Systematic Review and Meta-Analysis

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The impact of preoperative frailty status on outcomes after transcatheter aortic valve replacement

An update of systematic review and meta-analysis

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Abstract

Background: Frailty is a syndrome of impaired physiologic reserve and decreased resistance to stressors and can often be seen in high-risk patients undergoing transcatheter aortic valve replacement (TAVR). Preoperative frailty status is thought to be related to adverse outcomes after TAVR. We conducted this systematic review and meta-analysis to determine the impact of preoperative frailty status on outcomes among patients after TAVR.

Methods: PubMed, Embase, and the Cochrane Library were searched for relevant studies through January 2018. Fourteen articles (n=7489) meeting the inclusion criteria were finally included. Possible effects were calculated using meta-analysis.

Results: The pooled risk ratios (RRs) of late mortality (>6 months) and acute kidney injury after TAVR in frail group were 2.81 (95% confidence interval (CI) 1.90–4.15, $P<.001$, $I^2=84\%$) and 1.41 (95% CI 1.02–1.94, $P=.04$, $I^2=24\%$), respectively. Compared with non-frail group, significantly higher incidence of 30-day mortality (RR 2.03, 95% CI 1.63–2.54, $P<.001$, $I^2=0\%$) and life threatening or major bleeding after TAVR (RR 1.48, 95% CI 1.20–1.82, $P<.001$, $I^2=14\%$) was found in frail group. There was no significant association between frailty and incidence of stroke after TAVR (RR 0.93, 95% CI 0.53–1.63, $P=.80$, $I^2=0\%$).

Conclusion: Preoperative frailty status is proved to be significantly associated with poor outcomes after TAVR. Our findings may remind doctors in the field of a more comprehensive preoperative evaluation for TAVR candidates. More well-designed and large-sample sized prospective studies are further needed to figure out the best frailty assessment tool for patients undergoing TAVR.

Abbreviations: AKI = acute kidney injury, BMI = body mass index, CI = confidence interval, CSHA = Canadian Study of Health and Aging, GA = general anesthesia, LACS = local anesthesia or conscious sedation, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RR = risk ratio, TAVR = transcatheter aortic valve replacement, VARC = Valve Academic Research Consortium.

Keywords: aortic stenosis, complication, frailty, mortality, risk factor, TAVR

1. Introduction

The term "frailty"—a syndrome of impaired physiologic reserve and decreased resistance to stressors[1] initially derives from gerontology and is used to estimate health conditions and predict risks of adverse events for old population. In recent years, the use of frailty assessment has been expanded to the field of preoperative evaluation, especially in high-risk patients undergoing transcatheter aortic valve replacement (TAVR). An objective frailty assessment is recommended by 2 national guidelines to be integrated into pre-TAVR risk evaluation last year.[2,3] Several studies suggest that preoperative frailty status is associated with increased mortality.[4,5] Frail patients undergoing TAVR are more likely to have increased postoperative length of stay and higher incidence of postprocedural complications.[6–8] Acute kidney injury (AKI) is a frequent complication after TAVR, ranging from 8.3% to 57% of patients according to the Valve Academic Research Consortium (VARC) definition.[9] Patients suffering from AKI after TAVR tend to have higher 30-day and late mortality.[10,11] Results of former studies present a higher incidence of AKI after TAVR among frail patients, although most of them do not reach statistical significance.[6,12,13] Moreover, frailty assessment is proved to be a strong predictive indicator for functional outcomes and quality of life in patients undergoing TAVR.[6,14,15]

A previous meta-analysis suggests no significant association between frailty status and AKI after TAVR.[16] However, a recent large sample-sized observational study reveals a significantly higher risk of AKI after TAVR in frail patients.[13] It is possible that former studies are underpowered because of a relatively small sample size. In addition, the association between frailty and AKI after TAVR is ill-defined due to the heterogeneity of

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definitions used for AKI and frailty. We noticed that standard endpoint definitions promoted in VARC-2 consensus document were widely used in recent studies to investigate relationship between frailty and outcomes after TAVR. It is apparent that results of these studies possess an improved comparability and interpretability. Here, we conducted this systematic review and meta-analysis to provide an update on relationship between preoperative frailty status and outcomes among patients undergoing TAVR.

2. Methods

The research is being reported in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines.[17] Ethical approval was not required considering the nature of the study.

2.1. Study selection

We searched PubMed, Embase, and the Cochrane Library through January 2018 without language restriction using the key search terms frailty and TAVR. Complementary references were further identified by reviewing relevant papers including review, meta-analysis, and these retrieved references.

The inclusion criteria were as follows: patients undergoing TAVR; participants grouped by preoperative frailty status or with full frailty assessment information; available data with odds ratio, risk ratio (RR), and hazard ratio or sufficient data to calculate them with 95% confidence interval (95% CI); studies reporting clinical outcomes after TAVR; and original articles designed as observational studies (retrospective or prospective cohort studies). Studies without a clear definition of frailty or recording frailty as a continuous variable were also excluded. No limitations were put on age of the participants and routes of operative access.

2.2. Types of outcome measures and data extraction

Frailty was recorded as a binary variable. The primary outcomes were late mortality (>6 months) and AKI after TAVR. Postoperative 30-day mortality, stroke and life-threatening or major bleeding were secondary outcomes. Weighted means were calculated based on the product of the number of patients.

Two reviewers (LiLi Huang and XiaoShuang Zhou) screened abstracts identified in the initial search. Once meeting the inclusion criteria, full-text were obtained and then reviewed in duplicate. Disagreements between the reviewers were resolved through consultations with 2 reviewers (XiaoYun Yang and Hai Yu). A data abstraction form was used to record the details of study characteristics, including journal, frailty definition, sample size, and so on. The primary outcome was late mortality (>6 months) after TAVR. Incidence of AKI and 30-day mortality and after TAVR was secondary outcomes.

2.3. Quality and bias assessment

Newcastle–Ottawa quality assessment scale was used to evaluate the quality of cohort studies from the following 3 aspects: selection (4 points); comparability (2 points); and outcomes (3 points). The score ranges from 0 to 9 points with ≥7 points considered high quality and <7 moderate or low quality.[18] Two reviewers performed quality assessments independently and the third reviewer would be consulted to reach consensus. For outcomes with the greatest number of studies, we created a funnel plot and used Egger test to assess publication bias.[19]

2.4. Statistical analysis

This meta-analysis was performed using Review Manager software 5.3 (RevMan, The Cochrane Collaboration, Oxford, UK). Due to various types of frailty assessment tools and different lengths of follow-up in each study, significant heterogeneity can be expected. For this reason, a random-effect model was applied through the whole calculating process. Point estimates and standard errors derived from included studies were combined by the generic inverse variance method of Der-Simonian and Laird.[20] Heterogeneity among pooled studies was reported as the I^2 test, where $I^2 > 50\%$ indicated substantial heterogeneity. Sensitivity analysis was further performed to explore possible cause for heterogeneity. A 2-tailed *P* value of <.05 was considered a criterion for statistical significance.

3. Results

3.1. Literature search and study characteristics

We identified 527 records through our search strategy. Three hundred seventy-two records were screened based on abstracts after duplicates removed. Possibly related articles were then assessed for eligibility via full-text reading. Finally, 14 articles with 7489 participants were included in this meta-analysis. The PRISMA flow diagram depicts selection process (see Fig. 1).

In total, 5 types of frailty definition were used among included studies. Seven studies[6–8,21–24] with 1220 participants defined frailty status by a frailty index score based on several indices, such as weight loss, hand grip strength, gait speed, albumin, and the Katz index of activity of daily living. Four studies[13,25–27] with 4583 participants referred to Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale. One studies combined CSHA Clinical Frailty Scale with several other indices for evaluation.[15] Geriatric Status Scale and Katz index were each applied in 1 study.[12,28]Table 1 shows characteristics of each included study. The proportion of patients identified as frail ranges from 4.6% to 62.4%. All studies reported either 30-day mortality or late mortality (>6 months) after TAVR, or both. Six studies[6,7,12,13,21,22] reported details of postprocedural complications based on the consensus guidelines of VARC[29,30] including AKI, stroke, and life threatening or major bleeding.

3.2. Meta-analysis of effects on primary outcomes

Compared with non-frail group, the risk of AKI after TAVR was higher in frail group (RR 1.41, 95% CI 1.02–1.94, $P = .04$, $I^2 = 24\%$), as shown in Fig. 2. The relationship between frailty and late mortality after TAVR was investigated in 10 studies (n = 2992). The pooled RR of late mortality in frail group was 2.81 (95% CI 1.90–4.15, $P < .001$, $I^2 = 84\%$) (see Fig. 3). Six of ten studies (n = 1029) applied the frailty index score to estimate frailty. The pooled RR of late mortality after TAVR in frail patients based on frailty index score was 2.69 (95% CI 2.06–3.50, $P < .001$, $I^2 = 0$) (see Figure, Supplemental Content 1, http://links.lww.com/MD/C672).

3.3. Meta-analysis of effects on secondary outcomes

Eleven studies (n = 7554) quantified the relationship between frailty and 30-day mortality after TAVR. Patients in frail group had a 2.03-fold increased hazard of 30-day mortality (95% CI 1.63–2.54, $P < .001$, $I^2 = 0\%$) (see Figure, Supplemental Content 2, http://links.lww.com/MD/C672). Compared with non-frail

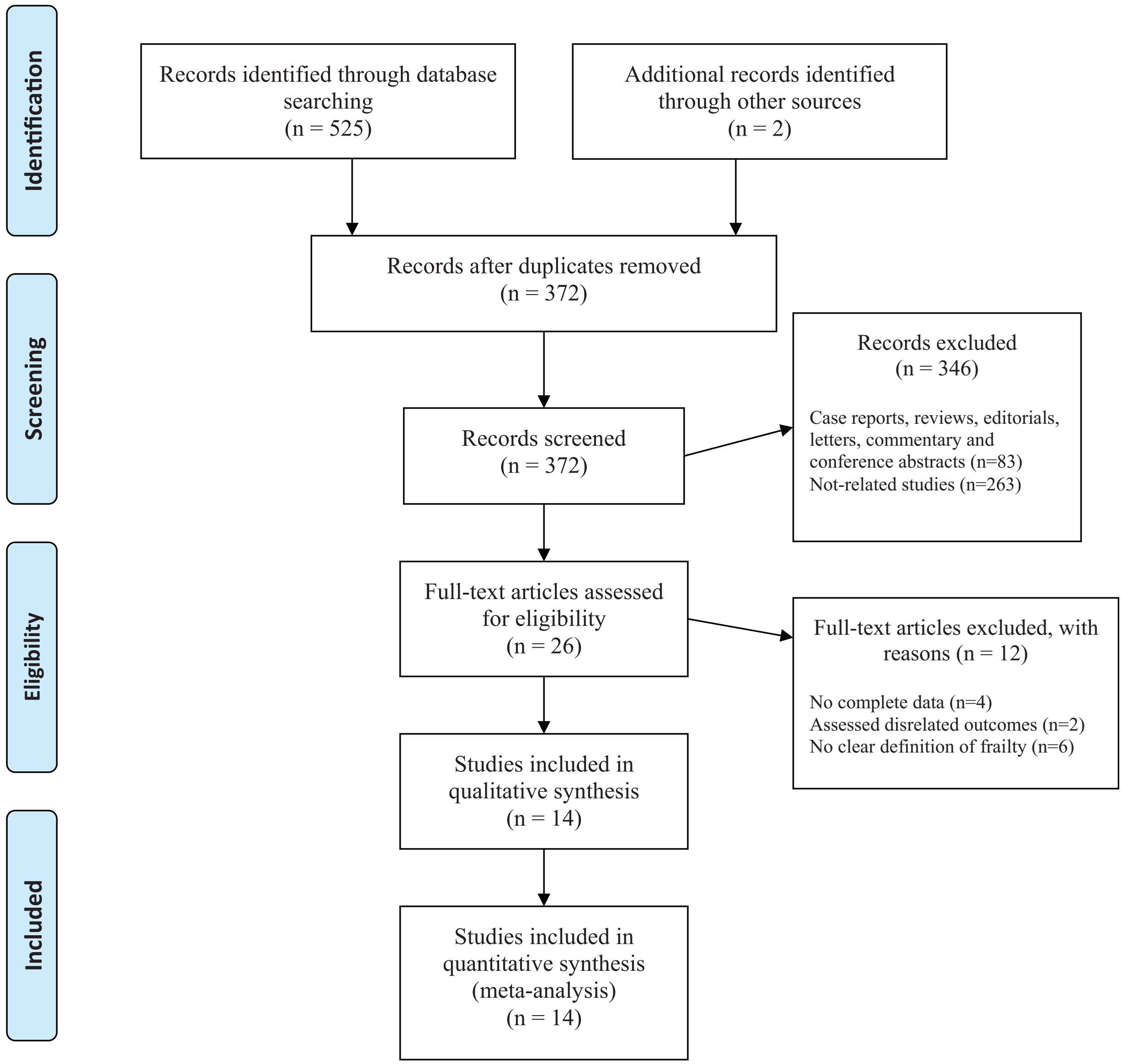

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Figure 1. Flow chart. PRISMA flow diagram of study selection process.

group, the risk of life threatening or major bleeding after TAVR was higher in frail group (RR 1.48, 95% CI 1.20–1.82, $P<.001$, $I^2=14\%$) (see Figure, Supplemental Content 3, http://links.lww.com/MD/C672). No significant relationship was found between frailty and incidence of stroke after TAVR (RR 0.93, 95% CI 0.53–1.63, $P=.80$, $I^2=0\%$) (see Figure, Supplemental Content 4, http://links.lww.com/MD/C672).

3.4. Study quality and risk of bias

Thirteen of included studies showed high quality and only one were rated as moderate to low quality. The average score of Newcastle–Ottawa quality assessment is 7. The study scoring <7 points did not adjust for potential confounders of the relationship between frailty and outcomes. Both funnel plot and Egger tests suggest no significant publication bias on relationship between 30-day mortality and preoperative frailty status among the 11 studies (Egger test for asymmetry $P=.441$) (see Figure, Supplemental Contents 5 and 6, http://links.lww.com/MD/C672).

4. Discussion

As far as we know, this meta-analysis is the first available evidence identifying the relationship between frailty and post-procedural complications including stroke and life-threatening or

Table 1

Details of included studies.

Trial	Journal	Frailty definition	Sample size	Proportion of frail, %	Primary outcomes	Secondary outcomes	Quality assessment (selection/comparability/outcome)
Capodanno 2014[28]	The American Journal of Cardiology	Geriatric Status Scale with ≥2 considered frail	1256	24.4	30-d mortality		4, 0, 3
Chauhan 2016[8]	American Heart Journal	Frailty index score based on hand grip strength, gait speed/15 feet walk test, ALB, and the Katz index of ADL score ranging from 0 to 4 out of 4 with ≥3/4 considered frail	342	30.4	30-d all-cause mortality 1-y all-cause mortality	Total postoperative LOS Discharge disposition Incidence of stroke	3, 0, 2
Green 2012[21]	JACC: Cardiovascular Interventions	Frailty index score based on gait speed, grip strength, ALB, and the Katz index of ADL score ranging from 0 to 12 with >5 considered frail	159	47.8	Procedural outcomes 30-d mortality 1-y mortality		4, 0, 3
Green 2015[22]	The American Journal of Cardiology	Frailty index score based on gait speed, grip strength, ALB, and the Katz index of ADL score ranging from 0 to 12 with ≥6 considered frail	244	45.1	1-y mortality	Outcomes at 30 d	4, 0, 3
Huded 2016[7]	The American Journal of Cardiology	Frailty index score based on 4 domains including shrinking, weakness, slowness, and low physical activity Score ranging from 0 to 4 with ≥3 considered frail	191	33.5	30-d mortality and hospital readmission Discharge to a rehabilitation facility Adverse events within 30 d Hospital LOS		4, 0, 3
Kleczynski 2017[25]	American Heart Journal	CSHA Clinical Frailty Scale ≥5	101	20.2	12-mo all-cause mortality		4, 0, 3
Kobe 2016[15]	Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery	FORECAST scores based on chair rise, weak, stair, CSHA Clinical Frailty Scale, serum creatinine level score ranging from 0 to 14 with ≥4 considered frail	130	54.6	30-d all-cause mortality and quality of life	Incidence of myocardial infarction, stroke, and resuscitation	4, 0, 3
Martin 2017[26]	Heart	CSHA Clinical Frailty Scale ≥5	2920	39.9	30-d mortality		4, 0, 3
Okoh 2017[6]	Catheterization and Cardiovascular Interventions	Frailty index score based on hand grip strength, gait speed/15 feet walk test, ALB, and the Katz index of ADL score ranging from 0 to 4 out of 4 with ≥3/4 considered frail	75	40	All-cause mortality	Postoperative 30-d health status Procedure-related complications Total postoperative LOS Functional outcomes Discharge disposition	3, 2, 3
Puls 2014[12]	EuroIntervention	Katz index < 6	300	48	30-d mortality Procedural mortality	Postprocedural complications Bleeding complications Incidence of AKI Access-related complications Prosthetic valve-associated complications Non-VARC defined events	4, 0, 3

(*continued*)

Table 1
(continued).

Trial	Journal	Frailty definition	Sample size	Proportion of frail, %	Primary outcomes	Secondary outcomes	Quality assessment (selection/comparability/outcome)
Rodríguez-Pascual 2016[23]	International Journal of Cardiology	CHS criteria based on low grip strength, slowness, low physical activity, exhaustion, and unintentional weight loss with ≥3 of the above criteria	109	62.4	Mortality		4, 0, 3
Seiffert 2014[27]	Clinical Research in Cardiology	Subjective assessment combined with the CSHA Clinical Frailty Scale ≥6	347	4.6	1-y mortality		4, 0, 3
Shimura 2017[13]	Circulation	CSHA Clinical Frailty Scale ≥ 5	1215	29.1	Postprocedural complications Outcomes at 30 days In-hospital outcomes	1-y mortality	4, 0, 3
Stortecky 2012[24]	JACC: Cardiovascular Interventions	Frailty index score based on MMSE, MNA, TUG, BADL, IADL, and preclinical mobility and disability score ranging from 0 to 7 with ≥3 considered frailty probable	100	49	30-d all-cause mortality and MACCE 1-y all-cause mortality and MACCE		4, 0, 3

ADL = activity of daily living, AKI = acute kidney injury, ALB = albumin, BADL = Basic Activities of Daily Living, CHS = Cardiovascular Health Study, CSHA = Canadian Study of Health and Aging, FORECAST = Frailty predicts death One yeaR after Elective CArdiac Surgery Test, IADL = Instrumental Activities of Daily Living, JACC = Journal of the American College of Cardiology, LOS = length of stay, MACCE = major adverse cardiovascular and cerebral events, MMSE = Mini Mental State Exam, MNA = Mini Nutritional Assessment, TUG = Timed Get Up and Go test, VARC = Valve Academic Research Consortium.

major bleeding. In this systematic review and meta-analysis, we found that the risk of 30-day and late mortality (>6 months) after TAVR was significantly higher in frail group. Preoperative frailty status was demonstrated to be a risk factor of AKI and life-threatening or major bleeding after TAVR, while incidence of stroke was comparable in 2 groups.

Compared with previous meta-analysis, our research reconfirmed the relationship between preoperative frailty status and increased mortality after TAVR. Frailty assessment appeared to have a good predictive ability on both short- and long-term survivals. The result on relationship of frailty and AKI was not consistent with the study by Thongprayoon et al.[16] Our meta-analysis indicated a 1.41-fold increased risk of AKI after TAVR in frail patients, while no significant association was suggested in their study. It is probably because former studies were underpowered due to a relatively small sample size and various AKI definitions. Besides, we have made several improvements in methodology. First, literature screening process of our study was more precise. For example, body mass index (BMI) is one of additional risk factors indicative of frailty. The study by Yamamoto and colleagues, as stated in the article, only focused on the relation between BMI and clinical outcomes after TAVR and was not related to frailty.[31] Studies like this were filtered out. Second, we excluded studies using subjective frailty assessment, as objective frailty assessment was strongly proposed by national guidelines for TAVR candidates. We aimed to avoid artificial subjective interference and offer reliable hints for future studies.

Although 14 relevant studies were included in our study, only 3 reported on anesthesia.[13,24–25] A recent study by Husser et al[32] found use of local anesthesia or conscious sedation (LACS) in TAVR is safe, with fewer postprocedural complications and lower early mortality compared with general anesthesia (GA). We can assume that anesthesia may play an important role in TAVR patients with preoperative frailty status. But it is difficult to do further analysis based on different anesthesia due to limited data.

Importance of frailty in pre-TAVR assessment is being emphasized and gradually used in addition to the current risk scores such as the EuroSCORE (European System for Cardiac Operative Risk Evaluation) and the Society of Thoracic Surgeons to improve predictive accuracy.[33–36] However, promotion of its use in clinical practice is not easy due to the lack of a unanimous frailty assessment tool. There is no consensus on the most appropriate assessment tool for TAVR candidates. It is noteworthy that a recent study comparing the predictive value of 7 different frailty scales for older adults undergoing conventional surgery or TAVR found that a brief 4-item scale encompassing lower-extremity weakness, cognitive impairment, anemia, and hypoalbuminemia outperformed other frailty scales.[37] Testing effectiveness of different frailty measurements to work out an optimum assessment tool for TAVR candidates may be a research hotspot in the future.

There were also some limitations. First, this was a meta-analysis of observational studies and inherent limitations do exist due to the nature of these studies. Second, some of included studies did not make adjustments for potential confounders in the relationship between frailty and outcomes such as age and gender. Third, the measurements for frailty were diverse among included studies. We further did sensitivity analysis to minimize the bias.

In summary, existing evidences show a specific correlation between preoperative frailty status and outcomes after TAVR. It

Study or Subgroup	Frail Group Events	Frail Group Total	Non-frail Group Events	Non-frail Group Total	Weight	Risk Ratio M-H, Random, 95% CI
Green 2012	3	76	3	83	4.0%	1.09 [0.23, 5.25]
Okoh 2017	2	30	0	45	1.1%	7.42 [0.37, 149.32]
Puls 2014	50	144	47	156	49.3%	1.15 [0.83, 1.60]
Shimura 2017	47	353	67	862	45.6%	1.71 [1.21, 2.44]
Total (95% CI)		**603**		**1146**	**100.0%**	**1.41 [1.02, 1.94]**
Total events	102		117			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.95$, df = 3 (P = 0.27); $I^2 = 24\%$
Test for overall effect: Z = 2.09 (P = 0.04)

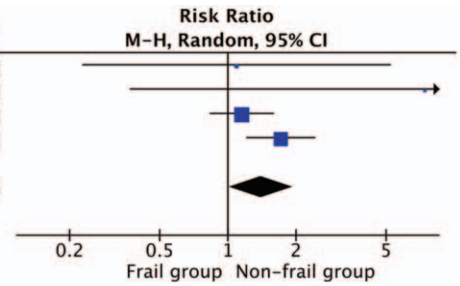

Figure 2. Forest plot of included studies comparing the risk of AKI after TAVR in frail versus non-frail patients. Patients in frail group were significantly at higher risk of AKI after TAVR, compared with non-frail patients. Squares represent RR and horizontal lines represent the 95% CI for each study. A diamond data marker represents the pooled RR across studies. AKI = acute kidney injury, CI = confidence interval, RR = risk ratio, TAVR = transcatheter aortic valve replacement.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Chauhan 2016	1.137833	0.2343	11.8%	3.12 [1.97, 4.94]
Green 2012	1.255616	0.4581	8.1%	3.51 [1.43, 8.61]
Green 2015	0.9162908	0.2958	10.7%	2.50 [1.40, 4.46]
Kleczynski 2017	4.168988	0.6561	5.6%	64.65 [17.87, 233.91]
Okoh 2017	0.6097656	0.2814	11.0%	1.84 [1.06, 3.19]
Puls 2014	0.9820785	0.2303	11.8%	2.67 [1.70, 4.19]
Rodríguez-Pascual 2016	1.118415	0.4568	8.1%	3.06 [1.25, 7.49]
Seiffert 2014	0.3435897	0.0697	13.8%	1.41 [1.23, 1.62]
Shimura 2017	0.4824262	0.1883	12.5%	1.62 [1.12, 2.34]
Stortecky 2012	1.302913	0.5675	6.6%	3.68 [1.21, 11.19]
Total (95% CI)			**100.0%**	**2.81 [1.90, 4.15]**

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 56.35$, df = 9 (P < 0.00001); $I^2 = 84\%$
Test for overall effect: Z = 5.18 (P < 0.00001)

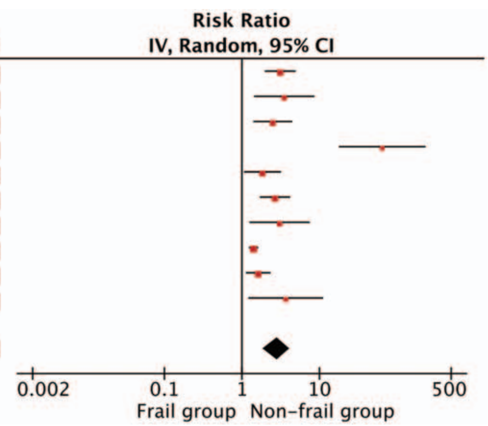

Figure 3. Forest plot of included studies comparing the risk of late mortality (>6 months) after TAVR in frail versus non-frail patients. Patients in frail group were significantly at higher risk of late mortality after TAVR, compared with non-frail patients. Squares represent RR and horizontal lines represent the 95% CI for each study. A diamond data marker represents the pooled RR across studies. CI = confidence interval, IV = inverse variance, RR = risk ratio, SE = standard error, TAVR = transcatheter aortic valve replacement.

is imperative to find effective clinical interventions for this setting. Prehabilitation to reduce frailty has been reported to improve postsurgical outcomes in a variety of populations.[38,39] In addition, we think an individual anesthesia regimen may be benefit to frail patients. Future studies may compare LACS and GA in frail patients and provide evidence for clinicians.

5. Conclusion

Preoperative frailty status is proved to have a strong predictive ability of both 30-day and late mortality after TAVR. The findings from our study also suggest significant associations between frailty and postprocedural complications including AKI and life threatening or major bleeding. Well-designed and large-sample sized prospective studies are further needed to find out the best frailty assessment tool for TAVR candidates and researchers should as well pay attention to exploring effective interventions for frail patients.

Author contributions

Conceptualization: LiLi Huang, XiaoYun Yang, Hai Yu.
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Formal analysis: LiLi Huang, XiaoShuang Zhou, XiaoYun Yang, Hai Yu.
Methodology: LiLi Huang, XiaoShuang Zhou, XiaoYun Yang, Hai Yu.
Supervision: XiaoYun Yang.
Validation: LiLi Huang, Hai Yu.
Writing – original draft: LiLi Huang, Hai Yu.
Writing – review & editing: LiLi Huang, XiaoYun Yang, Hai Yu.

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