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Transcatheter aortic valve implantation outcomes in patients with sarcopenia: protocol for a systematic review and meta-analysis

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Complete List of Authors:	Luo, Kai; Sichuan University, Department of Anesthesiology Yang, Lei; Sichuan University, Department of Anesthesiology; Chinese Academy of Medical Sciences, Department of Anesthesiology Li, Yu; Sichuan University, Department of Anesthesiology; Chinese Academy of Medical Sciences, Department of Anesthesiology
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Transcatheter aortic valve implantation outcomes in patients with sarcopenia: protocol for a systematic review and meta-analysis

Kai Luo[1], Lei Yang[1,2], Yu Li[1,2]

[1]Department of Anesthesiology, West China Hospital, Sichuan University, No. 37, Guoxue Xiang, Chengdu 610041, China

[2]Department of Anesthesiology, West China Hospital, Sichuan University and The Research Units of West China, Chinese Academy of Medical Sciences, Chengdu, China.

Corresponding author

Name: Yu Li

Address: Department of Anesthesiology, West China Hospital, Sichuan University, No. 37, Guoxue Xiang, Chengdu 610041, China

E-mail: liyu1936@163.com

Abstract

Introduction

Sarcopenia, which represents a central biological substratum of frailty and increases the incidence of adverse events and mortality after elective esophageal cancer surgery, gastrectomy, and pancreatic surgery, has been recently suggested as a predictor of outcomes in patients undergoing transcatheter aortic valve implantation (TAVI). However, the results of these studies are variable, and therefore, we would like to perform a systematic review and meta-analysis of the current literature to evaluate sarcopenia as a predictor of outcome post-TAVI.

Methods and analysis

Two investigators will search electronic databases independently, including PubMed, EMBASE, Web of Science, Medline, and The Cochrane Library. In addition, four clinical trial registries and the related references will be manually retrieved. Included studies will be assessed for risk of bias according to Cochrane and certainty of evidence using the Grading of Recommendations Assessment. Subgroup analyses and sensitivity analyses will be performed if substantial heterogeneity is encountered. Review Manager (version 5.4) software will be used to perform the whole data analysis. The results will be presented as forest plots, and heterogeneity between the included studies will be assessed by Cochran's Q and I2 tests.

Ethics and dissemination

No ethical approval is needed, as we will recruit from previously published studies in which informed consent was obtained. The results will be disseminated in a peer-reviewed journal upon completion.

PROSPERO registration number CRD42022349525.

Strengths and limitations of this study

Transcatheter aortic valve implantation (TAVI) represents the current mainstay of treatment for patients affected by severe aortic stenosis (AS). However, preoperative risk stratification models are imperfect, and the effect of sarcopenia on postoperative outcomes remains unclear.

To the best of our knowledge, this is the first systematic review and meta-analysis to estimate the effect of sarcopenia in predicting outcomes post-TAVI.

This extensive systematic review and meta-analysis is an applied study based on clinical

practice that will provide high-level evidence to evaluate the impact of sarcopenia on clinical outcomes in patients undergoing TAVI.

The gold standard for noninvasive muscle wasting assessment in clinical practice is an abdominal computed tomography (CT) scan, and the assessment of sarcopenia may interfere with the final data because its adoption in clinical practice remains limited by a lack of standardized definition.

Inherent to all meta-analyses is the potential for heterogeneity among the selected studies. Meanwhile, the measurement of sarcopenia is not uniform, and our analysis may use several tools that were used to assess muscle areas with a different threshold to define sarcopenic patients and may interfere with the outcome. However, sensitivity and subgroup analysis can be used to resolve this disagreement.

Introduction

Transcatheter aortic valve implantation (TAVI) represents the current mainstay of treatment for older adults affected by severe aortic stenosis (AS) and those with high or prohibitive surgical risk[1, 2]. Several clinical, functional, and anatomical predictors of procedural success and long-term outcomes have been identified[3-5]. To address new treatment targets and improve current management strategies, sarcopenia has been recently suggested as a predictor of outcomes in patients undergoing TAVI[6]. For TAVI planning and perioperative preparation, a computed tomography (CT) scan is routinely performed and may cover the complete thorax and abdomen. In addition to assessing preoperative cardiopulmonary function, a CT scan can also be used to measure body composition.

Sarcopenia, which is defined as the loss of skeletal muscle mass and functioning due to aging[7, 8], represents a central biological substratum of frailty and reflects a state of declined functional capacity and increased vulnerability to disease, disability, and death[9-11]. The psoas muscle area (PMA) obtained from axial cuts on CT scan, which has been validated as a surrogate for muscle mass[12], low muscle mass as a measure of sarcopenia is easily measured from preoperative CT images. Sarcopenia is considered an independent marker of life quality and prognosis and has been demonstrated to herald adverse outcomes across a range of clinical conditions[9, 10, 13]. Sarcopenia has been observed to be a strong prognostic indicator for perioperative complications and increased short- and long-term postoperative mortality and morbidity[14-16], including cognitive impairment[17], mental disorders[18], acute kidney injury[19, 20], and even survival[16, 21, 22]; meanwhile, the sarcopenia cohort was associated with longer ICU stays and hospital stays[16]. However, the evidence comes mainly from patients undergoing noncardiac surgery, with limited evidence and recommendations for sarcopenia as a predictor of poor outcomes after TAVI.

Studies have suggested that sarcopenia is highly prevalent among patients undergoing TAVI, negatively affects important outcomes[23] and is an independent predictor of outcomes in patients undergoing TAVI. Therefore, we will perform further analysis to assess the impact of sarcopenia on mortality and postoperative complications in patients following TAVI.

Methods

This protocol was registered on PROSPERO (CRD42022349525) and will be reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

(PRISMA-P) statement guidelines[24]. The results of this systematic review and meta-analysis will be published in a specialist journal or presented at a conference. This protocol is based on existing studies without patients or the public being involved directly.

Search strategy

Articles will be retrieved from five databases, including PubMed, EMBASE, Web of Science, Medline, and The Cochrane Library, four clinical trial registries (Australia-new Zealand Clinical Trials Registry, ClinicalTrials.gov, International Registry of Standard Randomized Controlled Trial Numbers and Chinese Clinical Trial Register), and the related references will be manually retrieved. The following search algorithm and Medical Subject Headings (MeSH) terms will be used: [(sarcopenia) and (TAVI)]. A specific search strategy is presented in Table 1 using PubMed as an example.

Table 1 Search strategy of PubMed

Search	Query
#1	"Sarcopenia"[MeSH Terms]
#2	"Sarcopenia"[All Fields] OR "Sarcopenias"[All Fields] OR "Muscle mass"[All Fields] OR "Muscle area"[All Fields]
#3	#1 OR #2
#4	"Transcatheter aortic valve implantation"[MeSH Terms]
#5	"Transcatheter aortic valve implantation"[All Fields] OR "Transcatheter aortic valve replacement"[All Fields] OR "TAVI"[All Fields] OR "TAVR"[All Fields]
#6	#4 OR #5

#7	#3 AND #6

Search results will be exported to an Endnote database. Two investigators (L K and Y L) will each independently search the database and read the titles/abstracts of all the records, and full-text articles will be retrieved if they are judged potentially eligible by an investigator. Both investigators will evaluate the full texts of all the potentially eligible retrieved articles, and the article will be excluded for an explicit reason. The two researchers will cross-check the data after completion of data extraction. Irreconcilable disagreements between the two researchers will be resolved by consensus with a third independent reviewer (L Y). The study flow is presented in Fig 1.

Inclusion and exclusion criteria

The inclusion criteria

(1) adult patients aged 18 or older;

(2) randomized controlled trials or observational studies (cohort, cross-sectional, or case–control studies) published as original articles that evaluated and compared the effect of sarcopenia in patients undergoing TAVI;

(3) a reference group composed of nonsarcopenic patients;

(4) Sufficient quantitative data, such as contingency tables, ORs, relative risks, or hazard ratios with 95% confidence intervals (CIs), were provided;

The exclusion criteria:

(1) unfinished or ongoing studies;

(2) Case reports, comments, animal studies, meta-analyses and systematic reviews.

Outcomes

The primary outcome is short-term mortality (30-day mortality). Secondary outcomes are long-term mortality (> 30 days), length of ICU stay, need for ICU admission (the number of patients in the sarcopenia or nonsarcopenia group needs ICU admission), length of hospital stay and total complications.

Data collection and bias assessment

Two investigators will collect the following items: authors, publication year, age, BMI, ASA classification, sample size, diagnostic criteria for sarcopenia, and characteristics of the included population. If the outcome data were presented in the form of a graph and could not be directly extracted, we will use a plot digitizer or contact the corresponding author.

Two investigators (L K and Y L) will independently use the Quality in Prognosis Studies (QUIPS) critical assessment tool to assess the risk of bias for the included studies[25, 26]. The scale mainly includes study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain is assessed against criteria, thereby resulting in a rating of 'high', 'moderate', or 'low' risk of bias. Any discrepancies in the assessment will be resolved by consensus or third-author arbitration.

GRADE (Grading of Recommendations, Assessment, Development, and Evaluation)[27] will be used to assess the quality of evidence for short- and long-term mortality, length of ICU stay, need for ICU admission, length of hospital stay and complications. We will rate the quality of the evidence as 'high', 'moderate', 'low', and 'very low' based on the risk of bias,

inconsistency, indirectness, imprecision, and other considerations.

Statistical analysis

Review Manager (version 5.4) software will be used to perform the whole data analysis. The mean difference (MD) with 95% confidence intervals (CI) will be chosen to calculate continuous variables, while risk ratios (RR) with the same CI will be employed to present dichotomous outcomes. Continuous results will be presented as the mean and standard deviation, and if the median is displayed, we will convert the median and interquartile range to the mean and standard deviation using the statistical formula[28, 29]. Statistical heterogeneity across studies will be evaluated with a corresponding *P* value derived from the chi-square test and I^2 test, and $I^2 > 50\%$ or $P < 0.10$ is regarded as significantly heterogeneous. If the included studies are homogeneous ($p \geqslant 0.10$ and I2 <50%), we will use the fixed-effects model to estimate the outcome data. A random-effect model will be used to aggregate the data owing to significant heterogeneity, and we will identify any potential sources of heterogeneity and conduct subgroup analysis. Subgroup analysis and meta-regression analysis will be conducted to explore the possible sources of heterogeneity and inconsistency, such as participants' mean age, diagnosis of sarcopenia and race. In addition, leave-one-out jackknife sensitivity analysis will be conducted by removing one study at a time before repeating the analysis to verify the robustness of the results.

Subgroup and sensitivity analysis

Subgroup analyses may be performed depending on the number of studies identified. The level of heterogeneity across included studies and strength of evidence for heterogeneity will

be examined using the Cochrane Q and I2 statistics with associated 95% CI, an I^2 of 50% and above is considered a substantial level of heterogeneity. The random effect models will be used because of potential heterogeneity between study variations in population, regions or assessment methods of sarcopenia across studies, or the fixed effect model will be used if tests of heterogeneity among studies are not significant. A range of sensitivity analyses may be conducted to examine the methodological quality and potential sources of heterogeneity of the included studies. Sources of variations may include tool for assessment of sarcopenia, age, preoperative comorbidities and the level of care from different centers. These will be stratified and separate sensitivity analyses conducted, leave-one-out jackknife sensitivity analysis will be used to verify the robustness of the results. A minimum of two studies are generally considered sufficient to perform a meta-analysis, if the level of heterogeneity is high between studies and pooled analysis of the studies is not possible, a narrative summary of the outcome of the selected studies will be presented in a systematic review and report the reasons for the results.

Patient and public involvement

No patients or the public were directly involved in the design, writing or editing of this systematic review protocol.

Discussion

This is the first study to demonstrate that body composition analysis using pre-TAVI CT is feasible. TAVI candidates are elderly, with a high morbidity of sarcopenia, and it will be a growing problem with an aging population. The aim of this study is to investigate the impact

of sarcopenia on outcomes post-TAVI to provide important predictive information for general medical management strategies, nursing goals, and rehabilitation expectations.

Our study will provide a reliable basis for clinical practice. As pre-TAVI CT scans are currently routinely performed, they may provide important complementary information for sarcopenia assessment. On the one hand, it highlights sarcopenia as a risk predictor in TAVI patients and evaluates sarcopenia as an objective, readily available tool to be introduced in clinical practice. On the other hand, sarcopenia as a risk predictor suggests a potential role for the correction of sarcopenia to improve post-TAVI outcomes, such as protein supplementation and exercise training.

Limitations exist in this meta-analysis. First, the measurement of muscle mass and the definition of sarcopenia are not uniform and will inevitably have a negative impact on the outcomes. In addition, more than 90% of all TAVI cases are currently performed via the transfemoral route. To avoid protracted recovery associated with thoracic access, transapical vascular access and subclavian, carotid, and transcarotid routes are usually favored. However, we can attempt to solve this problem by subgroup analysis if sufficient studies are included. Meanwhile, publication bias was unavoidable, as we selected published articles.

Ethics statements

Patient consent for publication: Not applicable.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Contributions:

L K registered the methods on the PROSPERO website and drafted the manuscript. The manuscript was subsequently revised for critical intellectual content by L K, Y L, and L Y.

Competing Interest statemen

No competing interest

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Figure Legend

Figure 1 is provided without any warranty of any kind, either express or implied, the flow chart will be used to document the process of selecting articles for inclusion in this systematic review and meta-analysis.

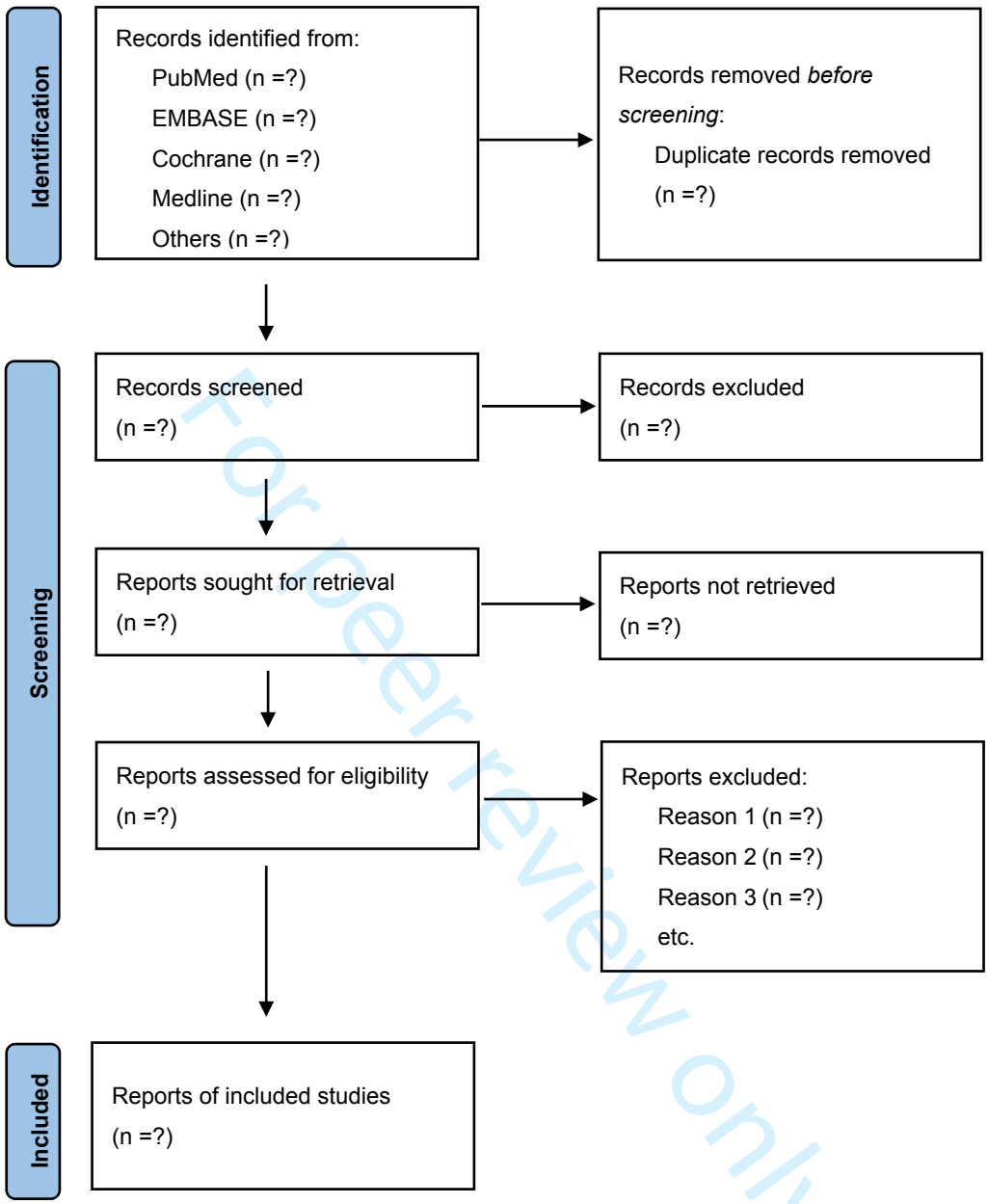

Fig 1. Flowchart showing selection of articles for review

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5 to Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7 to Page 8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 7 to Page 8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7 to Page 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 2
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7 to Page 8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	No
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 5 to Page 6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6
Study characteristics	17	Cite each included study and present its characteristics.	Not applicable
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Not applicable
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Not applicable
	23b	Discuss any limitations of the evidence included in the review.	Not applicable
	23c	Discuss any limitations of the review processes used.	Page 9
	23d	Discuss implications of the results for practice, policy, and future research.	Page 9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 9
Competing interests	26	Declare any competing interests of review authors.	Page 9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 5

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review (√)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such (√)
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (√)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (√)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (√)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments (×)
Support:		
Sources	5a	Indicate sources of financial or other support for the review (√)
Sponsor	5b	Provide name for the review funder and/or sponsor (×)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol (×)
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known (√)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (√)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (√)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (√)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (√)

Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (√)
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (√)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (√)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (√)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (√)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (√)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised (√)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) (√)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) (√)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned (×)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) (√)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (√)

√: The items has been presented in the manuscript
×: Not applicable

BMJ Open

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

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

Kai Luo[1], Lei Yang[1,2], Yu Li[1,2]

[1]Department of Anesthesiology, West China Hospital, Sichuan University, No. 37, Guoxue Xiang, Chengdu 610041, China.

[2]Department of Anesthesiology, West China Hospital, Sichuan University and The Research Units of West China, Chinese Academy of Medical Sciences, Chengdu, China.

Correspondence to:

Yu Li

Department of Anesthesiology, West China Hospital, Sichuan University, No. 37, Guoxue Xiang, Chengdu 610041, China

liyu1936@163.com

Abstract

Introduction

Sarcopenia represents a central biological substratum of frailty, which increases the incidence of adverse events and mortality after surgery for esophageal 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 until 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 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 (QUIPS) critical assessment tool and certainty of evidence using the GRADE. The analysis will be done with Review Manager (version 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. Upon 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 I^2 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.

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 minimize bias.
- We aim be as thorough as possible, including conducting sensitivity and subgroup analyses.
- We will use the Quality in Prognosis Studies (QUIPS) critical assessment tool to evaluate the methodological quality of included studies, while GRADE 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.

Introduction

Transcatheter aortic valve implantation (TAVI) remains the current treatment for 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 to women, who exhibited approximately half of the value (47%). Of the patients who underwent TAVI with a BMI <25, 73% had sarcopenia, which was considered a predictor of mortality [7]. In patients undergoing transcatheter aortic valve implantation (TAVI) for severe aortic stenosis, 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 pre-procedural 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 aging [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- 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 (LOS) and worse one-year health-related quality of life post-TAVI [24]. However, Guglielmo 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, e.g., 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. Additionally, 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-P) 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 until 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, e.g., 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 the online supplemental appendix.

The obtained search results will be exported to the endnote database. Two investigators (LK 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 flowchart 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 randomized controlled trials (RCTs) 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 Sarcopenia (AWGS) [27] and the European Working Group for Sarcopenia in Older People (EWGSOP1) [8] or EWGSOP2 [10].

(4) a reference group including non-sarcopenic patients;

(5) having sufficient quantitative data, including contingency tables, ORs, relative risks, or hazard ratios with 95% confidence intervals (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 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 digitizer will be used, or the corresponding author will be contacted.

Two investigators (LK and YL) will independently use the Quality in Prognosis Studies (QUIPS) 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.

GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) [30] system will be used to assess the quality of evidence for short- 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 (version 5.4) software will be used to perform the analysis. Continuous variables will be calculated using the mean difference (MD) with 95% confidence intervals (CI), while dichotomous outcomes, such as 30-day mortality, can be presented using the risk ratios (RR) with the same CI. Continuous results will be presented as the mean and standard deviation. If the median is displayed, the median and interquartile range can be converted to mean and standard deviation using the statistical formula [31, 32]. For each endpoint, the heterogeneity will be visualized 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 chi-square and I^2 tests. A value of $I^2 > 50\%$ or $P < 0.10$ is considered significantly heterogeneous. If the included studies are homogeneous ($P \geqslant 0.10$ 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, wherein any potential sources of heterogeneity will be identified and analyzed 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 centers. 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 ten studies are included in the meta-analysis, a funnel plot will be generated to assess publication bias. After synthesizing 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 Cochrane 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 centers. 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. Upon 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 aging 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 trans-carotid routes may be usually favored 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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Patient consent for publication

Not applicable.

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Contributors

Preparation of the manuscript, and figures was performed by K.L., L.Y. and all authors reviewed the final manuscript. Other specific contributions are as follows: Conception and design: K.L., L.Y. Collection and assembly of studies: K.L., L.Y. Manuscript writing: All authors. Drafting and revision of manuscript and Final approval of

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Competing interests

No competing interests.

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Figure title/legend

Figure 1. Flowchart

The flowchart will be used to document the process of selecting articles for inclusion in the systematic review and meta-analysis.

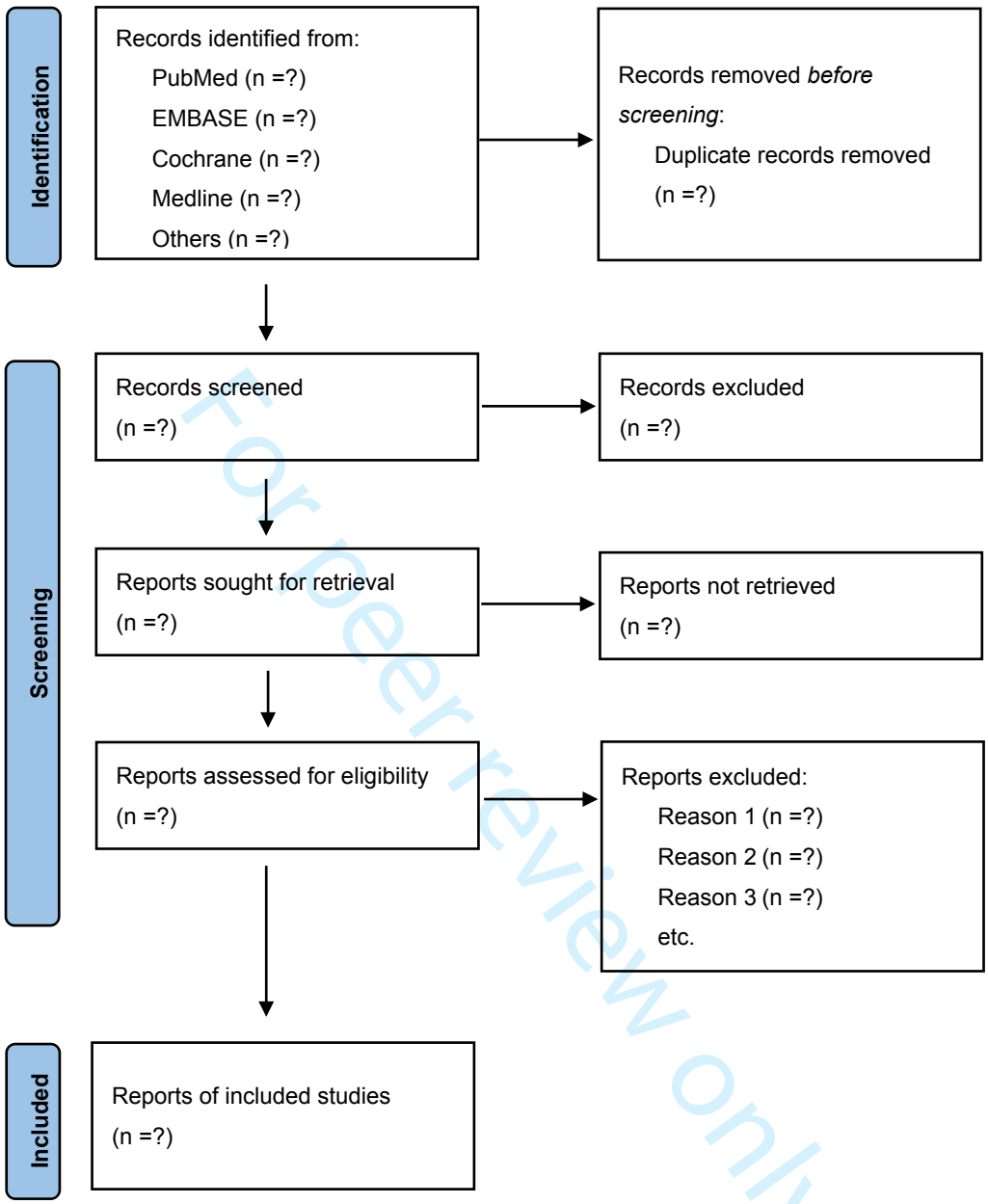

Fig 1. Flowchart showing selection of articles for review

Appendix

We will search the reference lists of all identified publications for additional studies. There is no restriction on the language of publication. The searches will be rerun prior to the final analyses and any further studies identified will be included

Search terms for PubMed	
Search	Query
#1	"Sarcopenia"[MeSH Terms]
#2	"Sarcopenia"[Title/Abstract] OR "Sarcopenias"[Title/Abstract] OR "Muscle mass"[Title/Abstract] OR "Muscle area"[Title/Abstract]
#3	**#1** OR **#2**
#4	"Transcatheter aortic valve implantation"[MeSH Terms]
#5	"Transcatheter aortic valve implantation"[Title/Abstract] OR "Transcatheter aortic valve replacement"[Title/Abstract] OR "TAVI"[Title/Abstract] OR "TAVR"[Title/Abstract]
#6	**#4** OR **#5**
#7	**#3** AND **#6**

Search terms for MEDLINE	
Search	Query
#1	Sarcopenia. ab, ti.
#2	Sarcopenias. ab, ti.
#3	Muscle mass. ab, ti.
#4	Muscle area. ab, ti.
#5	**#1** OR **#2** OR **#3** OR **#4**
#6	Transcatheter aortic valve implantation. ab, ti.
#7	Transcatheter aortic valve replacement. ab, ti.
#8	TAVI. ab, ti.
#9	TAVR. ab, ti.
#10	**#6** OR **#7** OR **#8** OR **#9**
#11	**#5** AND **#10**

Search terms for the Cochrane Library (in Title, Abstract, Keyword)	
Search	Query
#1	MeSH descriptor: [Sarcopenia] explode all trees
#2	Sarcopenia
#3	Sarcopenias
#4	MeSH descriptor: [Muscle mass] explode all trees
#5	Muscle mass
#6	Skeletal muscle mass
#7	MeSH descriptor: [Muscle area] explode all trees
#8	Muscle area

#9	Muscle areas
#10	**#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9**
#11	MeSH descriptor: [Transcatheter aortic valve implantation] explode all trees
#12	Transcatheter aortic valve implantation
#13	Transcatheter aortic valve replacement
#14	TAVI
#15	TAVR
#16	**#11** OR **#12** OR **#13** OR **#14** OR **#15**
#17	**#10** AND **#16**

Search terms for EMBASE

Search	Query
#1	'Sarcopenia'/exp
#2	'Sarcopenia': ab, ti
#3	'Sarcopenias': ab, ti
#4	'Muscle mass'/exp
#5	'Muscle mass': ab, ti.
#6	'Muscle area'/exp
#7	'Muscle area': ab, ti.
#8	'Muscle areas': ab, ti.
#9	**#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8**
#10	'Transcatheter aortic valve implantation'/exp
#11	'Transcatheter aortic valve implantation': ab, ti.
#12	'Transcatheter aortic valve replacement': ab, ti.
#13	'TAVI': ab, ti.
#14	'TAVR': ab, ti.
#15	**#10** OR **#11** OR **#12** OR **#13** OR **#14**
#16	**#9** AND **#15**

Search terms for Web of Science

Search	Query
#1	Sarcopenia (Topic) OR Sarcopenia (Title) OR Sarcopenia (Abstract) OR Sarcopenias (Topic) OR Sarcopenias (Title) OR Sarcopenias (Abstract)
#2	Muscle mass (Topic) OR Muscle mass (Title) OR Muscle mass (Abstract) OR Muscle area (Topic) OR Muscle area (Title) OR Muscle area (Abstract) OR Muscle areas (Topic) OR Muscle areas (Title) OR Muscle areas (Abstract)
#3	**#1** OR **#2**
#4	Transcatheter aortic valve implantation (Topic) OR Transcatheter aortic valve implantation (Title) OR Transcatheter aortic valve implantation (Abstract)
#5	Transcatheter aortic valve implantation (Topic) OR Transcatheter aortic valve implantation (Title) OR Transcatheter aortic valve implantation (Abstract)
#6	TAVI (Topic) OR TAVI (Title) OR TAVI (Abstract)

#7	TAVR (Topic) OR TAVR (Title) OR TAVR (Abstract)
#8	**#4** OR **#5** OR **#6** OR **#7**
#9	**#3** AND **#8**

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review (page 1)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such (No)
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (page 3)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (page 1)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (page 12)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments (No)
Support:		
Sources	5a	Indicate sources of financial or other support for the review (page 12)
Sponsor	5b	Provide name for the review funder and/or sponsor (No)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol (No)
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known (page 3 to 5)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (page 6 to 7)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (page 6 to 7)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (page 6)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (page 6 and appendix)
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (page 8)

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (page 7 to 8)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (page 6 and page 7)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (page 7)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (page 7)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (page 8)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised (page 8 to 9)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) (page 8 to 9)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) (page 9 to 10)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned (page 10)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) (page 9)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (page 8)