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Comorbidities and long-term mortality after cardiac resynchronization therapy: a scoping review

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ADMINISTRATIVE INFORMATION

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INTRODUCTION

Review question / Objective The primary objective of the review is to scope the existing body of literature, in order to identify and characterize the evidence regarding comorbidities and long-term survival outcomes after cardiac resynchronization therapy (CRT).
Primary question: What is the current state of evidence regarding the impact of individual comorbidities on long-term mortality in patients undergoing cardiac resynchronization therapy (CRT)?
Secondary research questions: 1) What methodological approaches are used to analyze the relationship between comorbidities and long-term mortality in patients undergoing CRT? 2) What trends can be observed in the duration and definition of long-term follow-up? 3) Are there any noticeable gaps in the available literature concerning specific comorbidities or their associations with long-term mortality after cardiac resynchronization therapy? These secondary research objectives focus on the consistency of the methods used to investigate the impact of comorbidities on survival, the overall number of studies conducted on this topic, their levels of evidence, and any recurring patterns or knowledge gaps that may exist.

Background Cardiac resynchronization therapy (CRT) has evolved significantly since its development in the early 1990s as a therapeutic option for patients with advanced heart failure (HF) [1]. Ample research has led to strong recommendations for CRT implantation in patients with heart failure who remain symptomatic despite optimal medical therapy, who have a reduced ejection fraction, and who have electrical dyssynchrony characterized by a wide QRS complex generated by a left bundle branch block [2-5].
As more evidence emerged, additional patient profiles were also targeted, making CRT a more widely used and essential treatment for heart failure [6]. Clinical guidelines provide several evidence-based criteria to improve the selection process for CRT candidates [7,8].

However, approximately one-third of patients do not seem to experience considerable benefit in clinical status or echocardiographic parameters after CRT implantation [9]. This notable non-responder rate has remained relatively unchanged over the last decade [10], and efforts have focused on identifying key factors that may limit the effectiveness of CRT. Historically, research has focused on identifying predictors of a positive response to CRT, measured using various outcomes, such as clinical, echocardiographic, or electrocardiographic parameters [11-13]. However, this variability complicates a direct comparison of results across studies. The most frequent outcome that stands out across all studies is all-cause mortality. Considering this, the authors chose survival time after CRT as the common element for all evaluated studies.

Rationale Given the numerous baseline parameters correlated with various short-term or mid-term outcomes, our review will specifically focus on mapping the existing evidence from research on the interaction of individual comorbidities with long-term survival. By synthesizing the studies identified through a systematic literature search, our review seeks to raise awareness and inform clinicians and researchers about the current body of evidence while highlighting potential gaps.

METHODS

Strategy of data synthesis Data from the studies included in this review will be organized using structured formats such as .XLS or .CSV files. We will perform a descriptive synthesis using tables, graphs, and narrative summaries to present the characteristics and outcomes of the studies. Two independent reviewers will carry out the quality assessment, and any discrepancies will be resolved through discussion. If necessary, a third senior researcher will resolve any remaining disagreements. This approach ensures transparency, consistency, and methodological rigor in synthesizing the findings.

Eligibility criteria Inclusion criteria: original clinical research, without any type of reviews. Original research refers to various categories of publications, such as randomized controlled trials, cohort studies, case-control studies, either prospective or retrospective. The inclusion criteria consist of: adult patients with heart failure who undergo CRT implantation in studies investigating associations between individual comorbidities and long-term mortality, in any healthcare setting. Research articles will be considered if they clearly define a CRT population or a separate CRT study group. Additionally, the articles must focus on a comorbidity and report on mortality or survival outcomes assessed after long-term follow-up, regardless of the specific timeframe used. We will include all available evidence, independent of sample size, statistical power, or the nature of the findings.

Exclusion criteria will be established based on specific categories of studies and patient populations. The following types of publications will be excluded from consideration: reviews, editorials, conference abstracts, and case reports. Furthermore, studies that involve theoretical, experimental, or in vitro scenarios and those utilizing animal models will also be excluded. Regarding mortality outcomes, we will exclude articles that do not present clearly defined mortality or survival measures. Additionally, any articles referencing comorbidities using ambiguous terms, such as "comorbidity burden," will be excluded from our analysis. Our focus will be on biventricular pacing, and we will not consider alternative cardiac resynchronization strategies, including physiological pacing or left-ventricular-only pacing. Patients who received an upgrade to CRT therapy will also be excluded from the review. Patients with a diagnosis of corrected congenital heart disease (such as Tetralogy of Fallot), cardiac amyloidosis, cardiac sarcoidosis, or other structural or infiltrative cardiomyopathies will be excluded.

Source of evidence screening and selection The literature search will use PubMed, Scopus, and Cochrane Library databases. The search will be performed up to April 2025, adhering to general eligibility criteria, which include full-text availability and the requirement that studies are published in English. The search strategy will consist of combinations of keywords and Medical Subject Headings (MeSH) terms to identify studies focused on long-term survival in patients receiving CRT with associated comorbidities. The following terms or variations will be used in the query strings: follow-up, survival, death, mortality, cardiac resynchronization therapy, resynchronization therapy, biventricular pacemaker, biventricular defibrillator, biventricular device, CRT-P, CRT-D, long-term, tricuspid, mitral, atrial fibrillation, BMI, body mass index, overweight, underweight, obesity, diabetes, systolic pressure, hypertension, blood pressure, nonischemic cardiomyopathy, ischemic cardiomyopathy, coronary artery disease, coronary heart disease, chronic kidney disease, renal failure, CKD, and kidney failure. Boolean operators will be used to combine terms and

ensure comprehensive retrieval through optimised query strings, maximizing search sensitivity.
Two investigators will independently screen all the retrieved titles and abstracts to assess eligibility based on the predefined inclusion and exclusion criteria. Potential articles identified in the initial screening phase will undergo a full-text assessment by the same investigators. A data charting form will be used to ensure a standardized extraction of variables. A third investigator will perform a final review to ensure accuracy and resolve discrepancies. Disagreements concerning study selection and data extraction will be resolved by consensus, and if needed, through discussion with additional reviewers.

Data management Data extracted from eligible studies will be recorded using a structured data charting form developed by the review team. Key variables will include study metadata, study design, sample size, grouping parameters, type of CRT device with patient distribution to either CRT-P or CRT-D, duration of follow-up, presence of Kaplan-Meier curves, total number of deaths, and reported associations between increased mortality and specific comorbidities. Data that is charted will be reviewed for completeness and accuracy, with missing or unclear data points noted accordingly. The final dataset will be organized in tabular format using spreadsheet software. All members of the review team will validate final data tables.

Reporting results / Analysis of the evidence The analysis will categorize results by comorbidity, enabling each condition to be evaluated independently based on available studies. This structure facilitates a detailed and standardized presentation of results across heterogeneous studies and helps identify patterns in long-term outcomes based on comorbidities. A qualitative assessment or risk of bias scoring will not be conducted, as these are not typically performed in scoping reviews. There will be no quantitative evaluation, such as a meta-analysis, as this falls beyond the scope of the current review format and methodology.

Presentation of the results The results will be presented in a comprehensive table organized by major clinical themes, focusing on comorbidities. Each subsection (e.g., diabetes, renal dysfunction, atrial fibrillation) will list relevant studies in reverse chronological order to highlight the progression of evidence over time. The table will be constructed using a predefined charting form to ensure consistency and comparability across studies. The tabular presentation will be followed by a narrative data synthesis, summarizing key trends, methodological strengths and limitations, and notable findings. Visual figures like trend plots will highlight patterns and provide interpretive context.

Language restriction The search will be limited to English language publications.

Country(ies) involved Romania.

Keywords cardiac resynchronization therapy; biventricular pacemaker; CRT; CRT-D; CRT-P; comorbidity; mortality; survival; long-term; follow-up; prognosis; heart failure; dyssynchrony; reduced ejection fraction.

Dissemination plans The findings from the current literature review will be published as a research paper in an open-access medical journal. Furthermore, selected results, such as charts, figures, tables, key messages, or conclusions, may be presented in conference papers, oral presentations, posters, or shared on social media platforms.

Contributions of each author

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