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Malnutrition Predicts Adverse Outcomes After Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis

ABSTRACT

Background: Several studies have shown that malnutrition helps to predict the occurrence of adverse outcomes after transcatheter aortic valve replacement. However, there is still controversy and uncertainty regarding the prevalence and consequences of malnutrition. We performed a systematic review and meta-analysis to assess the relationship between malnutrition and poor postoperative outcomes in transcatheter aortic valve replacement.

Methods: Observational studies were searched in PubMed, EMBASE, Cochrane Library, Web of Science, and MEDLINE regarding the relationship between malnutrition and adverse outcomes after transcatheter aortic valve replacement, with the primary endpoint being all-cause mortality and secondary outcomes such as cardiovascular complications and readmission rates. This meta-analysis was registered in PROSPERO (number CRD42022310139).

Results: A total of 10 studies involving 5936 subjects were included in the systematic review and meta-analysis. The results showed that malnourished patients had an increased risk of all-cause mortality after transcatheter aortic valve replacement compared with non-malnourished patients (hazard ratios [HR] = 1.32, 95% CI [1.13, 1.53], $P < .01$). Subgroup analysis showed that in Asia, postoperative all-cause mortality was significantly higher in malnourished transcatheter aortic valve replacement patients than in non-malnourished transcatheter aortic valve replacement patients ($P < .01$), and in addition, sample size and follow-up time may have contributed to the large heterogeneity.

Conclusion: Malnutrition increases the risk of all-cause mortality in such patients and may predict the occurrence of adverse postoperative outcomes.

Keywords: Malnutrition, transcatheter aortic valve replacement, mortality

META-ANALYSIS

Mingqi Dong[1]
Jifang Cheng[2]
Li Gong[3]
Yajing Xiao[4]
Shengwen Shao[5]
Jianping Song[1]

[1]Department of Nursing, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou City, China
[2]Cardiac Intervention Center, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou City, China
[3]Department of Cardiology, Yuechi County People's Hospital, Sichuan Province, China
[4]School of Nursing, School of Medicine, Huzhou University, Huzhou City, China
[5]School of Medicine, Huzhou University, Huzhou City, China

Corresponding author:
Jianping Song
✉ zrxwk1@zju.edu.cn

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INTRODUCTION

Aortic stenosis (AS) is a progressively aggravating heart valve disease, and degenerative valve disease is becoming more common as the population ages.[1,2] In recent years, the advent of transcatheter aortic valve replacement (TAVR) has provided an effective treatment option for elderly patients who are unable to undergo surgical valve replacement, and as the number of TAVR procedures increases each year, the nutritional status of this group of patients has become an increasing concern.[3] Malnutrition is a common disease in elderly patients and it has been shown that malnutrition weakens the immune response of patients, stimulates T-cell energy deficiency, and produces a dysfunctional immune response that predisposes to infection and proteolytic metabolism, resulting in delayed wound healing.[4] In addition, patients with AS have a progressive decrease in ejection fraction, resulting in blood pooling in the body and pulmonary circulation, leading to slowed gastrointestinal motility and abnormal secretion of digestive enzymes, further exacerbating the state of malnutrition.[5] Several studies have shown that malnutrition is associated with increased short- and long-term mortality and that detailed nutritional assessment significantly predicts mortality 1 year after TAVR and helps prevent adverse postoperative outcomes.[6-8] However, there is uncertainty and controversy regarding the prevalence and consequences of malnutrition.

The value of malnutrition on prognosis has not been systematically assessed; therefore, this study retrospectively assessed the preoperative nutritional status of TAVR patients and determined the impact of malnutrition on postoperative mortality and clinical outcomes in TAVR to draw the attention of investigators and provide a basis for the treatment and nutritional management of TAVR patients.

METHODS

Systematic reviews and meta-analyses were performed according to the Preferred Reporting Items for Systematic and Meta-Analyses protocol and the meta-analysis checklist for epidemiological observational studies. The protocol was registered with the International Platform for Registration of Systematic Evaluation and Meta-Analysis Protocols (PROSPERO) on March 14, 2022 (registration number CRD42022310139), at https://www.crd.york.ac.uk/PROSPERO.

Literature Search

The search strategy was a computerized search of foreign language databases including PubMed, EMBASE, Cochrane Library, Web Science, and MEDLINE, using a combination of free words and subject terms, with English search terms: (transcatheter aortic valve replacement OR TAVR OR transcatheter aortic valve implantation OR TAVI) AND (Malnutrition OR Nutritional deficiency OR Nutritional deficiencies OR Undernutrition OR Malnourishment OR Nutritional Status OR Status Nutritional OR Nutrition Status OR Status Nutrition). Searches were conducted from the beginning of the database to February 2022, and results were limited to data from adult subjects without filtering for study design, language, or publication date; references to the acquired literature were queried to prevent omissions.

Eligibility Criteria

Inclusion criteria: (1) study type: a retrospective study, cohort study, or case-control study; (2) study population: patients receiving TAVR; (3) exposure factors: malnutrition diagnosed by assessment screening; (4) literature published in academic journals and with original data analysis, this study was conducted to ensure methodological rigor of the included literature, gray literature was not included; (5) these studies require a control group (no malnutrition) and report-adjusted hazard ratios (HR) (95% CI) for postoperative all-cause mortality between malnourished and non-malnourished populations; (6) written in English. Exclusion criteria: (1) incomplete data or lack of basic data even after contacting the authors; (2) repeated publications by the same authors or the same research group; and (3) conference papers, reviews, and case reports.

Study Selection and Data Extraction

After removing duplicates from all literature using EndNote software, 2 master's students trained in evidence-based nursing courses and with good English literature reading skills independently performed literature screening and data extraction; in case of disagreement, a third investigator intervened to negotiate the decision. The first initial screening was done by reading the titles and abstracts of the literature to exclude irrelevant literature, and then the full text was obtained for re-screening. The extracts were as follows: (1) study design information: first author's last name, year of publication, study type (retrospective or prospective), mean/median age, sex, body mass index (BMI), the Society of Thoracic Surgeons (STS) score, primary endpoint data, follow-up time, study area, sample size, the prevalence of malnutrition, and screening tools for malnutrition. (2) Study results and conclusions: results of studies reflecting all-cause mortality after malnutrition and TAVR, such as the risk ratio (HR) and its 95% CI.

Study Appraisal

The quality assessment was conducted independently by 2 investigators, with a third investigator intervening to negotiate the decision in case of disagreement. Cohort studies and case-control studies were evaluated using the Newcastle Ottawa Scale (NOS), which contains 3 aspects of study population selection, comparability between groups, and outcome measures, with 8 entries and a total score of 0-9. A score of ≥7 was considered high-quality literature.

Statistical Methods

The study was analyzed using Stata 14.0, and results are shown as mean ± standard error when normally distributed, otherwise, they are shown as median and interquartile range. Heterogeneity tests were analyzed using the Q test (test level $\alpha = 0.10$) and combined with I^2 to evaluate the magnitude of heterogeneity. If $P > .10$ and $I^2 \leq 50\%$, homogeneity between studies was indicated and a fixed-effects model was used for systematic evaluation; if $P \leq .10$ and $I^2 > 50\%$, heterogeneity between studies was indicated, and a random-effects model was selected for evaluation. Subgroup analysis was performed according to the basic characteristics of the included studies, and subgroup analysis was used to explore and reduce the sources of heterogeneity according to geography and malnutrition screening tools. Sensitivity analysis was used to evaluate the stability of the results. Begg's test and Egger's test were used to assess the potential publication bias of each literature, and differences were considered statistically significant at $P < .05$.

RESULTS

Study Selection

A total of 1887 articles were retrieved through a combination of free words and subject terms. A total of 10 articles were

HIGHLIGHTS

- Malnutrition predicts postoperative all-cause mortality in patients with transcatheter aortic valve replacement (TAVR).
- Nutritional status is part of risk stratification and is an actionable risk factor, and nutritional assessment can provide guidance for nutritional therapy and secondary prevention.
- Whether nutritional interventions can prevent the occurrence of adverse outcomes and delay disease progression after TAVR requires further study.

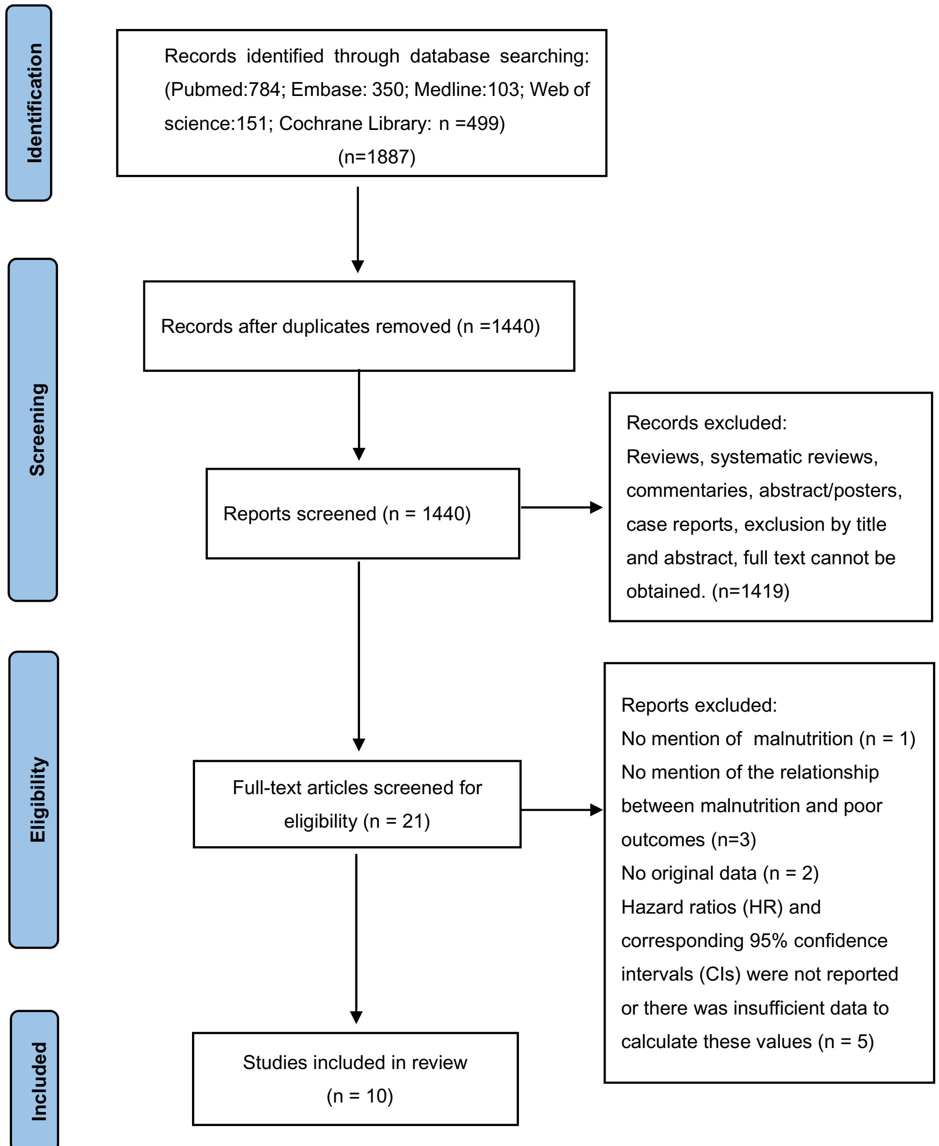

Figure 1. The flow diagram identifying the literature.

included according to the inclusion and exclusion criteria, as shown in (Figure 1).

Characteristics of the Studies Included in the Meta-analysis

A total of 10 studies published from 2018 to 2021[6,9-17] were included, see (Table 1), including 5936 TAVR patients with preoperative malnutrition prevalence of 27.3-65.3%, including 7 prospective cohorts[11-17] and 3 retrospective cohort studies.[6,10,15] Only 4[6,9,15,16] studies included heart failure or rehospitalization rates as an outcome indicator, while the remaining studies used only all-cause mortality as an indicator. Follow-up ranged from 0.3 to 2 years, with 1[16] study assessing all-cause mortality at 3 months, 2 studies[10,15] assessing all-cause mortality at 2 years postoperatively, and the remaining studies assessing all-cause mortality in patients at 1 year postoperatively. The mean age of TAVR patients ranged from 77 to 84 years. The included studies used different types of malnutrition screening tools, including the Control of Nutritional Status (CONUT), Mini Nutritional Assessment-Short Form (MNA-SF), Geriatric Nutritional Risk Index (GNRI), Nutritional Risk Index (NRI), and Prognostic Nutritional Index (PNI). A total of 3 articles[6,9,14] used 3 different malnutrition screening and diagnostic tools to predict patient prognosis. Cohort study quality was evaluated using the NOS Literature Quality Rating Scale, with 5 articles[6,9,11,12,14] being of moderate quality and the rest being[9,13,15-17] of high quality.

Postoperative All-Cause Mortality

A test for heterogeneity was derived from the inclusion of 10 cohort studies ($I^2 = 93.7\% > 50\%$, $P < .01$ for Q test), and random effects were selected for meta-analysis. There was extreme heterogeneity among the literature selected for this study (Figure 2), and the source of heterogeneity was highly suspected to be the malnutrition assessment tool, and subgroup analysis will be performed subsequently to continue the investigation of the causes of heterogeneity. The results of the random-effects meta-analysis showed that all-cause

Table 1. General Aspects of the Included Articles

Study	Research Type	Age (Years)	Country	Sample	Male/Female	BMI (kg/m²)	Prevalence (%)	Gauge	STS Score (%)	Follow-Up Duration (Year)	Primary Endpoint Data	Score
Kenichi (2018)	Prospective cohort study	84.0 ± 5.0	Japan	1613	477/1136	23.5 ± 12.3	32.7	GNRI	4.7 (2.1 ± 5.3)	1	All-cause mortality, cardiovascular disease mortality, non-cardiovascular disease mortality	7
Rocío (2018)	Retrospective cohort study	81.0 ± 6.5	America	941	405/536	29.1 ± 4.9	48.1	NRI	5.8 ± 3.8	2.1 ± 1.1	All-cause mortality	8
Taishi (2019)	Retrospective cohort study	84	Japan	95	28/67	21.9 ± 4.1	27.3	CONUT	5.2 (4.0 ± 7.1)	1	All-cause mortality, readmission rates due to heart failure	6
Shunichi (2020)	Prospective cohort study	83.5 ± 5.7	Japan	288	95/193	22.5 ± 4.0	65.3	MNA-SF	5.9 ± 4.5	1.1 ± 0.9	All-cause mortality	5
Kyusup (2020)	Prospective cohort study	78.7 ± 5.2	South Korea	412	198/214	23.9 ± 3.4	55.1	GNRI	3.2 (2.3 ± 5.1)	1	All-cause mortality	6
Hatim (2021)	Prospective cohort study	82.9	Germany	953	520/433	26.1 (23.8 ± 29.4)	35.2	GNRI	NR	1.8	All-cause mortality	7
Mehmet (2021)	Prospective cohort study	77.1 ± 7.8	Turkey	119	48/71	28.6 ± 3.4	Unclear	GNRI	7.6 ± 1.6	1	All-cause mortality	6
Keita (2021)	Retrospective cohort study	82.5 ± 7.3	America	968	557/411	27.2 ± 5.7	53.4	GNRI	4.8 (3.2 ± 7.3)	2	All-cause mortality, 30-day mortality, postoperative complications	7
Silvia (2021)	Prospective cohort study	83.1 ± 5.8	Germany	114	68/46	27.2 (16.4 ± 49.6)	50.0	PNI	NR	1	All-cause mortality, in-hospital mortality, and postoperative complications	6
Rocío (2021)	Prospective cohort study	80.2 ± 7.3	America	433	208/225	29.5 ± 5.2	61.4	GNRI	6.0 ± 3.5	0.3	All-cause mortality, hospitalization for heart failure, and postoperative complications	7

Unclear: not mentioned in the literature.
CONUT, Controlling Nutritional Status Index; GNRI, Geriatric Nutritional Risk Index; MNA, Mini Nutritional Assessment; NRI, Nutritional Risk Index; PNI, Prognostic Nutritional Index; STS score, Society of Thoracic Surgeons Risk Score.

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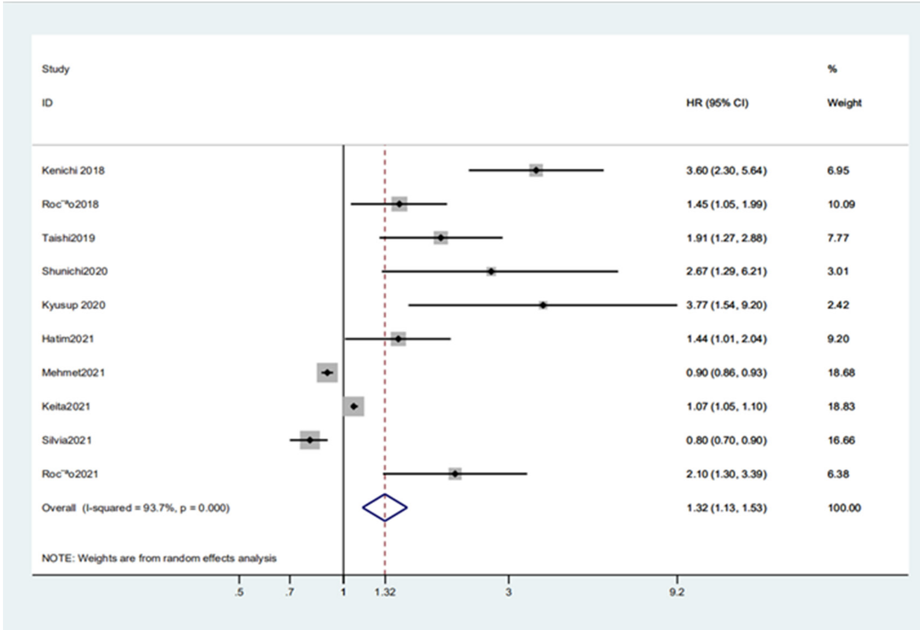

Figure 2. Result of the meta-analysis of hazard ratio values for all-cause mortality.

mortality in malnourished patients was 1.3 times higher than that in non-malnourished patients (HR = 1.32,95% CI: [1.13,1.53], *P* <.01), a statistically significant result, suggesting that preoperative malnutrition can significantly increase the risk of death after TAVR.

Postoperative Complications

Three studies reported the relationship between malnutrition and the occurrence of postoperative complications after TAVR. The study by Rocío et al[16] used GNRI to record the nutritional status of patients with a 3-month follow-up and showed that patients with worsening nutritional risk after TAVR had a higher risk in-hospital stroke incidence (8.0% vs. 0.7%, *P* =.011). The study by Keita et al[15] enrolled 968 consecutive patients treated with TAVR and divided the patients into 2 groups based on the median baseline of GNRI. The results showed that the low GNRI group (GNRI < 103) had higher rates of STS scores and renal insufficiency, but there were no significant differences in 30-day mortality, stroke, or bleeding between the 2 groups. A study by Silvia et al[9] showed no differences in complications between PNI groups. Currently, there are conflicting data on the relationship between malnutrition and patients presenting with postoperative complications, and given the small sample size and heterogeneity of studies, more studies will be needed in the future to describe the relationship between malnutrition and clinical outcomes in patients with TAVR.[18]

Hospital Resources

Two studies reported the relationship between malnutrition and rehospitalization in TAVR patients. A study by Rocío et al[16] showed a 39.7% rehospitalization rate for heart failure at 3 months after TAVR, a 50% adjusted reduction in the risk of rehospitalization for heart failure in patients with improved postoperative nutritional risk, and a 56% adjusted reduction in the risk of the composite endpoint of death and heart failure hospitalization. The study by Taishi et al[6] analyzed 95 patients treated with TAVR from December 2013 to February 2017, calculating preoperative patient CONUT, PNI, and GNRI, respectively, and showed that 12 (12.6%) were rehospitalized for worsening heart failure and19 (20.0%) had a composite outcome within 1 year after TAVR. In the Kaplan-Meier analysis, the composite endpoint of death and rehospitalization for heart failure was associated with higher CONUT scores and lower PNI scores (38.5% vs. 13.0%; *P* =.006, 39.3% vs. 11.9%; *P* =.002).

Subgroup Analysis, Sensitivity Analysis, and Publication Bias

Subgroup analyses were performed based on geography, sample size, follow-up time, and malnutrition screening tools. Results showed that in the ethnic subgroup, the difference between the 2 groups was statistically significant in Asia [HR = 2.74; 95% CI: (1.89-3.95), I^2 = 38.1%, *P* <.01) but not in Europe; studies with sample size greater than or equal to 300 predicted a higher risk of all-cause mortality after TAVR than studies with sample sizes less than 300 [HR = 1.85. 95% CI: (1.24-2.77), I^2 = 89.8%, *P* <.01]; studies with follow-up > 1 year predicted the risk of all-cause mortality after TAVR [HR = 1.37; 95% CI: (1.02-1.83), I^2 = 73.5%, *P* =.034]; in the subgroup of malnutrition screening tools, GRNI: (HR = 1.34, 95% CI: 1.12-1.60, I^2 = 95.4%, *P* <.01). Thus, sample size, follow-up time, malnutrition screening tool, and ethnicity resulted in greater heterogeneity, as shown in Table 2.

The results of the sensitivity analysis showed no significant change in the prognosis of malnutrition after exclusion from the literature, indicating that the results of this meta-analysis were stable (Figure 3).

The included prognostic literature was tested for publication bias based on Begg and Egger tests and funnel plots. The results of the Begg test showed that Kendall's score was −4 (z = 0.37, *P* =.711) (Figure 4). The results of the Egger test showed no significant difference (t = 0.83, *P* =.440) (Figure 5).

Table 2. Prognosis of Malnutrition Among Different Subgroups

	HR	95% CI	I^2 (%)	*Z*	*P*	Model
All studies	1.32	(1.13, 1.53)	93.7	3.62	<.001	Random model
Race						
Asian	2.74	(1.89, 3.95)	38.1	5.37	<.001	Random model
Caucasian	1.07	(0.93, 1.23)	94.4	0.93	.351	Random model
Time						
≤1	1.59	(1.14,2.20)	93.3	2.76	.006	Random model
>1	1.37	(1.02,1.83)	73.5	2.12	.034	Random model
Evaluation criteria of malnutrition						
GNRI	1.34	(1.12, 1.60)	95.4	3.21	.001	Random model
Other	1.46	(0.85, 2.51)	90.5	1.38	.169	Random model
Sample						
≥300	1.85	(1.24, 2.77)	89.8	2.99	.003	Random model
<300	1.08	(0.85, 1.39)	87.3	0.63	.527	Random model

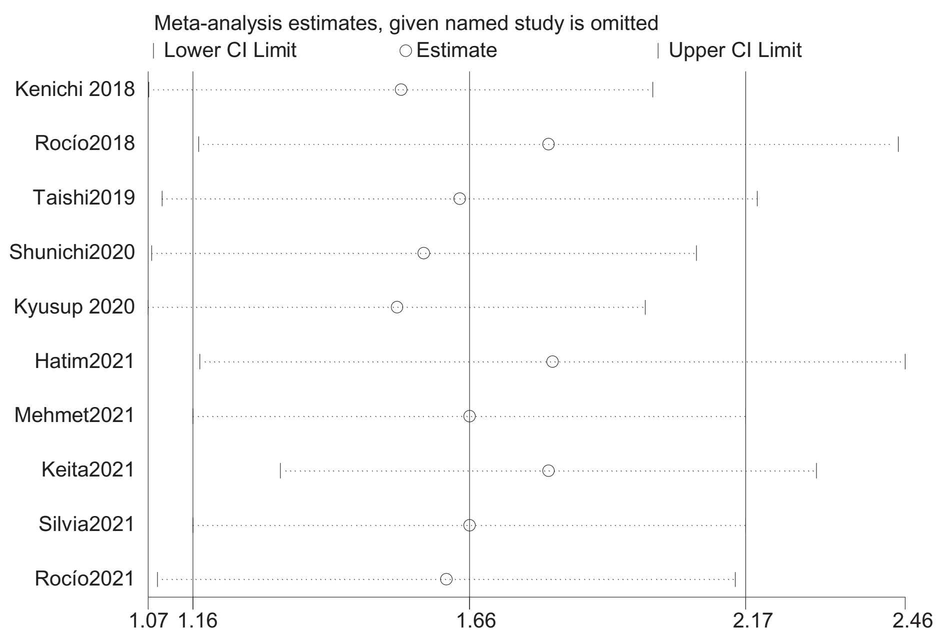

Figure 3. Result of the sensitivity analysis.

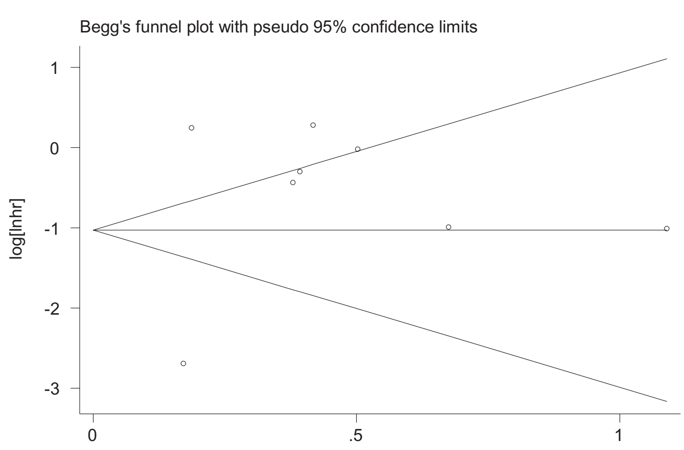

Figure 4. Funnel plot generated by the Begg test.

DISCUSSION

Transcatheter aortic valve replacement is increasingly used in clinical practice as a treatment for severe AS[19]; however, mortality after TAVR remains high, especially in older, frail patients,[20,21] and before undergoing TAVR treatment, patients' perioperative risk scores are calculated using conventional surgical risk models, such as the STS risk score,[22] and these assessments do not include nutritional assessment, which may affect our understanding of various patient characteristics. In addition, nutritional status is part of risk stratification and is an actionable risk factor, and nutritional assessment can provide guidance and secondary prevention for nutritional therapy.[23] Therefore, the relationship between malnutrition on adverse outcomes after TAVR should be explored to identify high-risk groups early and reduce their prevalence.

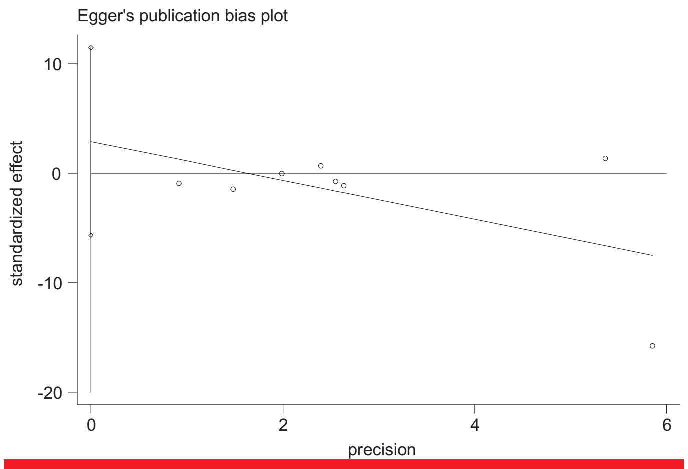

Figure 5. Funnel plot generated by the Egger test.

This systematic review and meta-analysis summarize the impact of malnutrition on the occurrence of adverse outcomes after TAVR. Based on the results of data from nearly 5936 subjects, the prevalence of malnutrition in TAVR patients ranged from 27.3% to 65.3%; the prevalence of malnutrition in TAVR patients assessed using the GNRI scale was 32.7%-61.4%, and the prevalence of malnutrition assessed by PNI, NRI, CONUT, and MNA-SF was 50%, 48.1%, 27.3%, and 65.3%, respectively, which may be related to different countries, sample sizes, and more severe diseases. In addition, the prevalence of malnutrition in heart failure patients was 37%-56%,[24] with 39%-51% of malnutrition assessed using MNA, which differs significantly from the prevalence of malnutrition in TAVR patients, which we found may be related to the average age of the included TAVR patients being >84 years and the lower BMI and Katz Index. Another finding was that malnourished patients had an approximately 1.3-fold increase in postoperative all-cause mortality compared with non-malnourished patients. A study involving 105 603 TAVR patients showed that malnutrition was a significant independent predictor of increased postoperative mortality, complications, and readmission rates,[25] which is consistent with previous studies.[26] Subgroup analysis showed that follow-up ≤1 year [HR=1.59, 95% CI: (1.14-2.20), I^2=93.3%, P <.01] and follow-up ≤1 year was a greater predictor of mortality than malnutrition in studies >1 year, and subgroups ≤1 year were included in studies with follow-up ranging from 3 to 12 months, which may lead to heterogeneity; in the malnutrition screening tool subgroup, lower GNRI was independently associated with postoperative all-cause mortality [HR=1.34, 95% CI: (1.12-1.60), I^2=95.4%, P <.01]. Geriatric Nutritional Risk Index is calculated from serum albumin and BMI, simple objective nutritional indicators suitable for routine use, quick and easy to use, and a valid parameter for predicting postoperative mortality in TAVR patients. Three of the included studies reported a mean BMI above 28 kg/m^2, which may underestimate malnutrition in overweight patients; in large sample size studies, in Asian countries malnutrition is a greater predictor of mortality (see Table 2). Therefore, future studies should investigate the differences in the nutritional status of TAVR patients based on different ethnicities and large sample sizes, with a focus on selecting more appropriate tools to assess the nutritional status of TAVR patients.

A meta-analysis[8] investigating the prognosis of malnutrition in TAVR patients concluded that malnutrition was associated with an increased risk of 1-year all-cause mortality in patients treated with TAVR, and the present study is consistent with the results of this study. The study included only scales containing simple objective indicators that estimate nutritional risk rather than assessing malnutrition. The present study included not only scales with objective indicators but also the Nutrition Assessment Questionnaire—MNA-SF, which takes into account not only the psychosomatic problems of the patient but also dietary and pharmacological mobility and has a better classification performance in identifying malnutrition. In terms of follow-up time, the risk of death in patients with combined malnutrition and follow-up time >1 year was 1.37 times higher than in patients without combined malnutrition [HR=1.37, 95% CI: (1.02-1.83), I^2=73.5%, P =.034], and the impact of malnutrition on long-term prognosis is important, but further studies are needed. In this study, malnutrition in TAVR patients was compiled and analyzed from a long-term prognostic perspective to provide a reference for subsequent studies.

Malnutrition is thought to promote manifestations of systemic inflammation leading to accelerated progression of cardiovascular disease and bone loss, while activation of neurohormonal and inflammatory pathways in patients with cardiovascular disease may increase catabolic demands and in this way create a vicious cycle.[27,28] During the perioperative period, the synthetic effects of nutrition may be diminished, and the early effects of TAVR on postoperative left ventricular remodeling are evident in patients. The maintenance of postoperative cardiac function must be enhanced;[29] therefore, the length of hospital stay is longer in malnourished patients. Another study confirmed that malnutrition is associated with frailty and sarcopenia in patients with TAVR.[30,31] Also, frailty is an independent risk factor for poor prognosis after TAVR.[32] Therefore, patients with poor nutritional status may be more prone to cardiac events, and it is recommended that patients be screened for nutritional status at admission and that nutritional interventions be performed if necessary. Current nutritional interventions are mainly aimed at the elderly, and fewer studies have been conducted specifically on nutritional interventions for patients with TAVR. In a multicenter randomized controlled trial, supplementation with vitamin D and leucine-rich whey protein was shown to improve muscle mass and lower extremity function.[33] This intervention may also apply to patients with TAVR. A large number of future randomized trials are needed to demonstrate that nutritional interventions can eliminate the negative impact of malnutrition on patient prognosis.

Study Limitations

The main limitations of this study are as follows: first, the small sample size of the studies included in this study may have influenced the results; second, some studies lacked information on adjusted risk ratios and their 95% CIs, and all-cause mortality was excluded from the analysis; third, the components of the studies were malnutrition and non-malnutrition, but the severity of the selected malnutrition was not disclosed; fourth, the definition of malnutrition varied widely across studies. Despite these limitations, malnutrition is considered to be a cause of death after TAVR.

CONCLUSION

In conclusion, this meta-analysis is the first to summarize the impact of malnutrition on poor outcomes after TAVR, provide evidence regarding the prevalence and prognosis of malnutrition in patients treated with TAVR, and confirm that malnutrition is significantly associated with poor outcomes after TAVR. Therefore, preoperative nutritional assessment can identify malnutrition and predict poor outcomes after TAVR, and according to guidelines, prevention and early nutritional interventions can help improve the nutritional status and prognosis of patients and have an important impact on their long-term survival.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (approval no: 20220586).

Peer-review: Externally peer-reviewed.

Author Contributions: M.D. and J.S. designed and conceived the study. M.D. and L.G. completed data collection and wrote the manuscript. M.D. and Y.X. participated in data analysis and manuscript preparation. S.S. and J.C. provided important suggestions for revising the article. J.S. approved the final version of the manuscript.

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Declaration of Interests: The authors declare that they have no competing interest.

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