## PEER REVIEW HISTORY

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## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Sarcopenia as a predictor of outcome after transcatheter aortic valve implantation: protocol for systematic review and meta-analysis |
| **AUTHORS** | Luo, Kai; Yang, Lei; Li, Yu |

## VERSION 1 – REVIEW

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| **REVIEWER** | Giuseppe Andò<br>University of Messina - Messina University Hospital, Department of Cardiology |
| **REVIEW RETURNED** | 11-Sep-2022 |

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| **GENERAL COMMENTS** | The Authors should clearly indicate how they will pool data from included studies to analyze the main outcome of their study, that is 30-day mortality. The staitsical methos are somehow generic when discussing continuous and dichotomous variables.<br>Please to consider to add this refernce (PMID: 32898383). |

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| **REVIEWER** | Zhe Li<br>Western University , Epidemiology and Biostatistics |
| **REVIEW RETURNED** | 13-Oct-2022 |

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| **GENERAL COMMENTS** | Overall, this is well-written systematic review protocol and I believe will add value to current research on TAVI populations. This is an interesting systematic review and will provide important prognostic information on TAVI patients. I think this protocol needs more clarifications on the rationale, inclusion and exclusion criteria and outcome definition. The discussion needs to be strengthened. My comments are attached.<br><br>Introduction<br>• The rationale on the need to evaluate the effects of sarcopenia on TAVI outcomes is needed. Why there is limited evidence from patients undergoing cardiac surgery if sarcopenia is highly prevalent among cardiac surgery?<br>• Sarcopenia is associated with adverse outcomes “across a range of clinical conditions”. I think you need to highlight the adverse outcomes associated with sarcopenia in TAVI patients.<br>• Is there any evidence on the prevalence of sarcopenia among TAVI patients?<br>• In the abstract (introduction), you mentioned that “the results of these studies are variable, and therefore, we would like to perform a systematic review and meta-analysis”, but in the manuscript, I did not see any comments on existing studies. Consider talking a bit more about existing studies on sarcopenia and TAVI.<br><br>Methods |

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| | • Search strategy – consider searching grey literature, i.e., conference articles.<br>• Inclusion and exclusion criteria – do you have any criteria concerning the number of participants?<br>• An important criterion you need to consider is the definition of sarcopenia. Is there a gold standard definition of sarcopenia? If yes, please indicate in the manuscript. If not, will you include all sarcopenia definitions?<br>• Data collection – given that your analysis will focus on odds ratios, hazard ratios, etc. You may want to extract the number of outcome events and participants from both exposure and non-exposure group?<br>• Secondary outcomes – how about other adverse events as you mentioned in INTRODUCTION, cognitive impairment and kidney injury? Consider outline these outcomes and refer to Consortium consensus for the valve academic research (https://doi.org/10.1016/j.jtcvs.2012.09.002)<br>• Have you considered including patient-centred outcomes given the relevance of sarcopenia to frailty?<br>• Subgroup analysis – perhaps indicate what subgroup analysis will be performed if the number of included studies allows and describe the rationale.<br><br>Discussion<br>• I am not quite sure if "this is the first study to demonstrate that body composition analysis using pre-TAVI CT is feasible" is appropriate. This might be the first systematic review to examine the effects of sarcopenia on TAVI outcomes, but I don't think this is the first study 'demonstrates' the pre-TAVI CT scan of body composition is feasible as this is a different research question. Please consider modifying this statement.<br>• You kept mentioning there was a high prevalence of sarcopenia among TAVI patients. What's the prevalence (or range of prevalence) of sarcopenia in TAVI? Please also cite references.<br>• More clarifications on the relevance of the study findings and clinical practice. What is the current practice? Is sarcopenia currently collected or evaluated pre-TAVI? Please cite references.<br>• If the definition of sarcopenia is not uniform, I would suggest you have a clear statement on the inclusion/ exclusion criteria in terms of sarcopenia definition in METHODS. |

**VERSION 1 – AUTHOR RESPONSE**

Responses to Dr. Giuseppe Andò, University of Messina - Messina University Hospital

1. Thank you very much for your valuable suggestions on the revision of the manuscript. We will collect the outcomes from the included studies. 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. 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 such as 30-day mortality. 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. For each endpoint, the heterogeneity will be visualized in forest plots and assessed by the Cochran's Q test and I2 statistic. A funnel plot will be generated to assess publication bias if more than 10 studies are included in a meta-analysis. The final report will be written using the PRISMA criteria after the data synthesis and classification outlined above. The statistical methods are somehow generic when discussing continuous and dichotomous variables.

We believe that sarcopenia is vulnerable to iatrogenic stressors, and prone to deterioration in the long term. Sarcopenia should be ultimately integrated into the complex decision-making between the operational and conservative approaches in candidates for TAVI. Relevant reference is cited (discussion: reference 33).

Responses to Ms. Zhe Li, Western University

Introduction

1. Sarcopenia can occur secondary to a systemic disease, especially one that may invoke inflammatory processes, e.g. malignancy or organ failure. Further, sarcopenia can develop as a result of inadequate intake of energy or protein, which may be due to anorexia, malabsorption, limited access to healthy foods or limited ability to eat (introduction: reference 10). Its adoption in clinical practice remains limited by a lack of standardized definition. Moreover, whether the clinical predictive value of sarcopenia is independent from currently adopted post-TAVI risk stratification tools remains poorly characterized.
2. Michael has shown that of the patients who underwent TAVI with sarcopenia negatively affected important outcomes, given rise to mortality and prolonged length of hospital stay (introduction: reference 25).
3. Transcatheter aortic valve implantation (TAVI) represents the current mainstay of treatment for older adults affected by severe aortic stenosis (AS). Sarcopenia is a complex process resulting from the interplay of biological aging, functional status, malnutrition, cachexia and inflammatory

states. As such, it represents a central biological substratum of frailty. It was reported that sarcopenia to be presented in the vast majority of men (80%) versus approximately half of women (47%) undergoing TAVI. And, the patients who underwent TAVI with a BMI <25, 73% had sarcopenia and that sarcopenia is a predictor of mortality (introduction: reference 7).

4. Sarcopenia is associated with shorter length of hospital stay (LOS) and better 1-year health-related quality of life. However, Guglielmo considered that sarcopenia overestimated additive prognostic value over current post-TAVI mortality risk estimators. Early safety, clinical efficacy and 30-day all-cause death were unaffected by sarcopenia (introduction: reference 3 and 24).

Methods

1. To find possibly relevant publications, researchers will manually search the reference lists of the collected studies including grey literature, i.e., conference articles.
2. We have no criteria concerning the number of participants for the include studies, but case reports will be excluded.
3. Studies in the field of sarcopenia are limited by the lack of a gold standard definition. Asian Working Group for Sarcopenia (AWGS) and the European Working Group on Sarcopenia in Older People (EWGSOP) published sarcopenia definition respectively that aimed to foster advances in identifying and caring for people with sarcopenia. Computed tomography (CT) is considered to be the gold standard for non-invasive assessment of muscle quantity/mass. Sarcopenia confirmed by a CT scan that is on the basis of AWGS, EWGSOP1 or EWGSOP2 definition will meet the inclusion criteria. If possible, subgroup analyses were performed according to different definitions.
4. In our study, at least one of the outcomes (30-day mortality, long-term mortality (> 30 days), length of ICU stays, need for ICU admission, length of hospital stays and total complications) from both exposure and non-exposure group will be extracted, and there is no limit to the number of participants.
5. The occurrence of other adverse events will be counted as a composite index (total complications, i.e., myocardial Infarction, stroke, bleeding complications, acute kidney injury, vascular complications, conduction disturbances and arrhythmias). (It was modified in **OUTCOMES**)

6. Both the concepts of frailty and sarcopenia are evolving, and frailty seems to be evolving into a framework to detect persons with high risk of disability. While sarcopenia—considered as an organ failure (muscle failure or muscle insufficiency)—is a frequent cause of physical frailty. In practice, frailty and sarcopenia show a significant overlap, sarcopenia includes low physical performance, which means that sarcopenia is an essential component of physical frailty. In our study, we would like to find prognostic factors for TAVI patients to guide preoperative risk assessment and prediction. However, we may not consider any published interventional study investigating the possible effects of targeted interventions on sarcopenia and related outcomes after TAVI.
7. 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 subgroup analyses conducted. As all of these factors can affect the outcomes post-TAVI except for sarcopenia.

Discussion

1. It was modified in **DISCUSSION** (To the best of our knowledge, this is the first systematic review and meta-analysis to examine the effects of sarcopenia on TAVI outcomes).
2. It was reported that sarcopenia to be presented in the vast majority of men (80%) versus approximately half of women (47%) undergoing TAVI. And, the patients who underwent TAVI with a BMI <25, 73% had sarcopenia and that sarcopenia is a predictor of mortality (introduction: reference 24).
3. Assessment of skeletal muscle mass as a marker of sarcopenia has been investigated in patients undergoing transcatheter aortic valve implantation (TAVI) for severe aortic stenosis. Sarcopenia is predictive of 30-day poor outcome and high-resource utilization. Measuring PMA from CT was technically easy and reproducible, while this exam is not readily available in many clinical scenarios, a pre-procedural scan of chest, abdomen and pelvis is routinely performed among TAVI candidates for interventional planning (introduction: reference 3).
4. Sarcopenia confirmed by a CT scan that is on the basis of AWGS, EWGSOP1 or EWGSOP2 definition will meet the inclusion criteria (It was added in **INCLUSION CRITERIA**).

## VERSION 2 – REVIEW

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| **REVIEWER** | Giuseppe Andò<br>University of Messina - Messina University Hospital, Department of Cardiology |
| **REVIEW RETURNED** | 04-Nov-2022 |

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| **GENERAL COMMENTS** | All concerns have been addressed, thank you |

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| **REVIEWER** | Zhe Li<br>Western University , Epidemiology and Biostatistics |
| **REVIEW RETURNED** | 14-Nov-2022 |

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| **GENERAL COMMENTS** | I do not have any other major concerns. |