INPLASY

Prognostic value of matrix metalloproteinase-2 in adult patients with heart failure: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - This study will not receive external financial support.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202650063

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 May 2026 and was last updated on 10 May 2026.

INTRODUCTION

Review question / Objective This systematic review and meta-analysis aims to evaluate the prognostic value of matrix metalloproteinase-2 (MMP-2) in adult patients with heart failure. The review question was structured according to the PICOS framework: Population (P): adults diagnosed with heart failure, including heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF); Intervention/ Exposure (I): blood concentration of MMP-2; Comparator (C): patients with different clinical outcomes or heart failure phenotypes; Outcomes (O): prognostic outcomes, including mortality, hospital readmission, disease progression, and clinical worsening; Study design (S): observational studies, including cohort and case-control studies. The objective is to investigate whether elevated MMP-2 levels are associated with worse prognosis and adverse clinical outcomes in patients with heart failure.

Condition being studied Heart failure is a chronic and progressive clinical syndrome characterized by the inability of the heart to pump blood efficiently to meet the metabolic demands of the body. It is associated with structural and/or functional cardiac abnormalities that impair ventricular filling or ejection. Heart failure is commonly classified according to left ventricular ejection fraction into heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF). The disease is associated with high morbidity, mortality, frequent hospitalizations, and reduced quality of life. Cardiac remodeling and extracellular matrix alterations play an important role in the progression of heart failure. Matrix metalloproteinase-2 (MMP-2) is an extracellular matrix remodeling enzyme involved in inflammatory processes, myocardial fibrosis, and ventricular remodeling. Increased circulating levels of MMP-2 may be associated with disease severity, adverse cardiac remodeling, and poor prognosis in patients with heart failure.

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METHODS

Search strategy The literature search will be conducted in the following electronic databases: MEDLINE/PubMed, Embase, Cochrane Library, and LILACS. Additional manual searches will be performed by screening the reference lists of the included studies. No language restriction will be applied, and only studies involving human participants will be considered.

The search strategy will combine controlled vocabulary terms, including Medical Subject Headings (MeSH) and Emtree terms, with free-text keywords related to heart failure, MMP-2, and prognosis. Boolean operators “AND” and “OR” will be used to optimize the search strategy.

The preliminary search strategy for PubMed will include the following terms:

("Heart Failure"[Mesh] OR "heart failure" OR HFrEF OR HFpEF OR HFmrEF) AND ("Matrix Metalloproteinase 2"[Mesh] OR "MMP-2" OR "matrix metalloproteinase-2") AND ("Prognosis"[Mesh] OR prognosis OR prognostic OR mortality OR hospitalization OR survival).

Equivalent search strategies adapted to the syntax of each database will be applied. The search process, including the databases searched, search dates, and complete search strategies, will be fully documented to ensure reproducibility and transparency.

Participant or population The review will include adult patients aged 18 years or older with a confirmed diagnosis of heart failure, including heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF). Studies involving hospitalized or outpatient individuals of both sexes will be eligible. Only human studies evaluating circulating levels of matrix metalloproteinase-2 (MMP-2) associated with prognostic outcomes in heart failure will be included.

Intervention The intervention/exposure evaluated in this review will be the measurement of circulating matrix metalloproteinase-2 (MMP-2) levels in adult patients with heart failure. The review will assess studies investigating the association between blood MMP-2 concentrations and prognostic outcomes, including mortality, hospital readmission, disease progression, and clinical worsening.

Comparator The comparator will include patients with different clinical outcomes or heart failure phenotypes, such as favorable versus unfavorable prognosis, survivors versus non-survivors, lower versus higher MMP-2 concentrations, and comparisons among HFrEF, HFmrEF, and HFpEF groups when available.

Study designs to be included Observational studies, including prospective or retrospective cohort studies and case-control studies, evaluating circulating MMP-2 levels and their association with prognostic outcomes in adult patients with heart failure will be included. Experimental studies, animal studies, in vitro studies, reviews, editorials, letters, case reports, and studies without primary data will be excluded.

Eligibility criteria Studies will be eligible if they include adult patients diagnosed with heart failure and report circulating MMP-2 levels associated with prognostic outcomes such as mortality, hospital readmission, disease progression, or clinical worsening. Only original observational studies with available primary data will be included. No language restriction will be applied. Studies involving pediatric populations, animal models, in vitro analyses, reviews, conference abstracts without sufficient data, editorials, letters, and duplicate publications will be excluded.

Information sources The electronic searches will be conducted in MEDLINE/PubMed, Embase, Cochrane Library, and LILACS. Additional studies may be identified through manual screening of the reference lists of included articles. Grey literature sources, such as theses and dissertations, may also be consulted when relevant. When necessary, corresponding authors of eligible studies may be contacted to obtain missing or additional data. Only studies involving human participants will be considered.

Main outcome(s) The primary outcome of this systematic review and meta-analysis will be the prognostic value of circulating MMP-2 levels in adult patients with heart failure. Prognostic outcomes will include all-cause mortality, cardiovascular mortality, hospital readmission, disease progression, and clinical worsening. Effect measures such as hazard ratio (HR), risk ratio (RR), odds ratio (OR), and standardized mean difference (SMD) with 95% confidence intervals will be extracted when available. Outcomes will be analyzed according to the follow-up period reported in the included studies.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of the included observational studies will be independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). This tool

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evaluates three main domains: selection of study groups, comparability between groups, and assessment of exposure or outcomes. Studies will be classified according to their total score as high, moderate, or low methodological quality. Any disagreements between reviewers will be resolved through discussion or consultation with a third reviewer. The quality assessment results will be presented in tables and considered during the interpretation of the findings.

Strategy of data synthesis A qualitative synthesis of the included studies will initially be performed, summarizing the main methodological characteristics and prognostic findings related to MMP-2 in heart failure. When sufficient methodological and statistical homogeneity is identified, a meta-analysis will be conducted using Review Manager (RevMan 5.4). Continuous variables related to circulating MMP-2 levels will be analyzed using mean difference (MD) or standardized mean difference (SMD) with 95% confidence intervals. Dichotomous outcomes, such as mortality and hospital readmission, will be analyzed using risk ratio (RR), odds ratio (OR), or hazard ratio (HR) when available. Statistical heterogeneity will be assessed using the I^2 statistic. Fixed-effect models will be applied when heterogeneity is low, while random-effects models will be used in cases of moderate or high heterogeneity. The results will be presented through forest plots, tables, and narrative synthesis.

Subgroup analysis Subgroup analyses will be performed when sufficient data are available. The analyses may include comparisons according to heart failure phenotype, including HFrEF, HFmrEF, and HFpEF; sex; type of prognostic outcome; follow-up duration; and methodological quality of the included studies. Additional subgroup analyses may be conducted according to the biological sample type and laboratory method used for MMP-2 measurement.

Sensitivity analysis Sensitivity analyses will be conducted to evaluate the robustness and consistency of the findings. Analyses may be performed by excluding studies with high risk of bias, studies with small sample sizes, and studies with incomplete or insufficient data. Additional sensitivity analyses may also assess the impact of different statistical models and the influence of individual studies on the pooled estimates.

Country(ies) involved Brazil — University of the Extreme South of Santa Catarina (UNESC), Criciúma, Santa Catarina.

Keywords Heart failure; MMP-2; Prognosis; Biomarker; Meta-analysis.

Contributions of each author

Author 1 - Gabriele Prestes - Supervised the protocol development, methodological planning, review design, and final approval of the protocol.
Email: gsp@unesc.net
Author 2 - Camille Scotti - Development of the protocol, formulation of the research question, eligibility criteria, and planned study selection.
Email: camillerscotti@gmail.com
Author 3 - Maria Laura Schneider - Development of the protocol, in the planning of the search strategy, in the eligibility criteria, and in the planning of data extraction.
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