Prognostic Value of Sarcopenia in Older Adults with Transcatheter Aortic Valve Implantation: A Systematic Review and Meta-Analysis

Yan-Wu Yang  
Sichuan University

Pan Pan  
Sichuan University

Xin Xia  
Sichuan University

Yi-Wu Zhou  
Sichuan University

Meiling Ge (gemeiling025@163.com)  
Sichuan University

Research Article

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Abstract

Background

Some studies associated sarcopenia and postoperative mortality in aortic stenosis patients undergoing transcatheter aortic valve implantation (TAVI), however, their findings were not consistent. Therefore, we conducted this systematic review and meta-analysis to summarize the prevalence of sarcopenia and its impact on mortality in patients undergoing TAVI.

Methods

Medline, EMBASE, and PubMed were searched from inception to October 14, 2022 to retrieve eligible studies that assessed sarcopenia in patients undergoing TAVI. The PRISMA (2020) was employed to evaluate study quality. Pooled sarcopenia prevalence was calculated with 95% confidence interval (CI), and heterogeneity was estimated using the $I^2$ test. Associations of sarcopenia with mortality of post-TAVI were expressed as hazard ratio (HR) or odds ratios (OR) and 95% CI.

Results

13 studies involving 5248 patients (mean age from 78.1 to 84.9 years) undergoing TAVI were included. There were eleven studies defined sarcopenia based on loss of skeletal muscle mass index (SMI), while only two studies used low muscle mass plus low muscle strength and/or low physical performance. Overall, the pooled prevalence of sarcopenia in patients undergoing TAVI was 49% (95% CI 41%-58%). Sarcopenia was associated with an increased risk of long-term ($\geq$ 1 year) mortality in patients after TAVI (HR 1.57, 95% CI 1.33–1.85, P < 0.001), with similar findings in the subgroups stratified by follow-up time, definition of sarcopenia, study location, and study design. Furthermore, the 1-, 2-, and 3-year cumulative probabilities of survival in patients with sarcopenia were significantly lower than non-sarcopenia (74.0% vs 91.0%, 68.3% vs 78.0%, and 72.6% vs 79.8%, all P < 0.05).

Conclusions

Although there are substantial differences in diagnostic criteria, sarcopenia is highly prevalent in patients undergoing TAVI and its linked to increased long-term mortality after TAVI. The standardization of sarcopenia diagnostic criteria would be beneficial and future longitudinal studies are needed to investigate the prevalence and prognostic value of sarcopenia in TAVI patients.

Background

Aortic stenosis is a degenerative disease that mainly occurs in aged 75 years and
Within the last decade, transcatheter aortic valve implantation (TAVI) has emerged as the standard care for aortic valve replacement (AVR) in patients with symptomatic severe aortic stenosis who are high risk for surgical AVR and an emerging treatment option for low-risk surgical patients. Despite the minimally invasive nature of TAVI, older patients with a substantial burden of comorbidity remain at substantial risk of incurring adverse events postoperatively. Therefore, identifying the modifiable factors associated with these adverse outcomes may inform clinical decision-making and management strategies.

Since the baseline functional status is a well-known predictor for operative risk, sarcopenia might be an underlying condition related to negative clinical outcomes of TAVI. Sarcopenia, a primarily age-dependent syndrome, has been defined as the age-related decline in skeletal muscle mass, muscle strength, and physical performance. The global prevalence of sarcopenia ranged from 8–36% in individuals < 60 years and from 10–27% in ≥ 60 years old. Previous studies have found that sarcopenia commonly coexists with cardiovascular diseases (CVDs) such as coronary artery disease, heart failure, and aortic stenosis. Moreover, sarcopenia is a risk factor for CVDs development and has a negative impact on prognosis. For example, sarcopenia has been demonstrated to be an independent risk factor for mortality in patients undergoing cardiac surgery. Therefore, many believe that a holistic approach through sarcopenia assessment may improve the decision-making process in TAVI.

Many studies regarding the predictive value of sarcopenia in patients post TAVI have been conducted. However, the results of these studies remain inconsistent and even controversial. For example, Brouessard et al. reported that sarcopenia was not correlated with rehospitalization and mortality at one year after TAVI. On the other hand, Heidari et al. found that sarcopenia was an independent risk factor for mortality in patients following TAVI. However, so far no meta-analysis has been published on how sarcopenia affects clinical outcomes in TAVI patients. On such bases, we performed the present systematic review and meta-analysis (i) to estimate the prevalence of sarcopenia in patients undergoing TAVI and (ii) to evaluate the impact of sarcopenia on clinical outcomes such as mortality after TAVI.

**Methods**

**Literature Search**

During the process of conducting this review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following online electronic databases were used for the literature search: Medline, EMBASE, and PubMed from date of initiation. Corresponding search formulae according to different database requirements were applied. The search period extended to October 14, 2022. To avoid omissions, the search scope included subject words, keywords, or full text. The pre-defined search terms were: “sarcopenia”, “muscle mass”, or “muscle area” and “TAVI” or “TAVR” or “transcatheter aortic valve implantation” or “transcatheter aortic valve replacement”. The detailed search strategies and results of each included database were shown in Table S1. We also identified additional
studies by searching the reference lists of the included studies and previous relevant narrative reviews and systematic reviews.

**Selection Criteria**

All eligible studies were included according to the following criteria: (i) Participants: sarcopenic patients undergoing TAVI or TAVR; (ii) Exposures: sarcopenia (currently, no unique definition exists for sarcopenia; hence, each study definition was applied); (iii) Comparison: non-sarcopenia; (iv) Outcomes: the association between sarcopenia and the risk of morality (short-term (≤ 30 days) and long-term (≥ 1 year); or other adverse outcomes (such as rehospitalization, length of hospital stay (LOS) and postoperative adverse events); (v) Study design: prospective or retrospective cohort studies. The exclusion criteria included (i) No clearly reported diagnostic criteria for sarcopenia; (ii) Narrative reviews, comments, editorials, case series, meeting abstracts, or corresponding letters; (iii) Sarcopenia treated as an outcome measure instead of a prognostic factor; and (iv) Non-English literature.

**Data Extraction**

We used a standardized extraction form to abstract data from each included study. The following information was extracted independently by 2 reviewers (YWY and MLG): the first author’s name, year of publication, study design, study location, number of enrolled patients, mean/median age, body mass index (BMI), Society of Thoracic Surgeons Predicted Risk of Mortality (STS) score, definition of sarcopenia, methods of measuring muscle mass or muscle function, prevalence of sarcopenia, median follow-up time, and outcome indicators. If the relevant data were not readily accessible, authors were contacted to obtain additional data and/or clarification.

**Statistical Analysis**

The primary outcome of this meta-analysis were (1) sarcopenia prevalence in patients undergoing TAVI and (2) the impact of sarcopenia on mortality in patients with TAVI. The prevalence of sarcopenia was pooled using a meta-analysis of single proportions. Subgroup data were provided according to method used to define sarcopenia and sex. The impact of sarcopenia on the incidence of mortality was evaluated by the pooled hazard ratio (HR) or odds ratios (OR) and 95% CI using random/fixed effects modelling with heterogeneity across studies assessed by the $I^2$ and the Cochran’s Q statistic. $P$ value of Q statistic $\leq 0.1$ or $I^2 \geq 50\%$ was defined as significant heterogeneity. For continuous outcomes, the number of total patients, mean time and standard error were extracted, and they were expressed as standardized mean differences (SMD) with 95% CI. Pre-planned subgroup analyses were carried out according to follow-up time, assessment of sarcopenia, study location, and study design. The secondary outcomes were rehospitalization, length of hospital stay and postoperative adverse events. We performed meta-analyses for these outcomes where possible; otherwise, we narratively reported the relevant results. We also pooled 1-year, 2-year, and 3-year cumulative mortality for patients with or without sarcopenia using the Freeman-
Tukey double arcsine transformation method[29]. However, we did not perform meta-regression analyses to explore the heterogeneity due to the small number of studies included in the meta-analysis of each outcome. Two-sided $P < 0.05$ were considered statistically significant, and meta package in R software (version 4.2.1) was used for all statistical analyses.

**Quality And Bias Assessment**

We applied the Quality in Prognostic Studies (QUIPS) instrument[30] to assess the risk of bias in individual studies. Each of the six QUIPS domains was rated as high, moderate, or low risk of bias. Studies with five or more low-risk domains were classified as “at overall low risk of bias,” those with two or more high-risk domains were classified as “at overall high risk of bias,” while the remaining studies were classified as “at overall moderate risk of bias”[31]. Publication bias was evaluated using the funnel plot and Egger’s test. Given that potential publication bias indicated, the trim-and-fill method was used to observe the change in pooled estimates following imputation of data from potentially unpublished articles. Moreover, sensitivity analysis was done to estimate the stability of the results.

**Results**

**Study Selection and Characteristics**

Figure 1 depicts the flow chart of the literature selection process. After searching three databases, 1387 studies were found to be potentially relevant to the search terms. After removing duplicates, 862 titles and abstracts were screened, resulting in 30 relevant studies for full-text screening, which resulted in 13 of these studies being included in our review.

Table 1 summarizes the characteristics of all studies included in this meta-analysis. The 13 studies[14–26] enrolled 5248 individuals who were included in the qualitative analysis. All the included studies were published after 2016. Of these, 5 reported retrospective data[16, 17, 20, 23, 26], and 8 were prospective cohort studies[14, 15, 18, 19, 21, 22, 24, 25]. The sample size of the included studies ranged from 81 to 1375. And the mean age of patients ranged from 78.1 to 84.9 years. In addition, the included patients were sampled from a diversity of populations, involving 3 studies conducted in Asia[20, 25, 26], 7 in America[15, 16, 19, 21–24], and 3 in Europe[14, 17, 18]

**Prevalence Of Sarcopenia**

Table 1 summarized the commonly used diagnostic criteria of sarcopenia. According to European Working Group on Sarcopenia in Older People (EWGSOP) [11], eleven studies defined sarcopenia by low muscle mass measured on CT-scan regardless of low skeletal muscle mass index (SMI)[14–17, 19, 21, 23–26], psoas muscle area (PMA)[17, 22] or psoas muscle area index (PMI)[21]. Another two studies[18,
20] defined sarcopenia by low muscle strength (handgrip strength) and physical performance (gait speed).

In the 13 studies included, sarcopenia prevalence wide ranged from 21–70% (Table 1), and the pooled estimated prevalence was 49% (95% CI 41%-58%) (Figure. 2). In addition, the subgroup analysis by different definitions of sarcopenia showed significant variations among the subgroups. The prevalence of sarcopenia was 50% (95% CI 42%-59%, 10 studies, 4642 cases) when defined by SMI, 47% (95% CI 14%-79%, 2 studies, 791 cases) by PMA, 40% (95% CI 35%-45%, 1 study, 381 cases) by PMI, and 38% (95% CI 0.3%-76%, 2 studies, 206 cases) by gait speed and grip strength (Figure. S1). There was no difference in pooled prevalence of sarcopenia in male (62%, 95% CI 45%-79%, 1624 cases) compared to female patients (48%, 95% CI 35%-61%, 2068 cases, \( P = 0.21 \)) (Figure. S2).

**Sarcopenia And Mortality**

Four studies (\( n = 2524 \)) reported the association of sarcopenia and short-term (\( \leq 30 \text{ days} \)) mortality after TAVI (Figure. 3). The risk of short-term mortality was 1.6–3.7% in sarcopenia patients as compared with 1.2–3.5% in non-sarcopenia patients. However, sarcopenia was not significantly associated with short-term mortality in both four studies, with OR ranging from 0.73 to 1.75, and the pooled OR was 1.23 (95% CI 0.70–2.14, \( P = 0.47 \); Figure. 3).

Eight studies (\( n = 4038 \)) quantified the relationship between sarcopenia and long-term mortality (\( \geq 1 \text{ year} \)) after TAVI. All the eight studies provided data on multivariate analysis, showing that sarcopenia was significantly associated with an increased risk of mortality, with a pooled adjusted HR of 1.57 (95% CI 1.33–1.85, \( P < 0.001 \); Figure. 4). In addition, there was a low heterogeneity between include studies (\( I^2 = 45\% , P = 0.07 \)).

We also found sarcopenia was consistently associated with a higher risk of long-term mortality (\( \geq 1 \text{ year} \)) across subgroups analyzed. Specifically, sarcopenia (vs. non-sarcopenia) was associated with a significantly increased risk of mortality in all the subgroup of follow-up time \( \geq 1 \text{ year} \), \( \geq 2 \text{ years} \), and \( \geq 3 \text{ years} \) with pooled adjusted HR of 2.63 (95% CI 1.14–6.04), 1.73 (95% CI 1.30–2.30), and 1.56 (95% CI 1.34–1.83), respectively. In addition, patients with sarcopenia had more than 1.4-fold risk of mortality regardless of the study design (prospective vs. retrospective), whether sarcopenia was defined by SMI or other methods, or whether the study location (Figure. 5). Sensitivity analysis demonstrated that individual studies did not significantly influence the pooled HR for mortality (Figure. S3).

**Sarcopenia And Cumulative Survival**

Eight studies provided the absolute number of deaths by sarcopenia status allowing combined incidence estimations. The 1-, 2-, and 3-year cumulative probabilities of survival in patients with sarcopenia were 74.0% (95% CI 58.0%-88.0%), 68.3% (95% CI 63.7%-72.7%), and 72.6% (95% CI 68.2%-76.8%). By
comparison, they were 91.0% (95% CI 78.0%-99.0%), 78.0% (95% CI 71.0%-84.2%), and 79.8% (95% CI 74.6%-84.5%), respectively in patients without sarcopenia (all \( P < 0.05 \)) (Table S2).

**Sarcopenia And Other Adverse Outcomes**

There were wide variations in the reporting of secondary outcomes across the included studies, with only three studies reporting comparable outcomes in relation to sarcopenia. In pooled analysis of contributing studies, there was no significant difference between patients with or without sarcopenia with LOS (SMD: \(-0.03, 95\% \text{ CI } -0.19\text{-}0.12, P = 0.07\)), rehospitalization (HR:1.00, 95% CI 0.86–1.16, \( P = 0.97 \)), stroke (OR:0.76, 95% CI 0.40–1.45, \( P = 0.40 \)), acute kidney injury (OR: 1.11 95% CI 0.62–1.96, \( P = 0.73 \)), and bleeding (OR: 0.77, 95% CI 0.51–1.17, \( P = 0.23 \)) (Figure. S4).

**Quality And Risk Of Bias**

Table S3 summarizes the quality assessment of individual studies. Of the 13 studies, five were at an overall moderate risk of bias[15, 16, 18, 22, 24], while eight were at an overall low risk of bias[14, 17, 19–21, 23, 25, 26]. Publication bias was observed amongst the eight studies reporting late mortality (Egger's test for asymmetry \( P = 0.03 \)). Therefore, the trim-and-fill method was performed by adding estimated HR of two potential unpublished articles to reach symmetry in the funnel plot (Figure. S5). The resulting pooled adjusted HR was 1.57 (95% CI 1.15–2.14), similar to our main finding (HR:1.57, 95% CI 1.33–1.85).

**Discussion**

In this systematic review and meta-analysis, we explored the relationship of pre-procedure sarcopenia and outcomes after TAVI in 13 studies involving 5248 patients. We have made several important observations. First, our review found that the pooled prevalence of sarcopenia was 49% in patients undergoing TAVI. Second, our meta-analysis revealed that sarcopenia was independently associated with higher long-term (\( \geq 1 \text{ year} \)) mortality of patients undergoing TAVI; however, sarcopenia failed to be associated with short-term (30-days) mortality after TAVI. Third, the association between sarcopenia and other adverse outcomes such as stroke, acute kidney injury, and bleeding appeared to be inconsistent in patients undergoing TAVI according to three small studies. Limited evidence implied that sarcopenia might not have an association with prolonged length of hospital stay and rehospitalization.

Sarcopenia was originally defined as the aging-related loss of skeletal muscle mass. Currently, most researchers defined sarcopenia not only according to the loss of skeletal muscle mass but also the decline in muscle strength (such as weak handgrip strength) and/or physical performance (such as slow gait speed) [11]. However, in the cardiovascular research field, the diagnosis of sarcopenia still mainly relies on the measurement of skeletal muscle mass such as muscle area at the third lumbar vertebra level (L3) measured by CT imaging [32]. In the present review, 8 of the 13 included studies applied this method...
to estimate skeletal muscle mass. And only one included study applied chest CT scans at the 7th and 12th thoracic levels (T7 and T12) to estimate muscle mass. However, the chest but not the abdominal CT scans were the routine for patients following TAVI[33]. Furthermore, the correlation between skeletal muscle measurements at the L3 and the T12 level was stronger[24]. Thus, further studies were required to determine the optimal cutoff points to define the sarcopenia using chest CT scans in patients undergoing TAVI.

Owning to various cutoff points of low muscle mass used to define the sarcopenia, the prevalence of sarcopenia in the included studies of our meta-analysis varied from 21–70%. Although sex-specific cutoffs for defining sarcopenia, there was no statistical difference in the pooled prevalence of sarcopenia in patients suffering TAVI between male and female. It was reasonable to conclude, therefore, that sex might not play a role on the prevalence of sarcopenia in patients with TAVI. However, previous studies reported that the association between sarcopenia and functional decline was more significant in men than in women[34, 35], which deserves further research into the influence of sarcopenia on sex-related differences.

Furthermore, we found sarcopenia was strongly associated with higher long-term (≥ 1 year) mortality after TAVI. This finding was in accordance with those of studies conducted in patients with other types of cardiac surgery, such as heart valve surgery [13], percutaneous coronary intervention (PCI)[36], and endovascular aneurysm repair[37]. In addition, sarcopenia independently predicts 1-year mortality even adjustment for STS score and key covariates, which supported assessment sarcopenia for patients undergoing TAVI, given that sarcopenia added easy-to-obtain functional information beyond that reflected in established risk score. Meanwhile various studies demonstrated that physiotherapy and nutritional interventions could have favorable effects on sarcopenia[38, 39]. Therefore, patients with sarcopenia might also benefit from interventions such as exercise training and nutritional supplementation pre-TAVI.

Based on the studies included in this review, sarcopenia failed to be associated with short-term (30-day) mortality or adverse outcomes such as LOS, rehospitalization, stroke or bleeding. Those findings reinforced the concept that short-term outcomes after TAVI both appear to be favorable and relatively unaffected by sarcopenia, implying that contemporary TAVI appears to be safe across the broad spectrum of patients with varying degrees of progressive muscle mass loss. This finding was not completely consistent with relevant results of studies on other types of cardiac surgery. For example, Ganapathi and colleagues found that physical frailty was associated with discharge to another location other than home and 30-day mortality in patients undergoing proximal aortic surgery[40]. Therefore, the association between sarcopenia and short-term mortality and other advent outcomes after TAVI needs further research in the future.

Several limitations should be considered. First, the language was restricted to English in the published articles included in this meta-analysis, some potentially eligible studies using other language may not be included. Second, definitions of sarcopenia in each study were applied in this review. Although in most of the included studies, definitions of sarcopenia were defined were based on CT scans, the scan levels and
the cutoffs varied across studies which might induced bias in our results. Finally, because there were only small number of studies estimate the early mortality, we were limited by the infrequent reporting of postoperative complications in relation to sarcopenia status, and these interpretations are open to competing risk bias. Therefore, whilst the observations of the effect of sarcopenia on early outcomes were important, further work was required in this area.

Conclusion

In conclusion, this meta-analysis shows that sarcopenia is highly prevalent in patients with TAVI (approximately 49%). Sarcopenia is associated with poorer long-term mortality in TAVI patients, but it appears not to be a predictor of short-term mortality and advent outcomes. Although current guideline already recommends measurement of physical performance as part of the screening before TAVI [41], our results additionally highlight that measurement of muscle mass should be recommended in patients before the procedure.

Abbreviations

TAVI
Transcatheter aortic valve implantation
CI
Confidence interval
HR
Hazard ratio
OR
Odds ratios
SMI
Skeletal muscle mass index
AVR
Aortic valve replacement
CVDs
Cardiovascular diseases
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SMD
Standardized mean differences
QUIPS
Quality in Prognostic Studies
PMA
Psoas muscle area
PMI
Psoas muscle area index.

Declarations

Authors’ contributions

Y.YW, G.ML participated in the design of the study. Y.YW, P.P, Z.YW, and G.ML were responsible for the coordination and acquisition of the data. Y.YW and XX performed the statistical analysis. All authors contributed to the preparation, critical review, and approved the final manuscript.

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Availability of data and materials

In this meta-analysis, all data generated or analyzed during this study are available from the results of the included studies in this article.

Competing interests

The authors declare no conflict of interest with this manuscript.

Ethics approval and consent to participate:

Not applicable in it.

Consent for publication:

Not applicable in it.

Acknowledgement:

Not applicable in it.

References


Tables

Table 1 is available in the Supplementary Files section.

Figures
Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.
Figure 2

The pooled overall prevalence of sarcopenia in patients undergoing TAVI. TAVI: Transcatheter Aortic Valve Implantation.

Figure 3

Forest plot for the association between sarcopenia and the risk of short term (≤30 days) mortality after TAVI. TAVI: Transcatheter Aortic Valve Implantation.
Figure 4

Forest plot for the association between sarcopenia and the risk of long term (≥1 year) mortality after TAVI. TAVI: Transcatheter Aortic Valve Implantation.

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**Common effect model**

**Random effects model**

Heterogeneity: $I^2 = 46\%$, $t^2 = 0.0233$, $p = 0.07$

1.57 [1.33; 1.85] 100.0% — 100.0%

1.66 [1.34; 2.06] — 100.0%

Figure 5

Association of sarcopenia and risk of mortality after TAVI in study subgroups. TAVI: Transcatheter Aortic Valve Implantation; SMI: skeletal muscle mass index; PMA: psoas muscle area; PMI: psoas muscle area index.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- table1.docx
- Supplement1.docx
- Supplement2.docx