

BMJ Open Sarcopenia as a predictor of outcome after transcatheter aortic valve implantation: protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Sarcopenia represents a central biological substratum of frailty, which increases the incidence of adverse events and mortality after surgery for oesophageal cancer, gastrectomy and pancreatic surgery. Recently, sarcopenia has been suggested as a predictor of outcomes in patients undergoing transcatheter aortic valve implantation (TAVI). However, since relevant data were variable, we aimed to perform a systematic review and meta-analysis of the current literature to evaluate sarcopenia as a predictor of post-TAVI outcomes.

Methods and analysis Two investigators will conduct independent searches in PubMed, EMBASE, Web of Science, MEDLINE and the Cochrane Library, from database inception to October 2022. The search will not be limited by language or region. Eligible studies will include reports investigating post-TAVI outcomes in patients with sarcopenia, who are aged >18 years and diagnosed using a CT scan. The primary outcome is short-term mortality (30-day mortality), while the secondary outcomes include long-term mortality (>30 days), length of intensive care unit (ICU) stay, need for ICU admission (the number of patients in the sarcopenia or non-sarcopenia group requiring ICU admission), length of hospital stay and overall complications. Included studies will be assessed for risk of bias according to the Quality in Prognosis Studies critical assessment tool and certainty of evidence using the Grading of Recommendations, Assessment, Development and Evaluation. The analysis will be done with Review Manager (V.5.4) software. If testing reveals little or no statistical heterogeneity, a fixed-effect model will be used for data synthesis; otherwise, a random-effect model may be employed. On encountering substantial heterogeneity, subgroup analysis and leave-one-out jackknife sensitivity analysis will be used to verify the robustness of the results. The obtained results will be presented as forest plots while Cochran's Q test and I² test will be used to calculate the heterogeneity (>50% indicating strong heterogeneity). **Ethics and dissemination** No ethical approval is needed for this study since we will be using data from previously published studies. The results will be disseminated in a peer-reviewed journal.

PROSPERO registration number CRD42022349525.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) remains the current treatment for

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This systematic review and meta-analysis will synthesise evidence regarding the effect of sarcopenia on outcomes after transcatheter aortic valve implantation.
- ⇒ We will strictly follow the guidelines for the conduct and reporting of systematic reviews and meta-analyses to minimise bias.
- ⇒ We aim to be as thorough as possible, including conducting sensitivity and subgroup analyses.
- ⇒ We will use the Quality in Prognosis Studies critical assessment tool to evaluate the methodological quality of included studies, while Grading of Recommendations, Assessment, Development and Evaluation will be used to determine the certainty of the evidence.
- ⇒ The included studies may have high heterogeneity in terms of methods and results, which could impact the robustness of the review findings.

older adults affected by severe aortic stenosis (AS) and those with high or prohibitive surgical risk.^{1 2} Previously, several clinical, functional and anatomical predictors were identified for procedural success and long-term outcomes.³⁻⁵ To address new treatment targets and improve current management strategies, sarcopenia was recently suggested as a predictor of outcomes in patients undergoing TAVI.⁶

Sarcopenia is highly prevalent among patients undergoing TAVI and is reported in a vast majority of men (80%) compared with women, who exhibited approximately half of the value (47%). Of the patients who underwent TAVI with a body mass index (BMI) <25 kg/m², 73% had sarcopenia, which was considered a predictor of mortality.⁷ In patients undergoing TAVI for severe AS, skeletal muscle mass was investigated as a marker of sarcopenia. Although it is technically easy and reproducible to measure psoas muscle area (PMA) from CT, it is not readily available



in many clinics. Hence, a preprocedural scan of the chest, abdomen and pelvis is routinely performed among TAVI candidates for interventional planning.³

Sarcopenia is defined as the loss of skeletal muscle mass and functioning due to ageing,^{8,9} which represents a central biological substratum of frailty reflecting a state of declined functional capacity, and increased vulnerability to disease, disability and ultimately death.^{10–12} The PMA obtained from axial cuts on a CT scan was validated as a surrogate for muscle mass.¹³ A low muscle mass is a measure of sarcopenia, which can be easily determined through preoperative CT images. Sarcopenia is demonstrated to herald adverse outcomes across a range of clinical conditions and is considered an independent marker of life quality and disease prognosis.^{10,11,14} Sarcopenia was observed to be a strong prognostic indicator for perioperative complications, which increased short-term and long-term postoperative mortality and morbidity,^{15–17} including cognitive impairment,¹⁸ mental disorders,¹⁹ acute kidney injury^{20,21} and even survival.^{17,22,23} Moreover, the sarcopenia cohort was associated with longer ICU and hospital stays,¹⁷ whose evidence was mainly observed in patients undergoing non-cardiac surgery. Yet, no full consensus has been achieved on sarcopenia being a predictor of poor outcomes after TAVI. Studies suggested that sarcopenia was associated with longer hospital stay and worse 1-year health-related quality of life post-TAVI.²⁴ However, Gallone G. *et al* believed that sarcopenia overestimated additive prognostic value over current post-TAVI mortality risk estimators; for example, it was shown that early safety, clinical efficacy and 30-day all-cause death remained unaffected by sarcopenia.³

Sarcopenia can occur secondary to a systemic disease, especially one that invokes inflammatory processes, for example, malignancy or organ failure. Furthermore, sarcopenia can develop as a result of inadequate intake of energy or protein, probably due to anorexia, malabsorption, limited access to healthy foods or limited ability to eat.¹⁰ Michael reported that patients who underwent TAVI with sarcopenia showed a negative effect on important outcomes,²⁵ increasing mortality or prolonging the length of hospital stay. However, the conclusion stating that sarcopenia negatively affected the outcomes of TAVI patients is cursory to be accepted since a few previous studies did not use the revised guideline-based criteria for diagnosing the disease. In addition, the qualitative systematic review of the included studies was previously performed without a meta-analysis. Therefore, we aim to perform further analysis to assess the impact of sarcopenia on mortality and postoperative complications in patients after TAVI.

METHODS AND ANALYSIS

This study was registered on PROSPERO (CRD42022349525) and this protocol was prepared according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

(PRISMA) statement.²⁶ The results of this systematic review and meta-analysis will be reported in accordance with PRISMA guidance.

Search strategy

Articles will be retrieved from five databases, including PubMed, EMBASE, Web of Science, MEDLINE and the Cochrane Library, from database inception to October 2022. The search will not be limited by language or region. Relevant publications will be searched manually for the reference lists of the collected studies, including grey literature, for example, conference articles. Studies will first be screened independently using the title/abstract and then in full versions to determine suitability for their inclusion in a review. During the search process, the main search terms will be combined with a free word search. The following search algorithm and Medical Subject Headings (MeSH) terms will be used: [(Sarcopenia) and (TAVI)]. Additional details regarding search strategies are provided in online supplemental appendix.

The obtained search results will be exported to the endnote database. Two investigators (KL and YL) will each independently search the databases and screen the titles/abstracts of all records. Full-text articles potentially judged as eligible by an investigator will be retrieved and evaluated by both investigators. An article will be excluded only for an explicit reason. After the completion of data extraction, both researchers will cross-check the data. If there is any irreconcilable disagreement between the two researchers, it will be resolved by consensus, with input from a third independent reviewer (LY). The template study flow chart is presented in [figure 1](#).

Inclusion and exclusion criteria

The inclusion criteria will be as follows:

1. Adult patients aged 18 or older.
2. Original published articles, including randomised controlled trials or observational studies (cohort, cross-sectional or case-control studies) evaluating and comparing the effect of sarcopenia on patients undergoing TAVI.
3. Definition of sarcopenia being supported by the Asian Working Group for Sarcopenia²⁷ and the European Working Group for Sarcopenia in Older People (EWG-SOP1)⁸ or EWG-SOP2.¹⁰
4. A reference group including non-sarcopenic patients.
5. Having sufficient quantitative data, including contingency tables, ORs, relative risks or HRs with 95% CIs.

The exclusion criteria will be as follows:

1. Unfinished or ongoing studies.
2. Case reports, comments, animal studies, meta-analyses and systematic reviews.

Outcomes

The primary outcome of this study is short-term mortality (30-day mortality), while the secondary outcomes will include long-term mortality (>30 days), length of ICU stay, need for ICU admission (the number of patients in

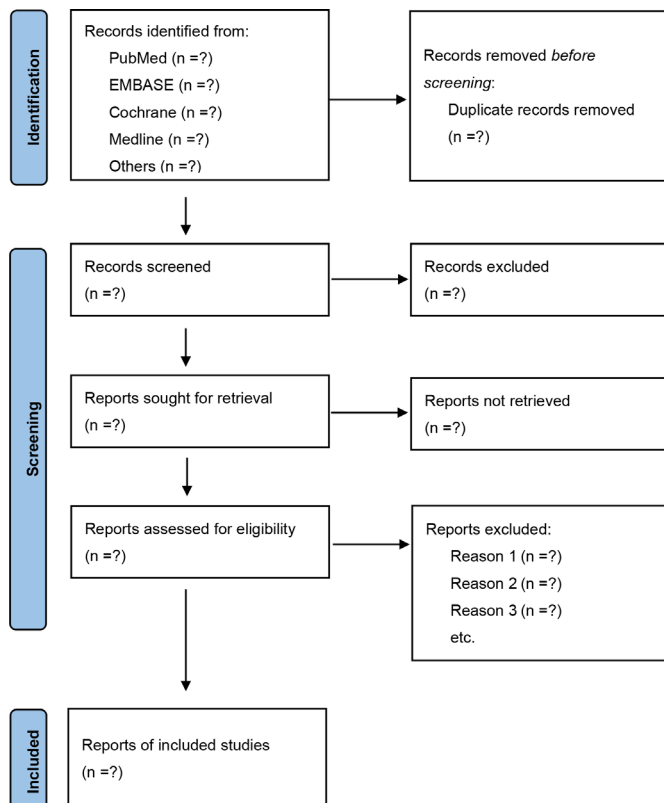


Figure 1 Flow chart will be used to document the process of selecting articles for inclusion in the systematic review and meta-analysis.

the sarcopenia or non-sarcopenia group requiring ICU admission), length of hospital stay, and overall complications (myocardial infarction, stroke, bleeding complications, acute kidney injury, vascular complications, conduction disturbances and arrhythmias).

Data collection and bias assessment

Both investigators will collect the following items from the included studies: authors, publication year, age, BMI, ASA classification, sample size, diagnostic criteria for sarcopenia and characteristics of the included population. In case the presentation of the outcome data is in the form of a graph and can not be directly extracted, a plot digitiser will be used or the corresponding author will be contacted.

Two investigators (KL and YL) will independently use the Quality in Prognosis Studies critical assessment tool and assess the bias risk in the included studies.^{28 29} The scale mainly includes study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain will be assessed against the criteria, resulting in a rating of either ‘high’, ‘moderate’ or ‘low’ risk of bias. Any discrepancies in the assessment can be resolved by consensus or third-author arbitration.

Grading of Recommendations, Assessment, Development and Evaluation³⁰ system will be used to assess the quality of evidence for short-term and long-term

mortality, length of ICU stay, need for ICU admission, length of hospital stay and other complications. Based on the risk of bias, inconsistency, indirectness, imprecision and other considerations, the quality of evidence will be rated as ‘high’, ‘moderate’, ‘low’ and ‘very low’.

Statistical analysis

Review Manager (V.5.4) software will be used to perform the analysis. Continuous variables will be calculated using the mean difference with 95% CIs, while dichotomous outcomes, such as 30-day mortality, can be presented using the risk ratios with the same CI. Continuous results will be presented as the mean and SD. If the median is displayed, the median and IQR can be converted to mean and SD using the statistical formula.^{31 32} For each endpoint, the heterogeneity will be visualised in forest plots and assessed using Cochran’s Q test and I^2 statistics. Statistical heterogeneity across studies will be evaluated using a corresponding p value derived from the χ^2 and I^2 tests. A value of $I^2 > 50\%$ or $p < 0.10$ is considered significantly heterogeneous. If the included studies are homogeneous ($p \geq 0.10$ and $I^2 < 50\%$), a fixed-effect model will be used to estimate the outcome data. However, a random-effect model will be used to aggregate data with significant heterogeneity, in which any potential sources of heterogeneity will be identified and analysed using subgroup analysis. Subgroup and meta-regression analyses will be conducted to explore the possible sources of heterogeneity and inconsistency, including the assessment tool for sarcopenia, age, preoperative comorbidities and the level of care obtained from different centres. Moreover, the robustness of the results will be verified using a leave-one-out jackknife sensitivity analysis conducted by removing one study at a time before repeating the analysis. If more than 10 studies are included in the meta-analysis, a funnel plot will be generated to assess publication bias. After synthesising the data and classifying it as outlined above, the final report will be written following the PRISMA criteria.

Subgroup and sensitivity analyses

Subgroup analyses will be performed depending on the number of identified studies. The level of heterogeneity across included studies and the strength of the supporting evidence will be examined using the Cochran Q and I^2 statistics with associated 95% CI. An I^2 value of 50% and above is considered a substantial level of heterogeneity. A random-effect model will be used if potential heterogeneity is seen among study variations, including population, regions or assessment methods of sarcopenia. However, if tests of heterogeneity among studies are not found to be significant, a fixed-effect model will be used. To examine the methodological quality and potential sources of heterogeneity in the included studies, a range of sensitivity analyses may be conducted. Sources of variations can include the assessment tool for sarcopenia, age, preoperative comorbidities and the level of care from different centres. These sources will be stratified,



and sensitivity analyses will be conducted separately. A leave-one-out jackknife sensitivity analysis will be used to verify the robustness of the results. Generally, a minimum of two studies are sufficient to perform a meta-analysis. If the level of heterogeneity between studies is high with no possibility of performing a pooled analysis, a narrative summary of the outcome will be presented in a systematic review along with the reasons for the obtained results.

Patient and public involvement

None.

Ethics and dissemination

No ethical approval is needed for this review as we will use data from previously published studies. On completion, the results will be disseminated in a peer-reviewed journal.

DISCUSSION

To the best of our knowledge, this will be the first systematic review and meta-analysis to examine the effects of sarcopenia on TAVI outcomes. Since TAVI candidates are elderly and exhibit high morbidity due to sarcopenia, it is becoming a growing problem among the ageing population. This study aims to investigate the impact of sarcopenia on post-TAVI outcomes, providing important predictive information for general medical management strategies, nursing goals and rehabilitation expectations.

Our study findings could provide a reliable basis for clinical practice. Sarcopenia is vulnerable to iatrogenic stressors and also prone to deterioration in the long term. Therefore, it ultimately needs to be integrated into the complex decision-making of choosing between the operational and conservative approaches in TAVI candidates.³³ Objectively, evidence has supported the simplification of the evaluation of sarcopenia for clinical purposes. Currently, pre-TAVI CT scans are routinely performed, which may provide important complementary information for sarcopenia assessment. Sarcopenia is highlighted as a risk predictor in TAVI patients, evaluating it as an objective and readily available tool to be introduced in clinical practice. However, sarcopenia, as a risk predictor, can also suggest the correction of sarcopenia using protein supplementation and exercise training, ultimately improving post-TAVI outcomes.

Nevertheless, this meta-analysis protocol may include some limitations. First, the measurement of muscle mass and the definition of sarcopenia may not be uniform across studies, which may impact the outcomes. Second, although more than 90% of all TAVI cases are currently performed via the transfemoral route, transapical vascular access along with subclavian, carotid and transcarotid routes may be usually favoured to avoid protracted recovery associated with thoracic access. However, this problem could potentially be addressed by subgroup analysis and including sufficient studies. Third, since we

will be selecting published articles, publication bias may be unavoidable.

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