Meta-Analysis of the Impact of Pre-Procedural Serum Albumin on Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement

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Summary
Pre-procedural serum albumin’s impact on prognosis after transcatheter aortic valve replacement (TAVR) has been studied. Literature on the prognostic role of serum albumin in the survival of patients undergoing TAVR shows conflicting results. This meta-analysis was conducted to evaluate the impact of pre-procedural serum albumin on outcomes after TAVR. A comprehensive literature search of EMBASE, MEDLINE, and the Cochrane Library was undertaken through July 2019. The primary end points were 30-day and one-year all-cause mortality after TAVR. Risk ratios (HRs) and 95% confidence intervals (CIs) were calculated using the random-effect model. Ten eligible studies with 8,236 patients were analyzed. Of the 8,236 patients undergoing TAVR, with a mean age of 83 years, 48.8% were men and were categorized into two groups according to low and normal serum albumin (cut-off value: 3.5 or 4 g/dL). Overall, low albumin was significantly associated with an approximately two-fold increase in 30-day all-cause mortality (HR, 2.09; 95% CI, 1.53-2.86) and a 61% increase risk for one-year mortality (HR, 1.61; 95% CI, 1.31-1.98) in patients after TAVR. Sensitivity analyses showed the results to be robust. The association of low albumin level with an increase in one-year mortality risk was not modified by study design, albumin cut-off value, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), and study quality. In conclusion, low albumin levels were associated with poor prognosis in patients after TAVR. Pre-procedural albumin can be used as a simple tool related to prognosis after TAVR.

Key words: Hypoalbuminemia, Aortic stenosis

Transcatheter aortic valve replacement (TAVR) has emerged as the treatment of choice for severe aortic stenosis in elderly patients who are either not candidates for surgery1,2) or who are at high risk for complications from surgery.3,4) Currently, data are emerging on intermediate5) and low-risk patients.6) Over the last decade, over 100,000 TAVR procedures have been performed worldwide, attesting to TAVR’s success and acceptance. Nevertheless, after TAVR, patient outcomes are variable, and there is an increasing need for improved risk stratification in patients undergoing the procedure.

Pre-TAVR risk assessments traditionally use the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score and the European System for Cardiac Operative Risk Evaluation (EuroSCORE 1 and 2) to predict early outcomes. These risk scores alone are insufficient for predicting TAVR outcomes.7) Recently, the updated Valve Academic Research Consortium (VARC)-2 stated that other anatomical and biological indices, which are not captured by classical preoperative risk models, are needed for risk and outcome assessments of patients undergoing TAVR.8)

Frailty tests were routinely used in pivotal TAVR randomized clinical trials for risk assessment. In addition, single-center studies have associated frailty with increased morbidity and mortality after TAVR.9,10) However, the heterogeneity of frailty definitions and the use of variable cutoffs and scales limits the use of these tools.11,12) This lack of consensus on frailty assessment tools is the major reason why frailty is often not evaluated in clinical practice.13)

Serum albumin is one of the key components of frailty.14) Moreover, albumin level is a simple marker that is easy to quantify and is not subject to inter or intraobserver bias. The serum albumin level is a tool that is proven useful for predicting prognoses in patients with several differential subsets of cardiovascular diseases.16,18) It remains unclear whether serum albumin influences out-
comes in patients who undergoing TAVR. Current data on the impact of serum albumin on TAVR outcomes are conflicting and unclear. Therefore the present meta-analysis aims to investigate serum albumin’s impact on short-term outcomes and follow-up survival after TAVR.

Methods

Search strategy: A systematic review of published literature was performed according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. Each author independently conducted a systematic search of MEDLINE, EMBASE, and the Cochrane databases from their inception to July 20, 2019, using the following key words: “TAVR” OR “transcatheter aortic valve implantation” OR “percutaneous aortic valve” AND “albumin” OR “hypoalbuminemia.” Initial searches were restricted to English language publications and studies conducted in humans. A secondary search, with no language restriction, identified no additional relevant articles. Reference lists of articles identified for inclusion in the meta-analysis were examined to identify additional potentially relevant studies.

Study selection: Two reviewers independently screened all possible articles for inclusion at the title and/or abstract level, with the disagreement resolved by consensus. Studies were considered for inclusion if they fulfilled the following criteria: (1) prospective or retrospective studies assessing the association between pre-procedural serum albumin levels and risk for all-cause mortality in patients undergoing TAVR; (2) primary outcome (all-cause mortality at 30 days and one year after TAVR) was reported based at pre-procedural serum albumin levels (reported as categorical); and (3) the follow-up period was no less than one month. Studies were excluded if any of the following criteria were applied: (1) duplicate of publication/overlap of patients; (2) conference abstracts, case reports, reviews, and editorials; (3) the outcome of interest (all-cause mortality) was not clearly reported or was impossible to extract or calculate from the published results; and (4) serum albumin levels were reported as a continuous variable.

Data extraction and quality assessment: All data were extracted from article text, tables, figures, and supplementary materials. The following data were extracted from each study: study name, year of publication, setting, study design, valve type, number of participants, mean age, study duration, effect estimates, and CIs or standard errors (or information required to compute these results).

Each study’s quality was assessed independently by two investigators (GL and X-H) using the Newcastle-Ottawa Scale (NOS). The NOS consists of three quality parameters: selection, comparability, and outcome. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for exposure or outcome. Therefore, a score ≥ 7 points indicates high quality, and a score < 7 points indicates low quality. Any discrepancies were resolved by consensus.

Data synthesis and analysis: Our meta-analysis and statistical analyses were performed by Stata 12.0 (StataCorp LP, College Station, Texas). A P value of < 0.05 was considered statistically significant unless otherwise specified. Publication bias was assessed using funnel plots and Duval-Tweedie’s trim-and-fill test. Heterogeneity was measured using the Cochran Q and I² statistic: for the Q statistic, a P value of < 0.1 was considered statistically significant for heterogeneity, and for I², a value of > 50% was considered significant for heterogeneity. The primary measurement was the pooled hazard ratios (HRs) of mortality from individual studies, calculated using a random-effects model (DerSimonian and Laird method), which accounts for heterogeneity among studies.

To identify the possible source of heterogeneity within these studies, a priori subgroup analysis was performed. Subgroup analyses were conducted by comparing the summary results of studies, grouped by study design, cut-off value of albumin, STS score, and study quality. Tests for interactions, using summary estimates, were performed using the method described by Altman and Bland. We performed a one-way sensitivity analysis to test the robustness of the results. The scope of this analysis was to evaluate the influence of individual studies by estimating the average HR in the absence of each study. The present work was performed in line with the guidelines proposed by the Meta-analysis Of Observational Studies in Epidemiology group.

Results

Results of the literature search: We retrieved 127 citations from database searches. After title and abstract screening, 106 citations were found to be irrelevant to this meta-analysis and excluded. After detailed evaluation of the remaining 21 full-text articles, 11 were excluded for the reasons described in Figure 1. Finally, a total 10 eligible studies with 8,236 patents were included.

Study characteristics: The baseline characteristics of the included studies and populations are listed in Table I. Among the included studies, most (9 studies) were retrospective in design. All studies included in the analysis were published within the last five years. The mean age of the enrolled patients was 83 years, and 48.8% of the patients were male. In most of the included studies, the patient population was divided into two groups, based on pre-TAVR serum albumin levels, using a cut-off value of 3.5 g/dL. Generally, the patients were at intermediate or high surgical risk based on the values of STS-PROM score. Based on the NOS, seven studies were of high quality and three were of low quality (Table II).

The impact of albumin on mortality in patients undergoing TAVR: The 30-day all-cause mortality was reported in six studies, and the one-year, all-cause mortality was reported in all the studies, except Gassa, et al. (reported 30-day mortality only). As shown in Figure 2, a low pre-procedural albumin level was significantly associated with an approximately two-fold increase in 30-day all-cause mortality (HR, 2.09; 95% CI, 1.53-2.86) in patients undergoing TAVR. There was no heterogeneity for the outcome (I² = 2.5%, P = 0.40). Sensitivity analyses found the result to be robust (Figure 3A).

In addition, the pooled analysis of nine unique stud-
Figure 1. Flow diagram of study selection according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.

I n t H e a r t J
January 2020 69

IMPACT OF SERUM ALBUMIN ON TAVR

Studies showed that a low albumin level was associated with a 61% increased risk for one-year mortality (HR, 1.61; 95% CI, 1.31-1.98, Figure 2), and significant heterogeneity was detected for this outcome ($I^2 = 63.6\%, P < 0.05$). Sensitivity analysis showed that the HRs for one-year mortality were similar without great fluctuation, ranging from 1.48 (95% CI 1.23 to 1.77) to 1.71 (95% CI 1.38 to 2.12) by the omission of the studies by Chauhan, et al. and Steinvil, et al. (Figure 3B). Subgroup analysis showed that the association of low albumin level with an increase in one-year mortality risk was not modified by study design, albumin cut-off value, STS score, and study quality (Table III).

Assessment of bias: Publication bias in the primary out-
| First author             | Year | Region(s) | Study design                               | Study Period | Valve Type    | Transfemoral, n (%) | Total, No. | Follow-up, m | Mean age, years | Men, % | albumin cut off value, g/dL | STS PROM (Mean) | EuroSCORE, (Mean) |
|-------------------------|------|-----------|--------------------------------------------|--------------|---------------|---------------------|-------------|---------------|------------------|--------|-----------------------------|----------------|------------------|
| Koilman, et al.         | 2015 | USA       | Retrospective review of data records       | 2007-2014    | ES/MC         | 355 (74.6)          | 476         | 12            | 83.5             | 72.9   | 3.5                         | 9.7             | NA               |
| Green, et al.           | 2015 | USA       | Retrospective review of multicenter randomized trial | 2007-2009    | ES (100%)     | 119 (48.8)          | 244         | 12            | 86.2             | 52     | 3.5                         | 10.9            | NA               |
| Bogdan, et al.          | 2016 | Israel    | Retrospective review of data records       | 2009-2019    | ES (31%) / MC (69%) | 150 (100%)       | 150         | 25.2          | 81               | 40     | 4                           | 5.5             | 17.1             |
| Hermiller, et al.       | 2016 | International | Retrospective review of multicenter randomized trial | 2011-2012    | MC (100%)     | NA                  | 3687        | 12            | 83.3             | 53.7   | 3.5                         | 8.9             | 22.2             |
| Chauhan, et al.         | 2016 | USA       | Retrospective review of data records       | 2012-2015    | ES/MC         | 236 (69%)          | 342         | 12            | 81.9             | 48     | 3.5                         | 7.7             | NA               |
| Yamamoto, et al.        | 2017 | Japan     | Retrospective review of multicenter registry | 2013-2016    | ES (92.3%) / MC (7.7%) | 969 (79.8)     | 1215        | 12            | 84.4             | 30     | 3.5                         | 6.8             | 12               |
| Grossman, et al.        | 2017 | Israel    | Retrospective review of single-center registry | 2008-2014    | ES/MC         | 303 (71.1)         | 426         | 12            | 85.2             | 43.2   | 4                           | 5.6             | 19.1             |
| Steinvi, et al.         | 2018 | USA       | Retrospective review of data records       | 2011-2016    | ES/MC         | NA                 | 498         | 12            | 82               | 49     | 3.5                         | 7.5             | NA               |
| van Mourik, et al.      | 2018 | The Netherlands | Prospective single-center registry     | 2012-2017    | ES/MC         | 557 (75.2)         | 741         | 12            | 81.9             | 44     | 4                           | 5.5             | NA               |
| Gassa, et al.           | 2018 | Germany   | Retrospective review of data records       | 2014-2015    | NA            | 372 (81.4%)        | 457         | 1             | 80.8             | 50.4   | 3.5                         | 5               | 12               |

ES indicates Edwards SAPIEN valve; MC, Medtronic coreValve; and NA, not available.
Figure 4A, B), which showed some asymmetry. We used a category-free net reclassification index (NRI) analysis was performed on the trim-and-fill test for further analysis and found no significant difference, with or without adjustment, for 30-day mortality (adjusted HR, 1.89 [95% CI, 1.33-2.69] [P < 0.001]; HR, 2.09, 95% CI, 1.53-2.80, Figure 4C) and 1-year mortality (adjusted HR, 1.28 [95% CI, 1.15-1.42] [P < 0.001]; 1.61; 95% CI, 1.31-1.98, Figure 4D), thereby ruling out large publication bias effects.

**Discussion**

The recently VARC-2 highlights the importance of additional risk factors, such as frailty, which the classical surgical risk scores do not evaluate, and also recommends serum albumin as a marker of biological reserve. However, the data regarding the prognostic value of albumin as a frailty marker is conflicting and unclear. In this meta-analysis of 10 observational studies, low pre-procedural serum albumin was associated with poor survival rates in patients undergoing TAVR.

The importance of frailty on post-TAVR outcomes is increasingly being recognized, and frailty status has been associated with poor outcomes after TAVR. Frailty is traditionally evaluated by a composite of four metrics: gait speed, dominant hand grip strength, serum albumin, and the Katz activities of daily living survey. However, its assessment incorporated different methods and physicians’ subjective assessments, which can have substantial variance according to method and observer interpretation. Moreover, some small, single-center studies have shown no impact of frailty on the survival of TAVR patients. Therefore, frailty is difficult to evaluate in daily practice, and a simplified method to detect frailty in patients after TAVR is needed and should integrate the comorbidity, disability, and vulnerability of the elderly.

Serum albumin, as an acute-phase reactant and the most abundant protein in plasma, is regulated by a variety of factors. Hypoalbuminemia is a marker of liver and renal dysfunction as well as subclinical systemic inflammation and endothelial dysfunction. Low serum albumin was previously shown to be associated with poor outcomes in several differential subsets of cardiovascular diseases. In addition, preoperative hypoalbuminemia is a recognized risk factor for perioperative mortality, infection and long-term mortality, for both cardiac and non-cardiac surgery. A previous pooled analysis reported that the causes of mortality after TAVR were widely variable, with both cardiac and non-cardiac origins. Albumin may be a biological parameter capable of expressing all these different etiologies and correlated with comorbidity, disability, and vulnerability - the three components recognized as a part of frailty.

Traditional risk assessment tools, such as the STS score and logistic EuroSCORE, are commonly used for mortality prediction after TAVR. These risk models are based on cohorts of patients who underwent surgery but are not specifically developed for patients who underwent TAVR. In this meta-analysis, most of the included studies adjusted the STS score and EuroSCORE, suggesting that low baseline albumin remained a strong independent mortality predictor. In the study by Grossman, et al., a category-free net reclassification index (NRI) analysis was performed on the trim-and-fill test for further analysis and found no significant difference, with or without adjustment, for 30-day mortality (adjusted HR, 1.89 [95% CI, 1.33-2.69] [P < 0.001]; HR, 2.09, 95% CI, 1.53-2.80, Figure 4C) and 1-year mortality (adjusted HR, 1.28 [95% CI, 1.15-1.42] [P < 0.001]; 1.61; 95% CI, 1.31-1.98, Figure 4D), thereby ruling out large publication bias effects.
Figure 2. Forest plot comparing the risk of 30-day (A) and one-year (B) all-cause mortality between patients with low and normal pre-procedural serum albumin groups. The diamond indicates the overall summary estimate for the analysis. The center of the diamond represents the point estimate, and the width represents the 95% confidence interval (CI). HR indicates the hazard ratio.

used to compare the ability of a model of STS or EuroSCORE-2 alone to classify mortality risk with and without the addition of baseline serum albumin. The NRI results showed that a significant percentage of individuals with low albumin levels, who would have been classified as being at relatively low risk according to risk scores alone, can be reclassified as being at higher risk when their albumin value is incorporated into the model. Moreover, 16% to 20% of participants who would have been classified as being at high risk of dying after TAVR when using only the STS score or the EuroSCORE-2 were correctly reclassified as being at lower risk when their albumin level was incorporated. Hebeler, et al. reported that the STS score alone was poorly predictive of
one-year mortality after TAVR, and albumin was the only frailty marker associated with higher mortality.44)

Hypoalbuminemia’s likely relation to mortality in the TAVR population may be explained by various reasons. Albumin is commonly correlated with more severe comorbidities, such as malignancy (sometimes occult), acute or chronic infective diseases, nutritional status, diabetes mellitus, and renal failure. Low serum albumin levels can lead to decreased colloid-osmotic pressure in plasma and, consequently, to a lower intravasal volume, resulting in a pre-renal acute kidney failure (AKI).45) At the same time, patients receive nephrotoxic contrast agents as part of the TAVR procedure, which supports peri-interventional AKI.45) In addition, patients with severe aortic stenosis often suffer from heart failure. Hypoalbuminemia can favor development of pulmonary edema or heart failure decompensation46) and has been reported to be an independent predictor of mortality in patients with acute or chronic heart failure.47,48)

In the future, a trial involving the pre-procedural administration of albumin to TAVR patients presenting hypoalbuminemia would be timely. In a recent, randomized trial of coronary bypass surgery, patients with hypoalbuminemia were administered 20% exogenous albumin before off-pump bypass surgery.49) The treatment was compared with placebo; the study found no difference in 30-day mortality and other clinical outcomes among groups, and pre-procedural substitution of albumin led to a decreased AKI rate. It is tempting to speculate that albumin substitution could remedy the difference in mortality risk between patients with low and normal preoperative serum albumin levels undergoing TAVR.

This systematic review and meta-analysis is the first to summarize the adverse impact of mortality associated with low albumin levels in patients after TAVR. Based on data from nearly 8,263 subjects, the results demonstrated that low albumin was significantly associated with an approximately two-fold increase in 30-day mortality and a 61% increased risk for one-year mortality. The study offers the heart team a simple, objective, and reproducible

Figure 3. Sensitivity analyses for all-cause mortality at 30 days (A) and one year (B).
biological marker of frailty assessment in patients referred for TAVR and suggests that serum albumin level might be used in addition to the classical surgical risk scores to complete the risk stratification of patients before TAVR.

Although our large meta-analysis provides some indications regarding albumin’s impact on TAVR outcomes, there are a few limitations to our analysis. First, this study was a meta-analysis performed on study-level data, and it lacked individual patient-level data. Most of the included studies were retrospective, and possible variables that were not adjusted may have influenced the results. Second, there was non-uniformity of valve types and ap-
proaches used among the included studies; these unmeasured factors may bias the results. Third, although the random-effects pooling method adjusts for heterogeneity, another limitation of this meta-analysis was the significant heterogeneity observed among studies. Thus, overall pooling should be viewed with caution and as hypothesis generating.

In conclusion, this meta-analysis provides the first summary of the effects of serum albumin on mortality and confirms that low serum albumin levels are significantly correlated with short-and mid-term all-cause mortality after TAVR. We suggest that baseline serum albumin could be a useful marker for risk stratification before TAVR.

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Disclosure

Conflicts of interest: None.

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