INPLASY

Diagnostic parameters of phase B1/B2 progression in chronic Chagas cardiomyopathy. A systematic review

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ADMINISTRATIVE INFORMATION

Support - This research has no funding source.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 May 2026 and was last updated on 6 May 2026.

INTRODUCTION

Review question / Objective Does the integration of multimodal biomarkers, parasite load (qPCR), cardiac magnetic resonance imaging (MRI), and comorbidity assessment improve the identification of patients with chronic Chagas disease in stage B1/B2 at high risk of progression to stage C, compared to the use of electrocardiogram (ECG) and/or echocardiogram alone, enabling early, personalized interventions?
Population: Adult patients with chronic Chagas disease in stage B1/B2 (asymptomatic with mild electrocardiographic/echocardiographic abnormalities). Assessment: Integrated evaluation of: 1. Multimodal biomarkers (NT-proBNP, high-sensitivity troponin, galectin-3), 2. Parasite load (qPCR), 3. Cardiac MRI (fibrosis/edema), 4. Comorbidities (diabetes, hypertension). Outcome: Progression to stage C (symptomatic heart failure, serious arrhythmias, or cardiovascular death).

Rationale Chronic Chagas cardiomyopathy (CCC) affects 30–40% of the 6–7 million people infected with Trypanosoma cruzi, constituting the leading cause of infectious heart failure in Latin America and a growing health problem in non-endemic regions due to migration. Its prognosis is grim: once patients develop symptoms (stage C), mortality reaches 50% within 5 years. The asymptomatic B1/B2 stages represent crucial therapeutic windows of opportunity, with annual progression rates to stage C of 1.85–5%. The main clinical challenge today is to identify early on which patients in these stages will progress, since the Rassi scale (2006)—designed to predict mortality, not progression—underestimates the risk in early stages where structural damage is still incipient. Recent evidence has revolutionized the understanding of CCC progression in four fundamental pillars: (1) parasite persistence quantified by qPCR; (2) Multimodal biomarkers such as NT-proBNP, high-sensitivity troponin, and galectin-3; (3) cardiac magnetic resonance imaging, which reveals focal fibrosis by late gadolinium enhancement in up to 40% of stage B1

patients; and (4) metabolic comorbidities such as hypertension, diabetes, and obesity, which act as progression accelerators. Despite this evidence, there is currently no integrated system that combines these four pillars to accurately predict progression from stages B1/B2 to stage C. This systematic review is justified because it will synthesize the available evidence to support the development of a multimodal predictive tool, enable early personalized interventions in high-risk patients, and optimize healthcare resources by concentrating costly technologies on those who could benefit most.

Condition being studied Chagas disease, caused by the protozoan Trypanosoma cruzi, is a parasitic zoonosis endemic to 21 Latin American countries, affecting 6–7 million people worldwide and spreading through migration to non-endemic regions. Chronic Chagas cardiomyopathy (CCC) is the most severe and frequent manifestation of the disease, developing in 30–40% of infected individuals. CCC progresses through stages: stage A (indeterminate, asymptomatic, no damage), stage B1 (asymptomatic with electrocardiographic abnormalities but preserved ventricular function), stage B2 (asymptomatic with incipient ventricular dysfunction), stage C (symptomatic with established heart failure), and stage D (terminal). This review focuses on stages B1 and B2, which represent crucial therapeutic windows of opportunity to prevent or delay progression to symptomatic disease. The annual progression rate from stages B1/B2 to stage C ranges from 1.85% to 5%, and once in stage C, mortality reaches 50% at 5 years, with a high risk of sudden death from ventricular arrhythmias, exceeding the prognosis of other etiologies of heart failure.

METHODS

Search strategy (("Chagas Disease"[Mesh] OR "Trypanosoma cruzi"[Mesh] OR "Chagas Cardiomyopathy"[Mesh]) AND ("Disease Progression"[Mesh] OR "Chronic Disease"[Mesh] OR "Asymptomatic Infections"[Mesh] OR "Indeterminate" OR "Indeterminate phase") AND ("Parasitology"[Mesh] OR "Parasitic Diseases"[Mesh] OR "Protozoan Infections"[Mesh]) AND ("Biomarkers"[Mesh] OR "Diagnostic Markers"[Mesh] OR "unmeasured" OR "not assessed") AND ("Comorbidity"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR "Immunocompromised Host"[Mesh]) AND ("Observational Study"[Mesh] OR "Cohort Studies"[Mesh] OR "Clinical Trials"[Mesh] OR "Randomized Controlled Trials"[Mesh] OR "Case-Control Studies"[Mesh]))

Estrategia Science Direct: (("Chagas Disease"[Mesh] OR "Trypanosoma cruzi"[Mesh]) AND ("Cohort Studies"[Mesh] OR "Clinical Trial") AND ("Biomarkers"[Mesh] OR "Comorbidity"[Mesh])).

Participant or population Adult patients (≥18 years) with chronic Chagas disease in phase B1 or B2, according to the standardized classification of the American Heart Association (asymptomatic with mild electrocardiographic and/or echocardiographic abnormalities).

Intervention Integrated assessment of the following four pillars: 1. Multimodal biomarkers (NT-proBNP, high-sensitivity troponin, galectin-3, among others). 2. Parasite load quantified by qPCR in peripheral blood. 3. Cardiac magnetic resonance imaging findings (fibrosis by late gadolinium enhancement, edema/inflammation by T1/T2 mapping). 4. Presence of metabolic comorbidities (hypertension, diabetes mellitus, obesity, chronic kidney disease).

Comparator The comparator is risk stratification based on classic parameters, specifically the exclusive use of electrocardiogram and transthoracic echocardiogram, exemplified by tools such as the Rassi scale (2006).

Study designs to be included Cohort studies (prospective and retrospective), case-control studies, randomized clinical trials, meta-analyses, and previous systematic reviews.

Eligibility criteria Inclusion criteria: Studies evaluating at least one of the four pillars (parasite burden by qPCR, multimodal biomarkers, cardiac magnetic resonance imaging, or comorbidities) as predictors of progression to phase C in adults with phase B1/B2 CCC. The outcome must be progression to phase C (symptomatic heart failure, serious ventricular arrhythmias, cardiovascular death). No language, country, or publication date restrictions.
Exclusion criteria: Case studies, case series, editorials, animal studies, pediatric populations, studies with predominantly phase A or C/D populations, and studies without full-text access.

Information sources Electronic databases: PubMed, ScienceDirect, and Cochrane Library. The search will be conducted from the inception of each database until May 2025. Grey literature sources and contact with authors may also be considered, as outlined in the protocol.

Main outcome(s) Progression of chronic Chagas cardiomyopathy from asymptomatic phases B1/B2 to symptomatic phase C. Progression is operationally defined as the occurrence of any of the following events during follow-up: 1) Symptomatic heart failure (NYHA ≥ II); 2) Severe ventricular arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, aborted sudden cardiac death, or need for an ICD); 3) Cardiovascular death; 4) Structural/functional deterioration (decrease in LVEF ≥10%, increase in LV end-diastolic volume ≥15%, or new fibrosis on cardiac magnetic resonance imaging). It will be analyzed as a dichotomous variable (progression yes/no) or as time to event.

Additional outcome(s) The independent predictive capacity of each pillar studied will be evaluated. Clinically useful cut-off points will be determined for biomarkers (e.g., NT-proBNP, high-sensitivity troponin, galectin-3), parasite load by qPCR, and imaging parameters (fibrosis extent, strain values). The interaction and incremental predictive value of combining two or more pillars compared to using them alone will be identified.

Data management Two independent reviewers will assess the studies according to the eligibility criteria. Data will be extracted on study design, population characteristics, parameters assessed (biomarkers, qPCR, CMR, comorbidities), main results, and limitations. Reference management software and statistical tools for meta-analysis will be used where feasible. The data will be managed to allow for a narrative synthesis and, if homogeneity permits, a quantitative meta-analysis.

Quality assessment / Risk of bias analysis Standardized and validated tools will be used according to the study design. For observational studies (cohort, case-control), the Newcastle-Ottawa Scale (NOS) will be applied. The evaluation will be performed independently by two reviewers.

Strategy of data synthesis Initially, a narrative or descriptive synthesis of the findings will be conducted, organized by the categories of the four pillars (biomarkers, parasitology, advanced imaging, comorbidities). A qualitative analysis of trends and the consistency of the evidence will be performed. If the included studies exhibit sufficient clinical, methodological, and statistical homogeneity, a quantitative meta-analysis will be conducted following the PRISMA 2020 guidelines for combining results, with the aim of proposing an integrated risk stratification algorithm.

Subgroup analysis We plan to explore heterogeneity based on predefined subgroups, if the data allow, such as differences between patients in phase B1 and phase B2, specific type of baseline electrocardiographic abnormality, and geographic context (endemic versus non-endemic countries). We will also analyze the modifying role of metabolic comorbidities (diabetes, hypertension) on the predictive value of biomarkers and imaging findings.

Sensitivity analysis To assess the robustness of the results, sensitivity analyses can be performed excluding studies with a high risk of bias, retrospective studies, or those using non-standardized cut-off points for biomarkers or parasite load. This will allow verification of whether methodological heterogeneity significantly affects the study's conclusions.

Language restriction No language restrictions.

Country(ies) involved México.

Other relevant information This systematic review stems from the need to update risk stratification paradigms in coronary artery disease (CAD). It is based on the general hypothesis that integrating a multimodal approach (parasite load by qPCR, serum biomarkers, cardiac magnetic resonance imaging findings, and metabolic comorbidities) more accurately identifies patients in stage B1/B2 at high risk of progression to stage C, compared to traditional stratification (ECG and echocardiogram). Expected outcomes of this research include a manuscript for publication in an indexed journal, a presentation at an academic conference, a proposed clinical algorithm for risk stratification, and the identification of future research directions.

Keywords Chagas disease; Chronic Chagas cardiomyopathy; Disease progression; Biomarkers; Systematic review; Cardiac magnetic resonance imaging; Comorbidity; Risk stratification.

Dissemination plans The results of this systematic review will be disseminated through the publication of a manuscript in an indexed scientific journal and its presentation at an academic conference in the relevant specialty (cardiology, infectious diseases, or epidemiology). It is expected that the findings will inform a proposed clinical algorithm for risk stratification.

Contributions of each author

Author 1 - Hugo Gonzalo Martínez-Maya - Author 1 is responsible for the conception of the protocol,

the design of the review, the execution of the search, the synthesis of data, its analysis, and the writing of the manuscript.
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