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Sarcopenia Defined by Multidimensional Factors and Its Prognostic Role in Heart Failure: A Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

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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 6 March 2025 and was last updated on 6 March 2025.

INTRODUCTION

Review question / Objective We will conduct a meta – analysis on the relationship between sarcopenia defined based on a multi – dimensional factor and the prognosis of heart failure (HF) patients. This study will aim to explore the association between sarcopenia and adverse clinical outcomes in HF patients. Through the evidence that will be obtained, this study will aim to provide clinicians with evidence – based medicine for the management of the condition in HF patients and will assist them in accurately identifying such high – risk patients.

Condition being studied Heart failure (HF), a clinical syndrome with impaired cardiac pumping, is highly correlated with aging, manifested by a decline in cardiac structure and function. Sarcopenia, a common geriatric syndrome, involves a decrease in muscle mass, strength, and physical function with aging. The two are closely and complexly interrelated, jointly affected by factors like age, obesity, chronic inflammation, malnutrition, and lack of physical activity. After HF onset, musculoskeletal system changes are crucial for HF – related symptoms.

The relationship between sarcopenia and HF prognosis is a cutting – edge clinical research area. However, relevant studies' conclusions on this relationship are contradictory. Sato K et al. found that AWGS – defined sarcopenia had no significant impact on MACE in elderly HF patients. Katano, S. et al. showed that AWGS – defined sarcopenia was associated with all – cause mortality in HF patients. Another study on acute HF patients found severe sarcopenia was linked to cardiac death or readmission. Chinese studies indicated the sarcopenia group had higher readmission rates and MACE incidence, but no differences in all – cause mortality and malignant arrhythmia. Meta – analyses also showed inconsistent results. Liu, Y. et al. found sarcopenia patients had higher risks of

all – cause mortality and MACE, but with heterogeneity due to regions and diagnostic criteria. Prokopidis, K. et al. found that while sarcopenia based on EWGSOP1 or AWGS criteria had no significant predictive value for all – cause mortality in HF patients, some components like low psoas major muscle mass and slow gait speed did increase the risk of death.

Recently, with deeper understanding of sarcopenia, more studies on its impact in HF patients have been published, using more comprehensive and standardized diagnostic criteria such as AWGS, EWGSOP2, and Ishii – score – based criteria.

METHODS

Participant or population The participants in this systematic review and meta-analysis will be adult patients (aged 18 years and above) who have been diagnosed with heart failure (HF). This population encompasses a wide range of individuals with different etiologies of HF, including but not limited to those with ischemic cardiomyopathy, dilated cardiomyopathy, and valvular heart disease-related HF. The heart failure can be in various stages, such as acute decompensated HF or chronic stable HF. The review will aim to include patients from different geographical regions, ethnic backgrounds, and genders to ensure a comprehensive assessment of the role of sarcopenia (defined by multidimensional factors) in the prognosis of HF within this adult patient population.

Intervention The "intervention" in this context is the presence of sarcopenia defined by multidimensional factors. Multidimensional factors for defining sarcopenia may include measures such as low muscle mass (assessed through techniques like dual-energy X-ray absorptiometry, bioelectrical impedance analysis, etc.), reduced muscle strength (e.g., measured by grip strength, knee extension strength), and decreased physical performance (e.g., gait speed, chair stand test results). The review will evaluate the impact of this sarcopenia status (present or absent) on the prognosis of heart failure patients. This includes outcomes such as all-cause mortality, cardiovascular mortality, hospitalization rates, and major adverse cardiac events (MACE).

Comparator The comparator group will be adult heart failure patients without sarcopenia. These patients will serve as a reference group to compare against the patients with sarcopenia (defined by the multidimensional factors). By comparing the prognosis of patients with and without sarcopenia, the review will determine whether the presence of sarcopenia is an independent predictor of worse outcomes in heart failure patients. The absence of sarcopenia will be determined based on meeting the normal or acceptable thresholds for the multidimensional factors used to define sarcopenia (e.g., having normal muscle mass, sufficient muscle strength, and adequate physical performance).

Study designs to be included The review will include observational studies such as cohort studies, case-control studies, and cross-sectional studies. These designs are suitable as they can help establish associations between sarcopenia (defined by multidimensional factors) and the prognosis of heart failure patients. Randomized controlled trials (RCTs) related to the natural history and prognosis of sarcopenia in heart failure patients will also be considered if available. However, given the nature of the research question focusing on the prognostic role, observational studies are expected to be the mainstay of the eviden.

Eligibility criteria In addition to the PICOS criteria, studies will be included if they clearly define sarcopenia using multiple dimensions. These dimensions may incorporate low muscle mass, reduced muscle strength, and decreased physical performance, as measured by validated methods such as dual – energy X – ray absorptiometry for muscle mass, grip strength dynamometry for strength, and gait speed tests for physical performance.

Studies will be excluded if they do not report relevant outcome data related to heart failure prognosis, such as all – cause mortality, cardiovascular mortality, hospitalization rates, or major adverse cardiac events (MACE). There are no language restrictions for the studies; thus, articles in all languages will be considered.

Information sources The primary electronic databases to be searched include PubMed, Embase, and the Cochrane Library. These databases cover a wide range of medical literature related to cardiology and geriatrics. Additionally, we will search the Web of Science to identify relevant studies. Grey literature sources such as conference proceedings from major cardiology and geriatrics conferences (e.g., American Heart Association Scientific Sessions, European Society of Cardiology Congress) will be explored. We may also contact the authors of relevant studies to request additional data or clarify any unclear aspects of their research. Clinical trial registers (e.g., ClinicalTrials.gov) will be searched to identify

ongoing or unpublished studies related to the topic.The primary electronic databases to be searched include PubMed, Embase, and the Cochrane Library. These databases cover a wide range of medical literature related to cardiology and geriatrics.

Main outcome(s) The main outcomes of the review will be all-cause mortality and cardiovascular mortality. These will be reported at different time points such as 1-year, 3-year, and 5-year follow-ups. The effect measures will be hazard ratios (HRs) with 95% confidence intervals (CIs) for mortality outcomes. For hospitalization, the rate of hospitalization due to heart failure will be an important outcome, and the odds ratios (ORs) with 95% CIs will be used as the effect measure. Major adverse cardiac events (MACE) including myocardial infarction, stroke, and heart failure exacerbation will also be evaluated, with HRs or ORs as the relevant effect measures.

Quality assessment / Risk of bias analysis For cohort and case-control studies, the Newcastle-Ottawa Scale (NOS) will be used to assess the quality. This scale evaluates selection of the study groups, comparability of the groups, and ascertainment of exposure and outcome. For cross-sectional studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies will be applied. RCTs will be evaluated using the Cochrane Risk of Bias tool, which assesses areas such as random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. Studies with a high risk of bias will be noted, and sensitivity analyses will be conducted to assess the impact of such studies on the overall results.

Strategy of data synthesis Meta-analysis will be employed for data synthesis. For studies with homogeneous characteristics (assessed by I^2 statistic, typically $I^2 < 50\%$ indicating low heterogeneity), a fixed-effects model will be used. If significant heterogeneity is detected ($I^2 \geq 50\%$), a random-effects model will be applied instead.
Statistical software such as Stata18.0 will be used for meta-analysis, while R or SPSS may be utilized for additional statistical manipulations and data management.

Subgroup analysis Subgroup analyses will be conducted based on multiple variables. These include research design (prospective vs. retrospective cohort studies), which may influence the quality and nature of data. Different clinical outcomes (e.g., mortality vs. hospitalization) will be analyzed separately to understand the specific impact of sarcopenia on each outcome.
Patient classification (inpatient vs. outpatient) will also form subgroups, as the care setting might affect the relationship between sarcopenia and heart failure prognosis. Muscle mass assessment tools (DXA vs. BIA) will be used to create subgroups to determine if the assessment method impacts the results.
Study population regions (Asia vs. Europe) will be considered to explore potential geographical differences, and sarcopenia diagnostic criteria (AWGS, EWGSOP, Ishii score) will be used to subgroup studies to evaluate how different definitions affect the association between sarcopenia and heart failure outcomes.

Sensitivity analysis Sensitivity analysis will be carried out by sequentially excluding individual studies from the meta-analysis. This will help identify if any single study has a disproportionate influence on the overall pooled results. By removing each study one at a time and re-running the meta-analysis, we can assess the stability of the effect estimates.
If the removal of a particular study leads to a significant change in the pooled effect size (e.g., a change in the direction of the association or a substantial shift in the magnitude of the hazard ratio or odds ratio), that study will be flagged as potentially influential.
We will also conduct sensitivity analyses based on different subgroupings, such as by research design or diagnostic criteria. This will help determine if the results are robust across different subsets of studies and provide a more comprehensive understanding of the relationship between sarcopenia and heart failure prognosis. If significant differences are found in sensitivity analyses, it will indicate areas where the evidence base is less certain and may require further investigation.

Country(ies) involved Department of Cardiology, Ningbo NO.2 hospital, Zhejiang, China; Department of Critical Care Medicine, Eastern Branch of Li Huili Hospital, Zhejiang, China.

Keywords heart failure; sarcopenia; prognosis; meta-analysis.

Contributions of each author
Author 1 - Jinmei Lu - Study conception and design, literature retrieval and screening, quality assessment, manuscript draft, critical revisions.
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