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Systematic Review

Serum albumin in patients undergoing transcatheter aortic valve replacement: A meta-analysis

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Transcatheter aortic valve replacement is becoming a more common therapeutic option for the treatment of aortic stenosis in patients at high risk for invasive surgery, but detecting which patients will benefit clinically can be challenging. Hypoalbuminemia is a useful prognostic marker for chronic inflammation in this population. We carried out a systematic review and meta-analysis of studies evaluating the prognostic value of serum albumin level in patients undergoing transcatheter aortic valve replacement. A literature search of PubMed, Embase, ScienceDirect, Web of Science, SciELO, BIOSIS, Wanfang, and CNKI databases was conducted. Articles published between January 2000 and December 2017 reporting on the prognostic value of low levels of serum albumin in patients undergoing transcatheter aortic valve replacement were analyzed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. 11 studies including 6456 patients met inclusion criteria for meta-analysis. A lower serum albumin level was associated with a lower survival rate at follow-up in patients who underwent transcatheter aortic valve replacement. A subgroup analysis of eight studies reporting adjusted hazard ratios indicated that low serum albumin was independently correlated with increased post-operative mortality. The hazard ratio of mortality risk associated with each 1 g/dL increment in serum albumin level was 0.46, suggesting a potential dose–response relationship between increased serum albumin level and increased survival rate in patients undergoing transcatheter aortic valve replacement. This meta-analysis provides strong evidence for the utility of serum albumin as a prognostic marker in aortic stenosis patients undergoing transcatheter aortic valve replacement, with low serum albumin levels (2.5-3.5 g/dL) suggesting poor prognosis.

Keywords

Albumin; transcatheter aortic valve replacement; mortality; meta-analysis

1. Introduction

Aortic stenosis (AS) is widespread, affecting approximately 3% of people aged over 75 years, its prevalence increasing with age (Joseph et al., 2017). AS is associated with a high mortality risk without aortic valve replacement (AVR), which has traditionally been performed via open surgery (Vahanian and Otto, 2010). Transcatheter AVR (TAVR) is a less invasive procedure that is increasingly being used to treat AS (Joseph et al., 2017). However, recent real world study estimates one-year mortality following AVR to be around 20% for intermediate to high risk patients (Brennan et al., 2017). To improve outcomes, accurate prognostication and early intensive management of high-risk patients is important (Vahanian and Otto, 2010). However, current risk assessment methods, (e.g., The Society for Thoracic Surgery Predictive Risk of Mortality (STS PROM) (O'Brien et al., 2009) or the Logistic European System for Cardiac Operative Risk Evaluation (Logistic EuroSCORE) (O'Brien et al., 2009), which are designed to predict surgical mortality for symptomatic AS patients planning to undergo AVR), have limitations tied to their weighting of chronological age and medical diagnoses without a comprehensive evaluation of the biological status of an elderly patients (McNallan et al., 2013; Von Haehling et al., 2013). Moreover, such risk models are tailored towards surgery rather than to TAVR, the latter commonly carried out in elderly patients with cardiovascular disease suffering from frailty (McNallan et al., 2013; Von Haehling

et al., 2013).

An ideal approach to risk stratification is to identify a priori the factors related to a lower survival rate, thereby allowing clinicians to select the optimal treatment protocol (Bhattacharyya et al., 2012; Vahanian and Otto, 2010). Few novel and definitive risk factors in AS have emerged in recent literature (Afilalo et al., 2014). Notably, however, there is some evidence suggesting that serum albumin concentrations of less than 3.5 g/dL represent a novel risk factor indicating frailty and poor prognosis in these patients (Kappetein et al., 2012).

Serum albumin, synthesised by the liver, is the most abundant serum protein in humans (Levitt and Levitt, 2016). Normal serum albumin is in the range of 3.5 to 5.0 g/dL, and hypoalbuminemia is usually defined as less than 3.5 g/dL (Artigas et al., 2016). Serum albumin level is a relevant prognostic factor in critically and seriously ill patients (Artigas et al., 2016; Levitt and Levitt, 2016). It is an important predictor of mortality in cardiovascular diseases (Findik et al., 2016; Grodin et al., 2016; Plakht et al., 2017), and elderly patients with AS often display hypoalbuminemia associated with malnutrition and chronic inflammation (Bogdan et al., 2016; Koifman et al., 2015; Yamamoto et al., 2017). Studies have been undertaken to assess whether there is any association between serum albumin levels and prognosis in AS patients undergoing TAVR, but results to date have been conflicting (Bogdan et al., 2016; Green et al., 2015, 2012; Koifman et al., 2015; Yamamoto et al., 2017). We therefore conducted a meta-analysis to evaluate the prognostic value of preoperative serum albumin levels in patients undergoing TAVR.

2. Methods

2.1 Search strategy

The meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) (Fig. 1). PubMed, Embase, ScienceDirect, Web of Science, SciELO, BIOSIS, Wanfang, and CNKI databases were analysed to detect studies that considered the prognostic value of serum albumin in patients undergoing TAVR. The final literature search was carried out on December 31, 2017. When data

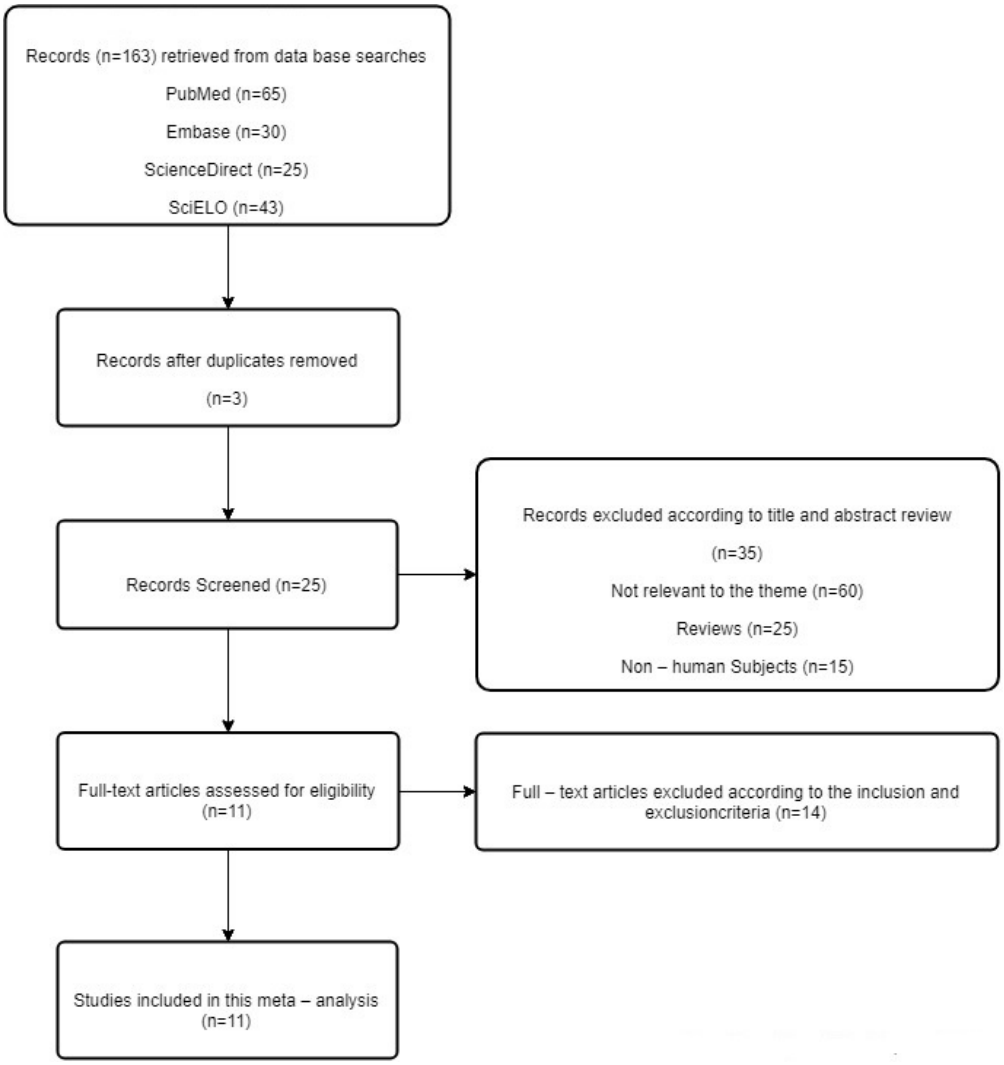

Figure 1. A flow chart represents the process whereby studies were assessed for eligibility against the inclusion and exclusion criteria set out in the methods section of this article. The number of studies is the bottom of the flowchart represents that of the selected studies that were ultimately considered eligible for inclusion in this meta-analysis.

were referenced in multiple publications from the same research group, the most recent study or that including the greatest number of patients was considered in the analysis. The reference lists of relevant articles were cross-matched with the search results. The primary endpoint was all-cause mortality rate after TAVI, either reported in the short ($\leq$ 30 days) or long term ($>$ 30 days), while the secondary outcomes were stroke, myocardial infarction, vascular complications, bleeding, pacemaker implantation, revision surgery and endocarditis. Cause of death was categorised as either cardiovascular and non-cardiovascular mortality. Serum albumin was sought as a secondary outcome.

2.2 Selection criteria

The inclusion criteria were: (a) prospective cohort or retrospective cohort studies; (b) patients diagnosed with AS and treated with TAVR; (c) preoperative serum or plasma albumin concentrations measured and analysed for associations with prognosis; and (d) risk estimates of the prognostic role of albumin, such as hazard ratio (HR) or relative risk (RR) with 95% confidence intervals (CIs), reported. The exclusion criteria were: (a) studies not meeting all the inclusion criteria; (b) letters, reviews, or case reports; and (c) studies on cells or experimental animals. In the case of multiple studies with overlapping data, only the study with the greatest sample size was included.

2.3 Data extraction and quality assessment

Two authors independently extracted data from each included study, and any disagreements between the two were settled by discussion. If HRs from univariate and multivariate analyses were provided, only those from the latter were used. Study quality was evaluated using the Newcastle-Ottawa scale, which assigns studies scores ranging from 0 to 9 points (Stang, 2010). Scores of 7 or more indicated high study quality, while those of 6 or less indicated low quality (Stang, 2010).

2.4 Statistical analysis

To assess the prognostic value of albumin concentration in TAVR patients, study-specific HRs with 95% CIs were pooled; given the probability of increased inter-observation variance, a random-effect meta-analysis (DerSimonian-Laird method) was applied (DerSimonian and Laird, 1986). A pooled HR of greater than 1 suggested worse prognosis in patients with low serum albumin concentrations. Inter-study heterogeneity was assessed via Cochran's Q test and the results complemented the I^2 method (Higgins et al., 2002). $I^2 > 50\%$ suggested a high degree of inter-study heterogeneity (Grant and Hunter, 2006). Effect modifiers or confounders were also assessed via meta-regression. Publication bias was assessed using funnel plots, the Begg test, and the Egger test (DerSimonian and Laird, 1986). Data analyses were carried out in STATA (Stata Corporation, College Station, TX, USA). Statistical tests were two-sided, and P values lower than 0.05 were deemed statistically significant.

3. Results

3.1 Literature search and included studies

160 articles were considered relevant in the literature review. Further to assessing titles and abstracts, 135 obviously irrelevant studies were discarded. The remaining 25 studies were assessed in detail. After full text review, 14 studies not meeting inclusion criteria were discarded. As such, 11 studies were finally considered in the meta-analysis (Fig. 1) (Bogdan et al., 2016; Chauhan et al., 2016; Goldfarb et al., 2017; Green et al., 2015, 2012; Grossman et al., 2017; Hermiller et al., 2016; Koifman et al., 2015; Osnabrugge et al., 2015; Rodríguez-Pascual et al., 2016; Yamamoto et al., 2017).

The main features of these studies are shown in Table 1. In total, data pertaining to 6456 TAVR patients, who both underwent TAVR and whose serum albumin was measured prior to surgery, were available for analysis. Of the eleven studies, five were prospective cohort studies, and the other six were retrospective cohort studies from USA, Spain, Japan and Israel. Articles were published between 2000 and 2017. These articles reported on risk estimates of the prognostic value of low albumin concentration in AS patients, risk estimates of the mortality associated with each 1 g/dL increase in albumin concentration, and risk estimates. The average patient age was 70-86 years, and 29-83% of patients were male. Malnutrition and wasting were evaluated via serum albumin on the day prior to TAVR in all studies.

3.2 Definition of serum albumin

Different cut-off concentrations of serum albumin were employed in different studies. It was defined as $<$ 3.5 g/dL (in accordance with the recently updated Valve Academic Research Consortium (VARC)) in five of the studies (Chauhan et al., 2016; Goldfarb et al., 2017; Green et al., 2015; Koifman et al., 2015; Yamamoto et al., 2017), 3.3 g/dL in three studies (Hermiller et al., 2016; Osnabrugge et al., 2015; Rodríguez-Pascual et al., 2016), and 4 g/dL in one study (3). With the exception of four studies (Green et al., 2012; Goldfarb et al., 2017; Koifman et al., 2015; Rodríguez-Pascual et al., 2016), serum albumin data were available as a dichotomised variable as compared to outcomes.

3.3 Preoperative serum albumin and mortality

Results from primary pooled statistics (n = 5341 patients) showed that a low serum albumin level was associated with a significantly increased risk of early ($\leq$ 30 days) death following TAVR (HR = 1.16, 95% CI: 1.05-1.29, P = 0.005; Table 2, Fig. 2). No significant heterogeneity was observed among these studies (I^2 = 0%; Chi^2: 1.48; Cochrane Q, P = 0.96). Ten studies (n = 6212 patients) quantified the relationship between serum albumin level and late mortality ($>$ 30 days) following TAVR (HR = 1.10, 95% CI: 1.04-1.17, P = 0.002; Table 2, Fig. 3). No heterogeneity was observed among these studies (I^2 = 0%; Chi^2: 6.48; Cochrane Q, P = 0.69). After excluding low-quality studies, low serum albumin was still associated with increased mortality risk (HR = 1.09, 95% CI: 1.03-1.16; P = 0.003; Table 2, Fig. 7).

Only five studies (n = 1405) reported univariate adjusted HRs, where low serum albumin was associated with a significantly increased risk of $>$ 30-day mortality in patients with TAVR (HR = 1.18, 95% CI: 1.04-1.34, P = 0.01; Table 2, Fig. 4). No heterogeneity was observed among these studies (I^2 = 0%; 95% Chi^2: 0.91; Cochrane Q, P = 0.92). Eight studies (n = 5677) reported univariate adjusted HRs, which yielded a marginal reduction in the risk of death amongst patients with low serum albumin level amongst patients with TAVR (HR = 1.08, 95% CI: 1.02-1.15, P = 0.01; Table 2, Fig. 5). No heterogeneity was observed among these studies (I^2 = 0%; 95% Chi^2: 4.32; Cochrane Q, P = 0.74).

There was no heterogeneity among the four studies reporting

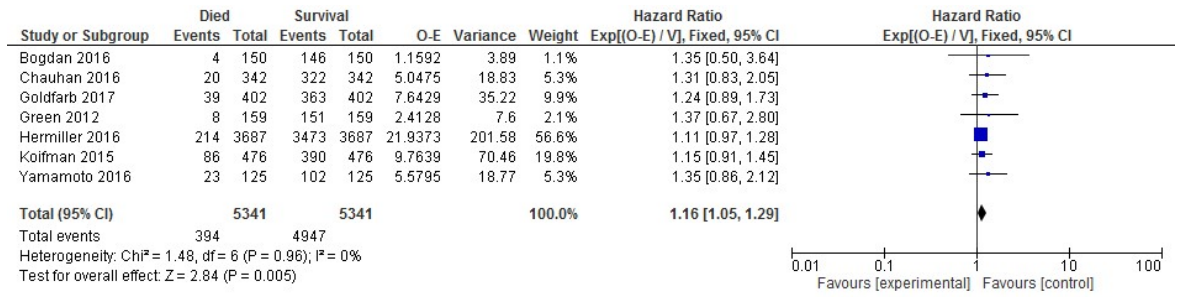

Figure 2. A forest plot represents the statistical effect of low serum albumin concentration on the risk of mortality at 30 days follow-up, including overall, univariate and multivariate evaluations.

risk estimates of mortality associated with each 1 g/dL increment in albumin concentration (I^2 = 0%). The HR of the mortality risk associated with each 1 g/dL increment in serum albumin level was 1.14 (95% CI: 1.01-1.29; *P* = 0.04), suggesting a potential dose-response relationship between increased serum albumin level and decreased risk of mortality in patients undergoing TAVR (Fig. 5). After excluding low-quality studies, the HR of mortality risk associated with each 1 g/dL increment in serum albumin was 1.09 (95% CI: 1.03-1.16; *P* = 0.003; Table 2, Fig. 7).

3.4 Publication bias

There was a possible risk of publication bias among the studies reporting risk estimates of the prognostic value of low serum albumin concentrations in AS patients (Fig. 4), with Egger and Begg *P* values of 0.04 and 1.00, respectively. There was no risk of publication bias among the studies reporting risk estimates of mortality associated with each 1 g/dL increment in albumin concentration, with Egger and Begg *P* values of 0.58 and 0.84, respectively (Fig. 8).

Table 1. Characteristics of the 11 studies included in the meta-analysis.

Author, year	Country	Study design	n*	Mean age (years)	Male gender (%)	Follow-up (months)	Confounding factors	Quality
Rodríguez-Pascual et al. (2016)	Spain	Prospective cohort	109	83	42.2	24.5	None	5
Chauhan et al. (2016)	USA	Retrospective cohort	342	81.8	47.7	14.9	Frailty score, gait speed, hand grip strength, Katz index of independence in activities of daily living, and other baseline characteristics	8
Yamamoto et al. (2017)	Japan	Prospective cohort	1215	84.4	29.7	12	acute coronary obstruction, disabling stroke, acute kidney injury, vascular complications, red blood cell transfusion, etc.	8
Hermiller et al. (2016)	USA	Retrospective cohort	3687	83.3	53.7	12	Assisted living, home oxygen, wheelchair bound, Katz index of independence in activities of daily living, grade III/IV left ventricular diastolic dysfunction, gait speed,	9
Bogdan et al. (2016)	Israel	Retrospective cohort	150	81	39	25	Multivariate analysis	7
Green et al. (2015)	USA	Prospective cohort	244	86	51	12	None	5
Koifman et al. (2015)	USA	Retrospective cohort	476	84	83	12	Age, gender, African American race, serum albumin, chronic lung disease, ejection fraction < 40%, aortic valve area, etc.	7
Osnabrugge et al. (2015)	USA	Retrospective cohort	471	84	49.1	12	Multivariate analysis	7
Kappetein et al. (2012)	USA	Prospective cohort	159	86	50	12	Multivariate analysis	7
Goldfarb et al. (2017)	Canada	Prospective Cohort	489	70	Nil	12	Age, sex, BMI, cirrhosis, ejection fraction, disability, frailty.	7
Grossman et al. (2017)	Israel	Retrospective study	426	83.8	45	12	EuroSCORE-2, VARC2	7

Table 2. Association Reported within included studies.

Author, year	Outcome (mortality)	Association	Serum Albumin	Univariate				Multivariate			
				Effect Estimate (HR)	95% CI £		*P*-value	Effect Estimate (HR)	95% CI		*P*-value
					Lower	Upper			Lower	Upper	
Rodríguez-Pascual et al. (2016)	98-weeky	All- cause mortality	Per 0.1 g/dL decrease < 3.3g /dl	0.5	0.38	0.66	< 0.004	-	-	-	-
Chauhan et al. (2016)	1-year	All- cause mortality	< 3.5 g/dl	-	-	-	-	3.12	1.8	5.42	< 0.001
Yamamoto et al. (2017)	1-year	All- cause mortality	< 3.5 g/dl	-	-	-	-	1.89	1.21	2.96	0.005
Hermiller et al. (2016)	30-day	All-cause mortality	< 3.3 g/dl	-	-	-	-	1.6	1.04	2.47	0.03
	1-year			-	-	-	-	1.4	1.04	1.91	0.03
Bogdan et al. (2016)	1-year	Low baseline albumin with All-cause mortality	3.67 ± 0.29 or ≤ 4 g/dl	4.56	1.54	13.48	0.01	4.64	1.51	13.21	0.01
	2-year			-	-	-	-	2.02	1.04	3.91	0.01
Green et al. (2015)	1-year	All-cause mortality	Per 0.1 g/dL decrease < 3.5 g/dl	1.25	0.88	1.78	0.21	-	-	-	-
Koifman et al. (2015)	1 year	All-cause mortality	Per 0.1 g/dL decrease < 3.5 g/dl	1.75	2.56	1.2	0.004	1.64	2.5	1.75	0.02
Osnabrugge et al. (2015)	6-month	All-cause mortality	< 3.3 g/dl	-	-	-	-	1.8	0.91	3.5	0.073
Kappetein et al. (2012)	348 days or more	Quartiles of albumin associated with increased mortality	3.8 g/dl*	-	-	-	-	1.51	1.03	2.21	0.03
Kappetein et al. (2012)	1 year	All-cause mortality	Per 0.1 g/dL decrease < 3.5 g/dl	-	-	-	-	0.53	0.4	0.82	0.005
Grossman et al. (2017)	1 year	All-cause mortality	4 g/dl	3.03	1.66	5.26	0.001	-	-	-	-

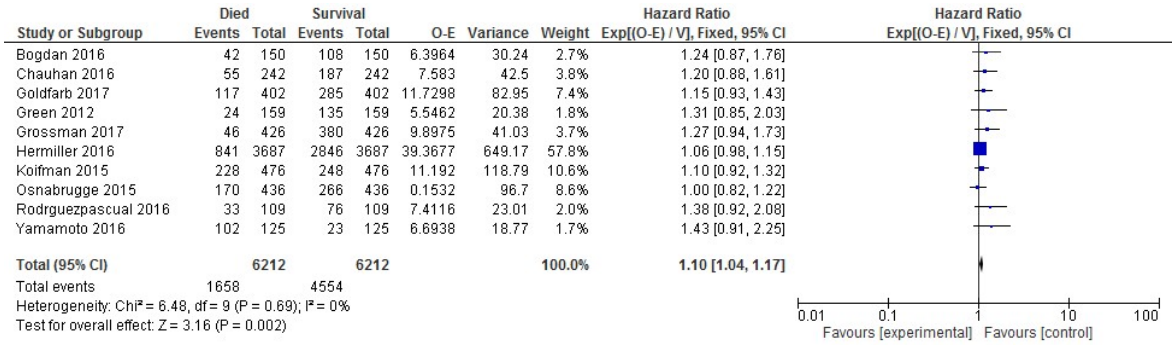

Figure 3. A forest plot represents the statistical effect of low serum albumin concentration on the risk of mortality quantified at a follow-up time greater than 30 days, including overall, univariate and multivariate evaluations.

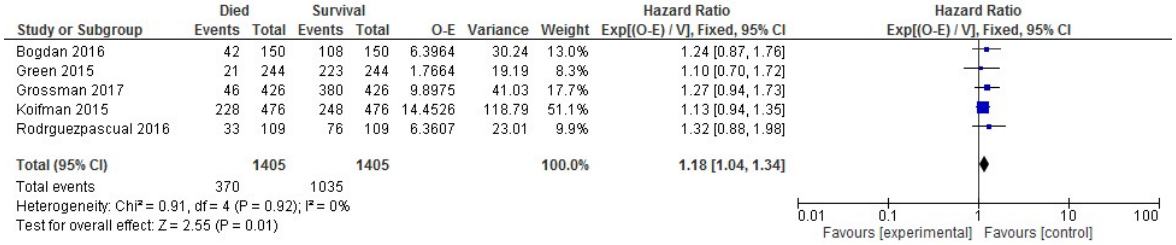

Figure 4. A forest plot represents the statistical effect of low serum albumin concentration on the risk of mortality quantified at a follow-up time greater than 30 days, following evaluation via a univariate Cox regression model.

4. Discussion

This meta-analysis of studies examining the prognostic importance of serum albumin levels in AS patients undergoing TAVR shows that a low preoperative serum albumin level is a significant predictor of post-procedural mortality. This indicates that measuring serum albumin levels prior to TAVR along with other preoperative factors may help to stratify patients. Meta-analysis of adjusted HRs indicated that low serum albumin was independently associated with increased mortality risk during follow-up. Furthermore, the HR of mortality risk associated with each 1 g/dL increment in serum albumin level was 0.46 ($P < 0.0001$), indicating a potential dose-response relationship between increased serum albumin level and decreased mortality risk. This meta-analysis provides the strongest evidence to date supporting the utility of serum albumin as a prognostic biomarker in patients undergoing TAVR, with low serum albumin levels indicating a poor prognosis.

Serum albumin levels are indicators of the severity of malnutrition and inflammation in many disease states. For instance, hypoalbuminemia significantly leads to poor prognosis in cancer, chronic kidney disease and sepsis (Cabrerizo et al., 2015). Several studies have assessed the prognostic role of serum albumin in cardiovascular diseases (Kurtul et al., 2016; Plakht et al., 2017; Su et al., 2012). In Plakht et al. (2017), low serum albumin concentration was significantly associated with long-term all-cause mortality after acute myocardial infarction (Plakht et al., 2017); Kurtul et al. (2016) found that serum albumin concentration was inversely associated with mortality risk in acute coronary syndrome patients (Kurtul et al., 2016); and Su et al. (2012) showed that serum albumin was a significant prognostic factor in patients with heart failure (Su et al., 2012). The findings from the present meta-analysis consolidate the notion that serum albumin is a useful prognostic biomarker in patients undergoing TAVR, thereby further supporting the evidence of its prognostic role in cardiovascular diseases. Our findings show that decreased serum albumin levels in TAVR patients are related not only to deterioration in nutritional status that adversely affects myocardial recovery after correction of AS, but also to poor functional outcomes. Therefore, in acute care, a current focus is on restarting enteral nutrition immediately after extubation, with patient-specific nutrition.

Low serum albumin concentration implies a dysfunctional liver synthesis, which can be caused by heart failure, cirrhosis and malignancies, amongst other conditions. Albumin helps control serum electrolyte levels and confers antioxidant effects (Rothschild et al., 1988). Serum albumin provides a simple but objective clinical risk stratification in patients with severe AS assessed for TAVR to make appropriate decisions regarding treatment options for individual patients.

5. Limitations

Differences in study design, sampling method, inclusion criteria and patient characteristics, and adjusted confounding factors, could result in a high degree of heterogeneity between studies. Furthermore, some studies were retrospective cohort studies, where biases are more likely than in prospective study. More prospective studies with larger sample sizes are needed to provide further evidence of the utility of serum albumin level as a prognostic biomarker in patients undergoing TAVR. A third limitation was that in some studies, the follow-up duration was less than one year, so the long-term prognostic role of serum albumin in AS patients needs further study. The number of included studies, especially in the subgroup analyses, was limited. In addition, the systematic review protocol was not registered in PROSPERO (the international

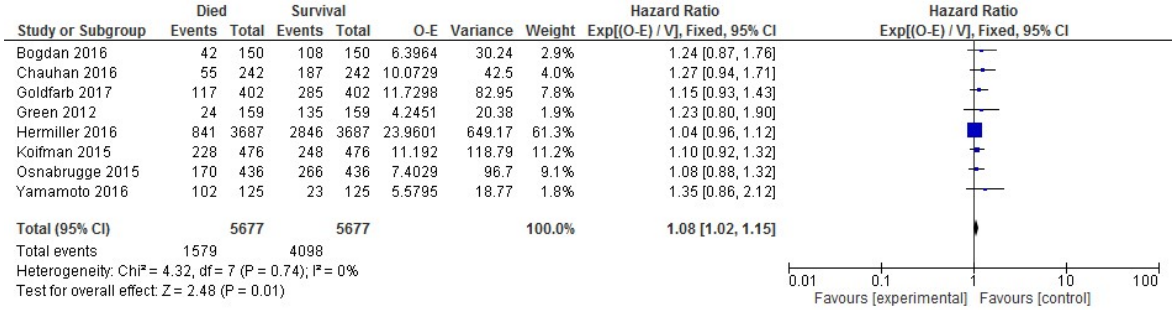

Figure 5. A forest plot represents the statistical effect of low serum albumin concentration on the risk of mortality, following evaluation via a multivariate Cox regression model.

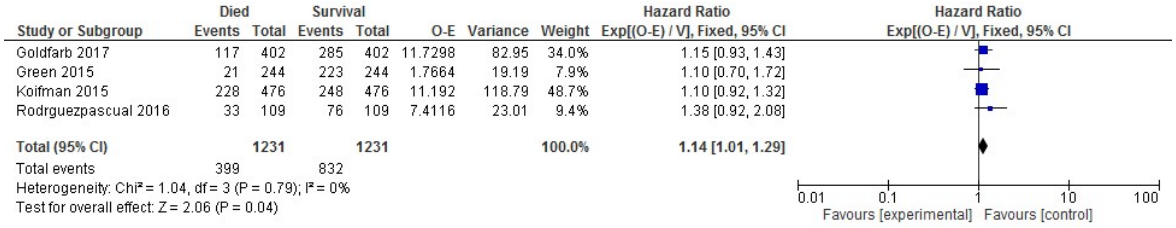

Figure 6. A forest plot represents the statistical effect of categorical serum albumin concentration on the overall risk of mortality, following appropriate statistical evaluation.

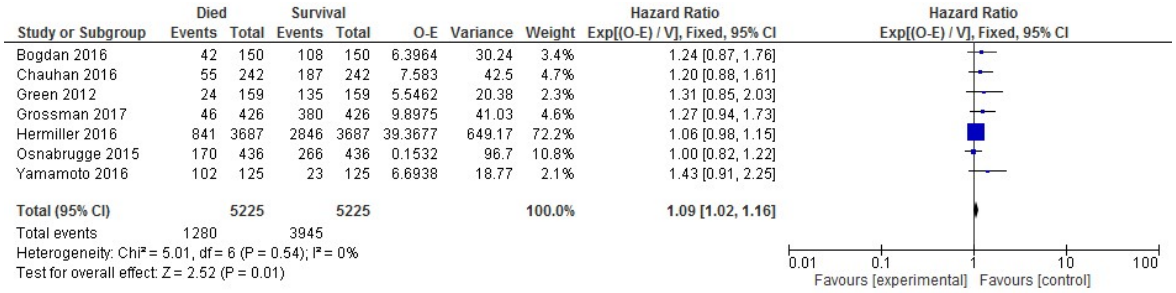

Figure 7. A forest plot represents the statistical effect of continuous serum albumin concentration on the overall risk of mortality, following appropriate statistical evaluation.

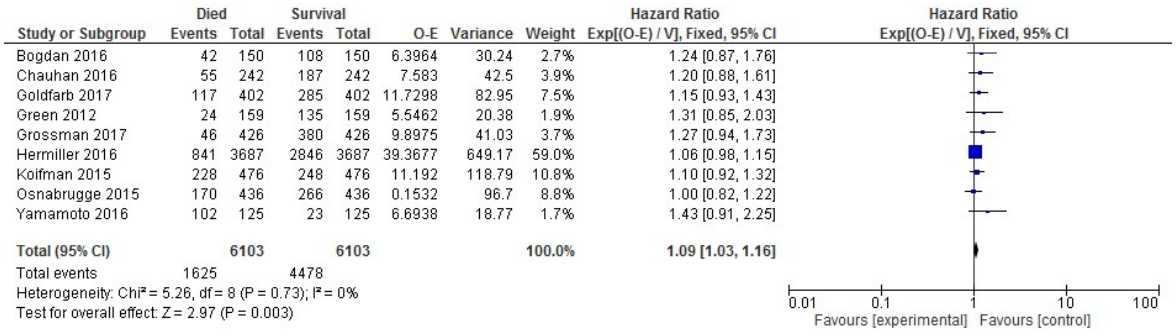

Figure 8. A forest plot represents the statistical effect of serum albumin concentration on the overall risk of mortality, following appropriate statistical evaluation, excluding studies whose quality was deemed low.

prospective register of systematic reviews), and it may have benefited from such a preliminary peer-review process.

In conclusion, this meta-analysis strongly supports the utility of serum albumin as a prognostic biomarker in AS patients undergoing TAVR, with a low serum albumin level (2.5-3.5 g/dL) suggesting a poorer prognosis. Serum albumin is a convenient and economical prognostic factor, which can be easily monitored for risk stratification in AS patients. More prospective studies with large sample sizes are needed to provide further evidence of the utility of serum albumin as a prognostic biomarker in patients un-

dergoing TAVR.

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Conflicts of interest

The authors declare no conflicts of interest.

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