINISTRATIVE INFORMATION****Support** - The costs will be born by the authors.**Review Stage at time of this submission** - The review has not yet started.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202690129**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 September 2026 and was last updated on 30 September 2026.**INTRODUCTION**

Review question / Objective The COVID-19 pandemic, caused by SARS-CoV-2, has represented one of the greatest public health challenges of the twenty-first century since its emergence in December 2019. Although the acute phase of the disease has been extensively investigated, a significant proportion of survivors develop persistent symptoms known as long COVID (LC) or post-COVID-19 condition, defined by the World Health Organization (WHO) as the occurrence or persistence of symptoms beyond 12 weeks after the initial infection that cannot be explained by an alternative diagnosis (WORLD HEALTH ORGANIZATION, 2021).

Among the cardiovascular manifestations of LC, myopericarditis—concurrent inflammation of the myocardium and pericardium—has emerged as a clinical entity of increasing relevance. Cardiac magnetic resonance (CMR) studies in COVID-19 survivors have documented signs of persistent myocardial injury in 20% to 60% of cases, including edema, fibrosis, and pericardial effusion

(PUNTMANN et al., 2020; RAJPAL et al., 2021), although this proportion is probably overestimated when considering patients in the longer term after infection. Post-COVID myopericarditis (PCM) may present with chest pain, dyspnea, palpitations, arrhythmias, and, in severe cases, heart failure and sudden death./To synthesize the available scientific evidence on prognostic biomarkers in adult patients with long COVID-related myopericarditis, with a possible meta-analysis of the data obtained.

Rationale According to WHO estimates, long COVID affects more than 65 million people worldwide, with a substantial socioeconomic impact and effects on quality of life (WORLD HEALTH ORGANIZATION, 2021). In the cardiovascular setting, LC-related PCM is a potentially serious complication whose long-term prognosis remains poorly defined in the current literature.

The absence of validated prognostic biomarkers for post-COVID PCM poses considerable clinical challenges, including: (1) difficulties in stratifying the risk of sudden death and progression to

cardiomyopathy; (2) uncertainty regarding the duration of cardiology follow-up and protocols for returning to physical activity; (3) a lack of objective criteria for indicating endomyocardial biopsy or immunosuppressive treatment; and (4) limitations in defining endpoints for therapeutic clinical trials. A rigorous systematic review on this topic is warranted to: (1) synthesize the available knowledge on prognostic biomarkers in LC-related PCM; (2) identify knowledge gaps and methodological inconsistencies in the literature; (3) support the development of clinical follow-up protocols; (4) provide a foundation for planning multicenter prospective studies; and (5) generate scientific evidence directly relevant to public health policies in the post-pandemic setting.

Condition being studied The COVID-19 pandemic, caused by SARS-CoV-2, has represented one of the greatest public health challenges of the twenty-first century since its emergence in December 2019. Although the acute phase of the disease has been extensively investigated, a significant proportion of survivors develop persistent symptoms known as long COVID (LC) or post-COVID-19 condition, defined by the World Health Organization (WHO) as the occurrence or persistence of symptoms beyond 12 weeks after the initial infection that cannot be explained by an alternative diagnosis (WORLD HEALTH ORGANIZATION, 2021).

Among the cardiovascular manifestations of LC, myopericarditis—concurrent inflammation of the myocardium and pericardium—has emerged as a clinical entity of increasing relevance. Cardiac magnetic resonance (CMR) studies in COVID-19 survivors have documented signs of persistent myocardial injury in 20% to 60% of cases, including edema, fibrosis, and pericardial effusion (PUNTMANN et al., 2020; RAJPAL et al., 2021), although this proportion is probably overestimated when considering patients in the longer term after infection. Post-COVID myopericarditis (PCM) may present with chest pain, dyspnea, palpitations, arrhythmias, and, in severe cases, heart failure and sudden death.

METHODS

Search strategy The following electronic databases will be searched: PubMed/MEDLINE (National Library of Medicine, USA); Scopus (Elsevier); Embase (Elsevier); Cochrane Library (Wiley); Web of Science (Clarivate Analytics); Gene Expression Omnibus—GEO (NCBI, USA); and Database of Genotypes and Phenotypes—dbGaP (NCBI, USA). In addition, ClinicalTrials.gov, the LILACS portal (Latin American and Caribbean

Health Sciences Literature), and reference lists of included studies will be consulted (manual searching). The search period will cover publications from January 2020 to May 2026 in English, Portuguese, and Spanish.

The search strategy will use MeSH terms and keywords combined with Boolean operators (AND, OR, NOT). Example PubMed search strategy:

("Post-COVID-19 Condition"[MeSH] OR "Long COVID"[tiab] OR "post-acute sequelae of SARS-CoV-2"[tiab] OR "PASC"[tiab]) AND ("Myopericarditis"[tiab] OR "Pericarditis"[MeSH] OR "Myocarditis"[MeSH] OR "myopericarditis"[tiab] OR "perimyocarditis"[tiab]) AND ("Biomarkers"[MeSH] OR "biomarker"[tiab] OR "prognostic biomarker"[tiab] OR "troponin"[tiab] OR "NT-proBNP"[tiab] OR "C-reactive protein"[tiab] OR "cardiac magnetic resonance"[tiab] OR "late gadolinium enhancement"[tiab]) AND ("prognosis"[MeSH] OR "outcomes"[tiab] OR "mortality"[tiab] OR "risk stratification"[tiab]).

Participant or population The population of interest will follow the PICO framework: P—Population: Adults (≥ 18 years) diagnosed with long COVID/PASC-related myopericarditis, confirmed by clinical, laboratory, and/or imaging criteria.

Intervention Assessment of serum, immunological, or imaging biomarkers with potential prognostic value.

Comparator Healthy controls, patients with acute COVID-19 without cardiac complications, or patients with myopericarditis unrelated to COVID-19 (when available).

Study designs to be included • Observational studies (cohort, case-control, and cross-sectional studies), randomized clinical trials, and systematic reviews containing primary data.

Eligibility criteria Inclusion criteria

- Studies published between January 2020 and May 2026.
- Observational studies (cohort, case-control, and cross-sectional studies), randomized clinical trials, and systematic reviews containing primary data.
- Studies reporting data on prognostic biomarkers in patients with long COVID-associated myopericarditis.
- Long COVID diagnosed according to WHO, NICE, CDC, or documented equivalent criteria.
- Original studies including at least 10 adult participants with LC-related PCM.
- Publications in English, Portuguese, or Spanish.

The following electronic databases will be searched: PubMed/MEDLINE (National Library of Medicine, USA); Scopus (Elsevier); Embase (Elsevier); Cochrane Library (Wiley); Web of Science (Clarivate Analytics); Gene Expression Omnibus—GEO (NCBI, USA); and Database of Genotypes and Phenotypes—dbGaP (NCBI, USA). In addition, ClinicalTrials.gov, the LILACS portal (Latin American and Caribbean Health Sciences Literature), and reference lists of included studies will be consulted (manual searching). Exclusion criteria

- Single case reports and case series with fewer than 10 patients.
- Studies with exclusively pediatric populations (< 18 years).
- Studies restricted to the acute phase of COVID-19 (< 12 weeks), without late follow-up data.
- Studies that do not report biomarker data with a prognostic analysis (editorials, letters, and opinion pieces without original data).
- Preprints without peer review or with serious methodological inconsistencies.
- Studies of COVID-19 vaccination-associated myopericarditis without specific data on LC-related PCM.

Information sources The following electronic databases will be searched: PubMed/MEDLINE (National Library of Medicine, USA); Scopus (Elsevier); Embase (Elsevier); Cochrane Library (Wiley); Web of Science (Clarivate Analytics); Gene Expression Omnibus—GEO (NCBI, USA); and Database of Genotypes and Phenotypes—dbGaP (NCBI, USA). In addition, ClinicalTrials.gov, the LILACS portal (Latin American and Caribbean Health Sciences Literature), and reference lists of included studies will be consulted (manual searching).

Main outcome(s) Identification, synthesis, and quantification (where possible through meta-analysis) of the prognostic value of serum, immunological, and imaging biomarkers in adult patients with long COVID-related myopericarditis, including: high-sensitivity cardiac troponins (hs-cTnI, hs-cTnT); natriuretic peptides (NT-proBNP, BNP); C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR); inflammatory cytokines (IL-6, IL-1 β , TNF- α , IFN- γ); lactate dehydrogenase (LDH) and creatine kinase (CK-MB); cardiac autoantibodies (anti-myosin and anti- β 1-adrenergic receptor); and CMR findings (myocardial edema assessed by T2 mapping, late gadolinium enhancement [LGE], and global longitudinal strain).

Additional outcome(s) • Cardiovascular mortality and all-cause mortality during follow-up in the included studies.

- Cardiovascular hospitalization and major adverse cardiovascular events (MACE).
- Development of heart failure with reduced or preserved ejection fraction.
- Severe ventricular arrhythmias and the need for an implantable cardioverter-defibrillator (ICD).
- Recurrence of myopericarditis and pericardial constriction.
- Clinical, demographic, and temporal characteristics of patients in the included studies (symptom onset, duration, and progression).

Data management Data extracted from the included studies will be systematically recorded in a standardized data extraction form and stored in an electronic database. The database will include study identification, methodological characteristics, participant characteristics, exposures or prognostic factors, outcomes, effect measures, and other variables relevant to the systematic review and meta-analysis. Data will be checked for accuracy and consistency, and any discrepancies identified during data extraction or review will be resolved by discussion among the researchers. The final dataset will be securely stored and used exclusively for the purposes of this systematic review and meta-analysis.

Quality assessment / Risk of bias analysis Study quality will be assessed using the following tools, as recommended by Higgins et al. (2022): observational studies: ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) and the Newcastle-Ottawa Scale (NOS); randomized clinical trials: RoB 2 (Cochrane Risk of Bias Tool 2.0); systematic reviews: AMSTAR-2; certainty of evidence: GRADE (Grading of Recommendations Assessment, Development and Evaluation).

Strategy of data synthesis Given the systematic review design, the primary synthesis will be qualitative and descriptive. When studies demonstrate sufficient methodological and clinical homogeneity, a meta-analysis will be performed using RevMan 5.4 (Review Manager, Cochrane Collaboration) or R (metafor and meta packages), following the recommendations of Higgins et al. (2022). A random-effects model (DerSimonian and Laird) will be used because of the expected heterogeneity between studies.

For dichotomous outcomes (mortality, hospitalization, and recurrence), odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (95% CIs) will be calculated. For continuous outcomes (biomarker levels and ejection fraction),

weighted mean differences (WMDs) or standardized mean differences (SMDs) with 95% CIs will be calculated. For biomarkers with predictive value, pooled sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) will be calculated when the data permit.

Heterogeneity will be quantified using I^2 (low: 75%) and Cochran's Q test. Subgroup analyses will explore variables such as biomarker type (serum, immunological, or imaging), diagnostic criteria for PCM, time since SARS-CoV-2 infection, sex, severity of acute COVID-19, viral variant, and use of anti-inflammatory therapy. Publication bias will be assessed using funnel plots and Egger's test when there are ≥ 10 studies per outcome.

Subgroup analysis If sufficient data are available, subgroup analyses will be performed according to relevant clinical and methodological characteristics of the included studies. Potential subgroups may include age, sex, severity of COVID-19, time since acute infection, presence of comorbidities, and methodological characteristics of the studies. Subgroup analyses will be conducted only when an adequate number of studies and sufficient data are available.

Sensitivity analysis Sensitivity analyses will be performed, when sufficient data are available, to assess the robustness of the meta-analysis findings. These analyses may include excluding studies with a high risk of bias, removing individual studies one at a time (leave-one-out analysis), and evaluating the influence of studies with extreme effect estimates or substantial methodological differences. The stability of the pooled estimates will be assessed after these exclusions.

Language restriction English, Spanish and Portuguese.

Country(ies) involved Brazil.

Keywords Post-COVID-19 Condition, Long COVID, post-acute sequelae of SARS-CoV-2, PASC, Myopericarditis, Pericarditis, Myocarditis, myopericarditis.

Dissemination plans The findings of this systematic review and meta-analysis will be disseminated through publication in a peer-reviewed scientific journal and presentation at relevant scientific conferences. The results may also be incorporated into the author's Master's dissertation and shared with the academic and scientific community.

Contributions of each author

Author 1 - Estevão Silva - Responsible for study conception and design, development of the research protocol, literature search, study selection, data extraction, database organization, interpretation of the findings, and preparation of the manuscript. He will also participate in the critical review and approval of the final manuscript. Email: estevao.infectologia@gmail.com

Author 2 - Marcus Bolivar - Responsible for scientific and methodological supervision of the study. He will critically review the selected studies, methodological procedures, data interpretation, and manuscript. He will also contribute to the discussion of the findings and review and approve the final manuscript.

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Author 3 - Braulio Couto - Responsible for scientific and methodological support throughout the study. He will critically review the selected studies, methodological procedures, data interpretation, and manuscript. He will also contribute to the discussion of the findings and review and approve the final manuscript.

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