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REVIEW PAPER

Usefulness of skeletal muscle area detected by computed tomography to predict mortality in patients undergoing transcatheter aortic valve replacement: a meta-analysis study

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Abstract

Measures of sarcopenia, such as low muscle mass measured from the readily available preoperative computed tomography (CT) images, have been recently suggested as a predictor of outcomes in patients undergoing transcatheter aortic valve replacement (TAVR). However, results of these studies are variable and, therefore, we performed a systematic review of current literature to evaluate sarcopenia as a predictor of outcome post TAVR. The search was carried out in electronic databases between 2008 and 2018. We identified studies that reported CT-derived skeletal muscle area (SMA) and survival outcomes post TAVR. Studies were evaluated for the incidence of early (≤ 30 days) and late all-cause mortality (> 30 days) post TAVR. Eight studies with 1881 patients were included (mean age of 81.8 years ± 12, 55.9% men). Mean body mass index was (28.2 kg/m^2 ± 1.1), mean Society of Thoracic Surgeons risk score (7.0 ± 0.6), and mean albumin level was (3.8 g/dL ± 0.1). Higher SMA was associated with lower long-term mortality [odds ratio (OR) 0.49, 95% confidence interval (CI) 0.28–0.83, p = 0.049], compared with low SMA. Also, higher SMA was associated with lower early mortality but was not statistically significant (OR 0.72; 95% CI 0.44–1.18; p = 0.285). CT-derived SMA provides value in predicting post-TAVR long-term outcomes for patients undergoing TAVR. This is a simple risk assessment tool that may help in making treatment decisions and help identifying and targeting high-risk patients with interventions to improve muscle mass prior to and following the procedures.

Keywords Transcatheter aortic valve replacement · Skeletal muscle area · Computed tomography · Frailty · Mortality

Introduction

The Society of Thoracic Surgeons (STS) score and European System for Cardiac Operative Risk Evaluation are frequently used as risk stratification tools before transcatheter aortic valve replacement (TAVR) in order to evaluate a patient's risk for such interventions [1]. In recent years, there was an increasing interest in frailty as a predictor of outcomes after surgical aortic valve replacement/TAVR, thus guiding risk stratification of those patients before the procedure [2]. Nevertheless, most of the proposed frailty indicators are difficult to measure objectively and are often estimated on the basis of subjective clinical judgment and questionnaires of patient functionality as well as relying heavily on physical performance tests which can be less feasible in very frail patients [2, 3]. In the aging population, frailty is often associated with sarcopenia, which is defined as an age-related disease described by a significant loss of muscle mass [4, 5]. Low

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muscle mass as a measure of sarcopenia is easily measured from preoperative computed tomography (CT) images and has garnered interest as an objective quantitative measure of frailty. Moreover, recent small reports suggested skeletal muscle mass as an independent predictor of outcomes in patients undergoing TAVR. We sought, therefore, to perform a meta-analysis of the available body of literature to examine the effect of low muscle mass on the clinical outcomes post TAVR.

Methods

Search strategy

With the help of an experienced librarian at MedStar Washington Hospital Center (F.K.), the search was carried out in three electronic databases, Medline/Ovid, Embase, and Scopus, between January 2008 and February 2018. This was done entirely as a keyword search because (1) we wanted to include results from Ovid Medline's non-indexed segments, and (2) the keyword search included all the citations found using MeSH terms ("Sarcopenia" and "transcatheter aortic valve replacement").

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". In addition, conference abstracts and presentations were considered using the Google search engine to ensure further that pertinent articles were not missed. The reference lists of included studies were screened as well for any eligible studies. This search was not limited by any language filters. The search strategy and search terms used are detailed in the Online Data Supplement.

Inclusion criteria

Eligible studies would have fulfilled all of the following inclusion criteria: (1) randomized controlled trials or observational studies (cohort, cross-sectional, or case-control studies) published as original articles or conference abstracts that evaluated and compared the effect of sarcopenia in patients undergoing TAVR; (2) sufficient quantitative data such as contingency tables, OR, relative risks, or hazard ratios with 95% confidence intervals (CIs); and (3) a reference group composed of non-sarcopenic patients. The outcomes of interest were short- and long-term mortality after TAVR.

Data extraction and outcome measures

Independent duplicate data extraction was done by two reviewers (G.H. and M.S.). The following data were extracted: first author, article title, study design, year of study, country of origin, year of publication, and tools used to assess muscle mass and muscle strength. Eligible studies were examined for the short-term (≤ 30 days) and long-term mortality (> 30 days). For continuous variables, we collected the means and standard deviations whenever possible. For dichotomous variables, we abstracted effect measures [relative risks, odds ratios (OR), or hazard ratios] and 95% CIs. Alternatively, we collected the event rates and populated a contingency table to calculate the effect measures.

Statistical analysis

The findings were evaluated in a descriptive manner based on the information provided by each of the included studies. Quantitative study results were expressed as OR with 95% CI. When available, ORs were reported. Otherwise, crude ORs were computed from the available results in the paper.

We assessed heterogeneity of the study using Chi square tests ($p > 0.1$ showed no significant heterogeneity among studies) and I^2 statistic ($I^2 > 25$, > 50, and $> 75\%$ showed low, moderate, and high heterogeneity, respectively). Statistical analyses were conducted using OpenMetaAnalyst [6]. All values are two-tailed, and $p < 0.05$ was set as the threshold for statistical significance.

Quality and bias assessment

The quality of the included studies was assessed by two authors independently based on the modified Newcastle-Ottawa-scale in this meta-analysis [7]. Modified Newcastle-Ottawa-scale uses a rating system to determine the quality of studies based on two categories, which include selection of participants, comparability between groups, and assessment of exposure or outcome. Modified Newcastle-Ottawa-scale is widely used and recommended by the Cochrane collaboration to assess the quality of nonrandomized studies, especially in cohort and case-control studies. Eight items relevant to the evaluation of quality were applied to this meta-analysis (online data supplement). Disagreements were resolved through discussion.

We intended to assess publication bias using funnel plot techniques, Begg's rank test and Egger's regression test, as appropriate given the known limitations of these methods.

Results

Eight studies with 1881 patients were included (Fig. 1) [8–15]. Long-term outcome data were available for six studies [8, 10–13, 15]. Based on the available information, 55.9% of the included patients were males, and the mean age of the enrolled patients was 81.8 years ± 12. The body mass

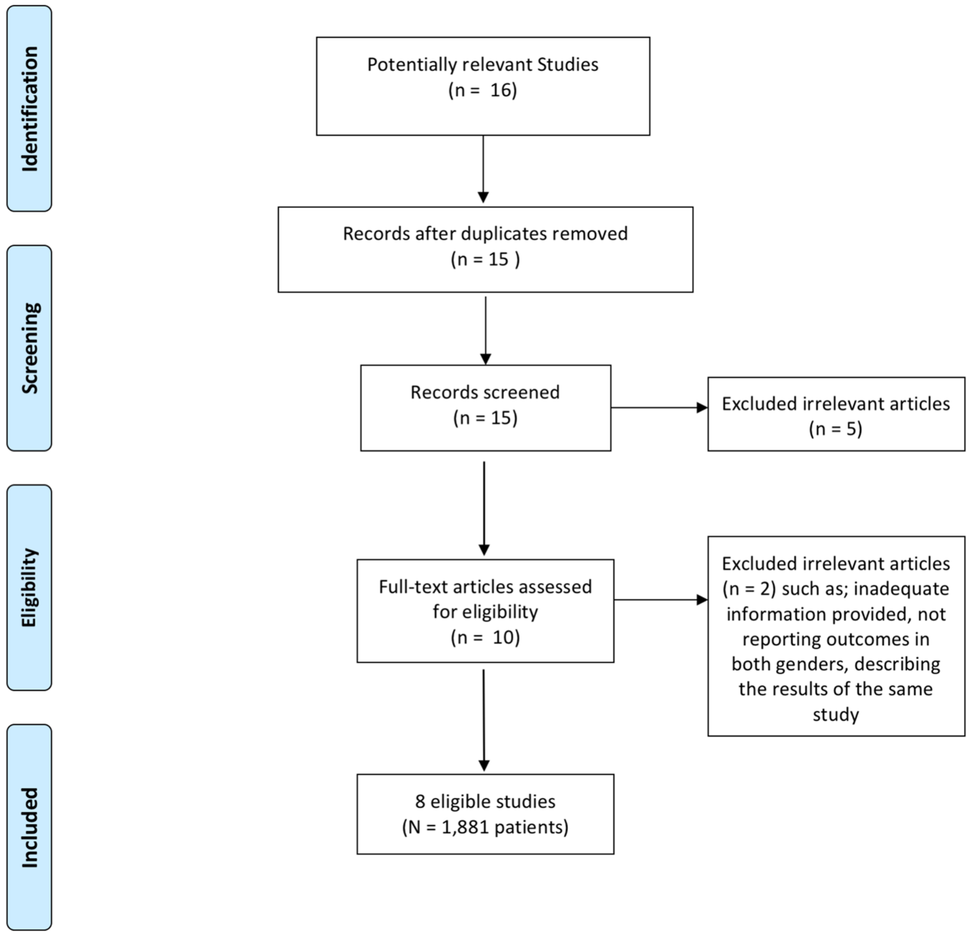

Fig. 1 Flow diagram of the meta-analysis with algorithm for the literature search results and inclusion into the study

index was 28.2 kg/m^2 ± 1.1, STS risk score was 7.0 ± 0.6, and albumin level was 3.8 g/dL ± 0.1. Roughly one-third (37.4%) of patients had diabetes, two-thirds (64.2%) had hyperlipidemia, and 81.4% had hypertension.

Five studies used the psoas muscle area to assess muscle mass [8, 9, 11–13]. One study used psoas muscle area indexed to body mass index [14], and two studies used the skeletal muscle index [10, 15]. Characteristics of the studies included in the analysis are described in Table 1.

We were unable to assess the publication bias as there were inadequate numbers of included studies to properly assess a funnel plot or more advanced regression-based assessments. The information regarding the intra/interobserver variability were available only from two studies [8,

Table 1 Characteristics of included studies

Study	Year	Study design	Sample size	Follow-up (months)	Country	Outcomes
Garg [8]	2017	Retrospective cohort	152	12	USA	Early poor outcome 30 days, 1-year mortality, high-resource utilization
Saji [12]	2016	Retrospective cohort	154	6	USA	All-cause mortality at 30 days and 6 months
Paknikar [11]	2016	Retrospective cohort	139	24	USA	late mortality, high-resource utilization
Mok [10]	2016	Prospective cohort	460	12	Canada	Mortality at 30 days and cumulative mortality
Garg [9]	2016	Retrospective cohort	103	12	USA	Early poor outcome 30 days, 1-year mortality, high resource utilization
Lindman [14]	2016	Retrospective cohort	330	1	USA	All-cause mortality at 30 days
Mamane [13]	2016	Prospective cohort	386	12	Canada	Length of stay, disability, all-cause mortality
Nemec [15]	2017	Retrospective cohort	157	12	USA	Postprocedural complications, length of stay 30 days and 1-year mortality

12]. Both inter-observer and intra-observer reproducibility for muscle area assessment were satisfactory, with a coefficient of variability ranging from < 2–5%.

Primary and secondary outcomes

When compared with sarcopenic patients, non-sarcopenic individuals have a lower risk for long-term mortality following TAVR OR 0.49, 95% CI 0.28–0.83, p = 0.049; Fig. 2a). Similarly, short-term mortality after TAVR was reduced in non-sarcopenic patients; however, it was not statistically significant (OR 0.72; 95% CI 0.44–1.18; p = 0.285; Fig. 2b). Despite all efforts, we were unable to eliminate the overall substantial statistical heterogeneity ($I^2 > 50\%$).

Discussion

We demonstrated that aortic stenosis patients with low muscle mass, measured on the preoperative CT images, had a 50% lower long-term mortality rate when compared to their peers with normal skeletal muscle mass. This summarizes the growing body of evidence on frailty in TAVR and offers better insight into the various scales that were developed and adapted to the highly frail and complex TAVR population in order to predict post-procedural poor outcomes [2, 16, 17].

In order to obtain a more objective evaluation to identify frail patients, preprocedural serum albumin level as a simple marker that is not subject to inter- or intraobserver bias was found to be independently associated with mortality in patients who undergo TAVR [18, 19]. Recently, the FRAILTY-AVR study compared different frailty scales in a prospective cohort of 646 patients undergoing TAVR and demonstrated a four-items scale encompassing lower-extremity weakness, cognitive impairment, anemia, and hypoalbuminemia to outperform other frailty scales [2]. Nevertheless, albumin is considered an acute-phase protein that has a relatively short half-life, with levels that are largely influenced by vascular injury, renal injury, and various cytokine levels which can reflect acute changes rather than representing a true frailty syndrome [20, 21].

Several tools are available for valid and reliable measurements of muscle strength and performance [22]. Tests such as handheld dynamometer, short physical performance battery, and gait speed over a short distance are frequently used as screening tools, and when scores on these parameters are below normal, further assessment of muscle mass might be more useful. In this current era of TAVR, CT remains the standard method for sizing the aortic annulus and assessing the access route patency before the procedure; therefore, muscle area measurement on CT images is readily accessible in almost all patients [23, 24].

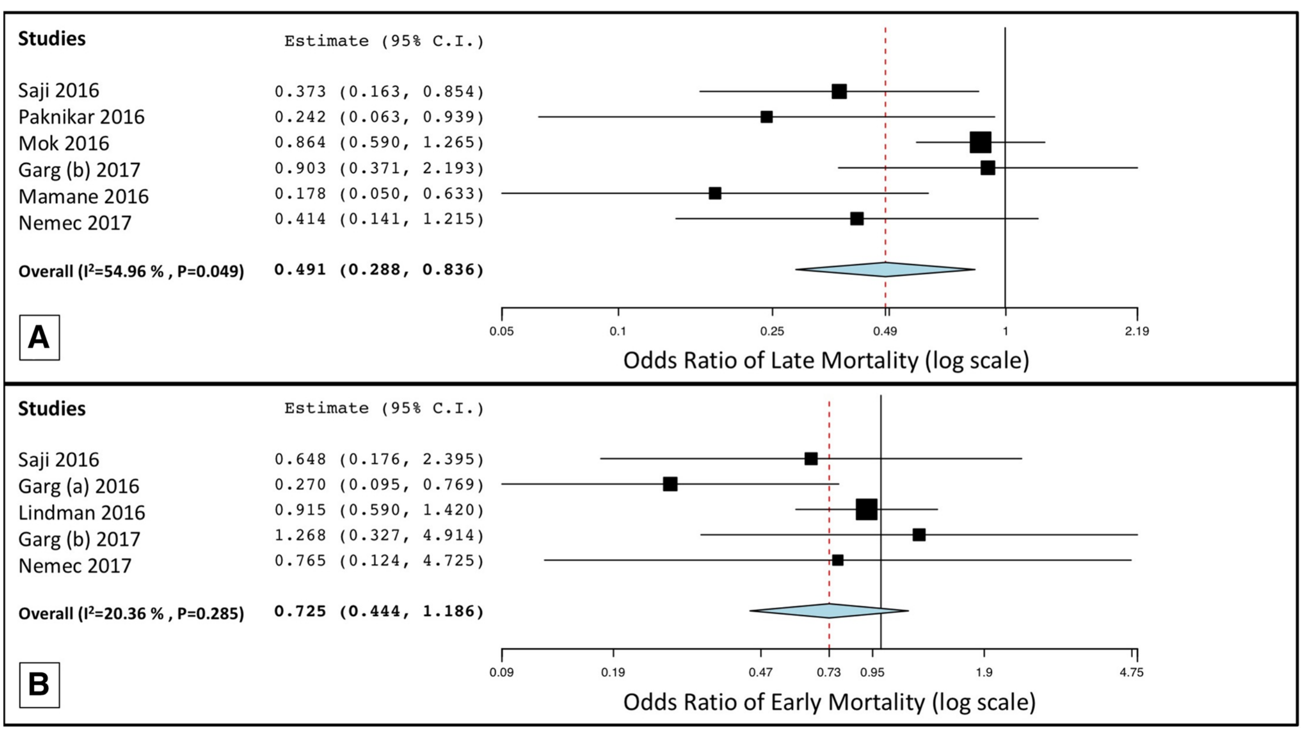

Fig. 2 Forest plots for the long-term (**a**) and short-term (**b**) mortality for non-sarcopenic patients who underwent TAVR compared to their sarcopenic counterparts. Heterogeneity across trials was evaluated with I^2 statistic. *CI* confidence interval

Table 2 Features of the tools that were used to assess muscle area in the included studies

Study	Vertebra level(s)	Density thresholds (Hounsfield unit)	Tool used to assess muscle mass	Comment(s)
Garg [8]	L3	n/a	BSA indexed PMA mm^2/m^2	PMA obtained from axial cuts on CT as a surrogate for global muscle mass Sarcopenia was defined as PMA indexed to body surface area less than the median
Saji [12]	L4	− 30 to 150	BSA indexed PMA mm^2/m^2	Three tertiles according to indexed PMA for each gender (men: tertile 1, 1708–1178 mm^2/m^2; tertile 2, 1176–1011 mm^2/m^2; and tertile 3, 1009–587 mm^2/m^2; women: and tertile 1, 1436–962 mm^2/m^2; tertile 2, 952–807 mm^2/m^2; and tertile 3, 806–527 mm^2/m^2
Paknikar [11]	L1 – L4	n/a	TPA	The areas of the left and right psoas muscles were summed to compute the TPA. TPA was standardized by gender to control for differences in body habitus
Mok [10]	L3	− 29 to 150	SMMI cm^2/m^2	Muscles that can be identified at L3 are psoas (major and minor), erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis Sarcopenia was defined as an SMMI 2 SDs less than the mean SMMI of young, healthy gender-specific reference ranges
Garg [9]	n/a	n/a	BSA indexed IPA	n/a
Lindman [14]	L4L5	n/a	PMABMI	Right and left psoas muscle area indexed to BMI
Mamane [13]	n/a	n/a	PMA	n/a
Nemec [15]	L3	− 29 to 150	SMI	The measurements included the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique, and rectus abdominis muscles For diagnosing sarcopenia, cutoff values of L3 muscle area of ≤ 52.4 cm^2/m^2 in men and ≤ 38.9 cm^2/m^2 in women were used

BSA body surface area, *PMA* psoas muscle area, *CT* computed tomography, *TPA* total psoas area, *SMMI* skeletal muscle mass index, *IPA* iliopsoas muscle area, *BMI* body mass index, *PMABMI* PMA indexed to BMI, *SMI* skeletal muscle index

Muscle mass has garnered interest as an objective quantitative measure of frailty that is independent of illness acuity and day-to-day changes in functional status required by other performance-based on frailty assessments, which may be unrelated to operative risk factors. Previous studies showed a prognostic value of skeletal muscle assessment in noncardiac as well as cardiothoracic surgeries [25]. The relationship between muscle mass and other known frailty markers is not well studies. A study by Cesari et al. [26] investigated the relation of the frailty syndrome with muscle, as assessed by computerized tomography scan, and found strong associations between that the different frailty syndrome component and muscle mass measurement.

The mechanism that links skeletal muscle mass and post-TAVR mortality is thought to be related to the central role of skeletal muscle in the frailty syndrome. Skeletal muscle is the main reservoir for amino acids in the body, which, when depleted, impairs several vital functions necessary for recovery [27]. Frail patients with low muscle mass have impaired muscle protein synthesis and a high risk of deconditioning after an invasive procedure; this is compounded by the vicious cycle of inadequate nutrition and decreased physical activity [28].

The impact of lower muscle mass after the procedure is not only limited to its undesirable effect on survival following TAVR, patients with SMA were found to be more likely to require discharge to rehabilitation facilities [8]. Therefore, CT-derived skeletal mass measurement might be considered a screening tool to identify vulnerable sarcopenic patients who might be targeted for specific interventions (e.g., protein supplementation and physical rehabilitation) to optimize their frailty status after the TAVR procedure [29, 30].

Limitation

Our study has several evident limitations. Inherent to all meta-analyses is the potential for heterogeneity among selected studies. However, heterogeneity testing did not indicate significant heterogeneity for the overall OR of mortality. The measurement of muscle mass and the definition of sarcopenia are not uniformed, and our analysis included studies with several tools that were used to assess muscle area with different threshold to define sarcopenic patients. These differences are highlighted in Table 2.

Conclusion

Our meta-analysis of all the available literature to date is suggestive of a benefit of CT-derived skeletal muscle area in providing a prognostic value and predicting post-TAVR long-term outcomes.

This method is a simple risk assessment tool that may improve risk stratification for TAVR procedure and guide clinical decisions and may perhaps be integrated into the STS score. It might also help identifying and targeting high-risk patients with nutritional and exercise interventions to improve muscle mass prior to and following the procedure.

More research is needed to validate these results with a prospective analysis of a larger cohort of patients or even through extracting data from the prior published randomized TAVR studies.

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Compliance with ethical standards

Conflict of interest Ron Waksman: Advisory Board: Abbott Vascular, Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips Volcano, Pi-Cardia Ltd.; Consultant: Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips Volcano, Pi-Cardia Ltd.; Grant Support: Abbott Vascular, AstraZeneca, Biosensors, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance. All other authors declared that they have no conflict of interest.

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