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INPLASY

Prognostic value of left atrial function in cardiac amyloidosis: protocol for a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No financial support was obtained for this work.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

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 25 August 2025 and was last updated on 25 August 2025.

INTRODUCTION

Review question / Objective We will assess whether quantitative measures of left atrial (LA) function obtained by echocardiography or cardiac magnetic resonance predict adverse outcomes in adults with cardiac amyloidosis.

Condition being studied Cardiac amyloidosis (CA) comprises light-chain amyloidosis (AL-CA) and transthyretin amyloidosis (ATTR-CA), including hereditary and wild-type forms. Both entities carry poor prognosis with progressive heart failure, arrhythmias, thromboembolism, and high mortality, and AL-CA generally shows a more aggressive course and shorter survival than ATTR-CA. The left atrium, given its thin wall and limited tissue characterization with standard imaging, is affected in cardiac amyloidosis not only secondary to left-ventricular diastolic dysfunction but also through direct amyloid infiltration, interstitial fibrosis, and fiber disorganization. This intrinsic injury manifests as reduced strain in the reservoir, conduit, and contractile phases and as frequent atrial enlargement, features independently associated with adverse cardiovascular events and increased mortality.

METHODS

Participant or population Eligible populations will consist of patients with confirmed CA diagnosed according to internationally accepted standardized criteria, using combinations of imaging modalities and, when available, histology or disease-specific biomarkers.

Intervention The prognostic factor will consist of quantitative left atrial function measurements obtained by echocardiography or cardiac magnetic resonance. We will include left atrial ejection fraction and strain metrics, specifically reservoir strain (LASr), conduit strain (LAScd), and contractile strain (LASct).

Comparator Per-unit increases/decreases in LA metrics, and/or categories defined by study-specific thresholds (e.g., high vs low LASr).

When necessary, we will standardize effects to a unit change for pooling.

Study designs to be included We will include observational cohort studies, prospective or retrospective, with longitudinal follow-up. Single-arm cohorts will be eligible if they report time-to-event associations between left atrial metrics and prespecified outcomes.

Eligibility criteria Additional inclusion criteria will require human adults, English or Spanish reports with sufficient data to extract or compute effect estimates and predefined diagnostic criteria for cardiac amyloidosis. Exclusion criteria will include cross-sectional or case-control designs without longitudinal outcomes, mixed cardiomyopathy cohorts without separable cardiac amyloidosis data, pediatric or animal studies, inadequate diagnostic definitions, absence of quantitative left atrial measurements, inability to derive effect estimates, duplicate or overlapping cohorts without unique data, and non-original publications such as editorials or narrative reviews.

Information sources We will conduct a comprehensive search of MEDLINE (via PubMed), Embase, Web of Science Core Collection, and LILACS from inception to the final search date without year limits. Search strategies will combine controlled vocabulary and keywords related to cardiac amyloidosis and the left atrium, adapted to each database using MeSH or Emtree with Boolean and proximity operators. We will restrict to adults and, when feasible at the search stage, to observational cohorts. We will include records in English and Spanish. Grey literature, preprint servers, and backward and forward citation tracking will supplement the database searches.

Main outcome(s) Outcomes will include all-cause mortality as the primary endpoint and cardiovascular mortality, atrial fibrillation, thromboembolic events, and heart-failure hospitalization or progression as secondary endpoints, reported as time-to-event or risk estimates.

Quality assessment / Risk of bias analysis We will assess risk of bias using QUIPS across six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting. Two reviewers will perform independent assessments after piloting and calibration; disagreements will be resolved by consensus or a third reviewer. Prespecified confounders will include age, sex, amyloidosis subtype, disease stage by biomarker staging systems, left-ventricular systolic and diastolic function, cardiac rhythm at imaging, renal function, and treatment status. For prognostic factor measurement, we will require adequate description of imaging modality, vendor or software, acquisition parameters, rhythm at acquisition, and reproducibility metrics such as inter- and intra-observer intraclass correlation coefficients. For outcome measurement, we will require explicit definitions, ascertainment sources, and completeness of follow-up. For attrition, we will evaluate loss to follow-up, missing-data mechanisms, and handling methods such as multiple imputation when appropriate. For statistical analysis, we will evaluate time-to-event modeling, checks of proportional hazards, specification of functional forms for continuous predictors, assessment of multicollinearity, and adequacy of confounder adjustment. Domain ratings will be low, moderate, or high. Overall risk of bias will be judged as high if confounding or prognostic factor measurement is high, moderate if at least one domain is moderate and no key domain is high, and low only if all domains are low.

Strategy of data synthesis We will extract adjusted effect estimates, prioritizing hazard ratios, and will harmonize direction so that greater left atrial impairment corresponds to higher risk. When scales differ, we will rescale to a common unit within each metric. We will pool log hazard ratios using random-effects inverse-variance models with restricted maximum likelihood, apply Hartung–Knapp adjustment, and report pooled effects with 95% confidence intervals, τ^2, I^2, and 95% prediction intervals. Small-study effects and publication bias will be examined with funnel plots and Egger's test when at least ten studies are available; otherwise assessment will be qualitative.

Subgroup analysis We will explore heterogeneity through prespecified subgroups: amyloidosis subtype, imaging modality, software vendor, cardiac rhythm at acquisition (sinus vs atrial fibrillation), adjustment set complexity, follow-up duration, and overall risk-of-bias category. When sufficient studies are available, we will test interactions using meta-regression; otherwise, comparisons will be descriptive and supported by influence analyses.

Sensitivity analysis We will run leave-one-out analyses to explore the influence of each study on the pooled effect and heterogeneity by iteratively refitting the primary random-effects model after removing one study at a time, recording the pooled log hazard ratio with 95% confidence interval, τ^2,

I^2, and the 95% prediction interval. We will classify a study as influential if its removal changes statistical significance or shifts the pooled log hazard ratio by more than one standard error of the full model, and we will present results in an influence plot and a summary table.

Language restriction English and Spanish.

Country(ies) involved Spain, Cuba.

Keywords Atrial Function, Left; Heart Atria; Amyloidosis.

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