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Measurement and prognosis of frail patients undergoing transcatheter aortic valve implantation: a systematic review and meta-analysis

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ABSTRACT

Objectives Our objectives were to review the literature to identify frailty instruments in use for transcatheter aortic valve implantation (TAVI) recipients and synthesise prognostic data from these studies, in order to inform clinical management of frail patients undergoing TAVI.

Methods We systematically reviewed the literature published in 2006 or later. We included studies of patients with aortic stenosis, diagnosed as frail, who underwent a TAVI procedure that reported mortality or clinical outcomes. We categorised the frailty instruments and reported on the prevalence of frailty in each study. We summarised the frequency of clinical outcomes and pooled outcomes from multiple studies. We explored heterogeneity and performed subgroup analysis, where possible. We also used Grading of Recommendations, Assessment, Development and Evaluation (GRADE) to assess the overall certainty of the estimates.

Results Of 49 included studies, 21 used single-dimension measures to assess frailty, 3 used administrative data-based measures, and 25 used multidimensional measures. Prevalence of frailty ranged from 5.67% to 90.07%. Albumin was the most commonly used single-dimension frailty measure and the Fried or modified Fried phenotype were the most commonly used multidimensional measures. Meta-analyses of studies that used either the Fried or modified Fried phenotype showed a 30-day mortality of 7.86% (95% CI 5.20% to 11.70%) and a 1-year mortality of 26.91% (95% CI 21.50% to 33.11%). The GRADE system suggests very low certainty of the respective estimates.

Conclusions Frailty instruments varied across studies, leading to a wide range of frailty prevalence estimates for TAVI recipients and substantial heterogeneity. The results provide clinicians, patients and healthcare administrators, with potentially useful information on the prognosis of frail patients undergoing TAVI. This review highlights the need for standardisation of frailty measurement to promote consistency.

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Strengths and limitations of this study

- This study examines the heterogeneity across different frailty assessment tools and determines the frequency of adverse outcomes and pools the prognosis after transcatheter aortic valve implantation in frail patients.
- This study uses a comprehensive literature search strategy and includes frail patients from randomised controlled trials and observational studies.
- This study excluded studies in which dimensions of frailty were assessed without reference to the goal of frailty assessment.

INRTODUCTION

Transcatheter aortic valve implantation (TAVI) has become an alternative, less invasive treatment option for patients with severe symptomatic aortic stenosis.[1] The evidence continues to accumulate and synthesis of the evidence to better understand the prognosis of frail patients who undergo TAVI may be helpful.[2]

Frailty is a biological syndrome characterised by an increased vulnerability to stressors.[3] When exposed to stressors, such as chronic illness and surgery, frail patients are susceptible to adverse events, procedural complications, prolonged recovery, functional decline and reduced survival.[4] Clinical research has identified frailty as an important risk factor for mortality and morbidity following TAVI.[5] Health economics research has shown that compared with non-frail patients, frail older adults undergoing cardiac surgery incurred substantially higher hospitalisation costs.[6] Given the clinical and economic implications of TAVI, searching for and synthesising outcomes of frail patients undergoing TAVI may provide information that can help to optimise the selection of TAVI candidates and ultimately improve decision making related to treatment of aortic stenosis.[2]

When considering valve procedures, clinical practice guidelines recommend assessing frailty as one component of risk.[7] We performed a systematic review of the literature to identify studies reporting the prognosis of frail patients undergoing TAVI. With no single standard method of measuring frailty and a diversity of frailty measurements, the optimal approach to assessing frailty in patients undergoing TAVI is unclear.[2 5] We catalogued frailty measures used in identified studies, to perform subgroup analyses for studies using the most common measures.

METHODS

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines[8] and follows the Meta-analysis Of Observational Studies in Epidemiology guidelines.[9]

Literature search and eligibility criteria

We searched PubMed, EMBASE, PsycINFO, Cochrane Library, Web of Science and ClinicalTrials.gov for articles published between January 2006 and 23 September 2020 (online supplemental appendix A). Conference abstracts from relevant conferences held in the last 3 years were also searched. The detailed inclusion and exclusion criteria were described in detail in the protocol.[10] We included patients with aortic stenosis, diagnosed as frail, who underwent a TAVI procedure. We only included studies that intended to measure frailty with a defined method of frailty assessment. Studies were excluded if baseline frailty status was measured after the TAVI procedure. We included all forms of TAVI, regardless of procedural approach and types of valves. Outcome measures included mortality, clinical outcomes or quality of life. We included studies describing non-comparative cohorts of patients undergoing TAVI who have been diagnosed with frailty and studies describing comparative cohorts of frail and non-frail patients undergoing TAVI in which outcomes were reported separately for frail patients. Authors (ZL, ED, AH, RB and MY) independently assessed study eligibility. Disagreements were resolved by consulting a third reviewer.

Risk of bias assessment

The risk of bias in individual studies was appraised independently by two authors (ZL and ED) using the Quality in Prognosis Studies (QUIPS) tool.[11] We classified studies with four or five low risk domains as having a low risk of bias overall, studies with two or more high-risk domains as high risk of bias overall, and the remaining studies as moderate risk of bias overall.

Data synthesis and meta-analysis

Prespecified statistical details were described in the protocol.[10] We summarised the method of measuring frailty used in each study including the frailty tool used, dimensions of frailty measured, the cut-off for frail status and the prevalence of frailty in the study population as measured by the frailty tool. We only extracted data from the most commonly used frailty instruments if multiple frailty instruments were applied in the same patient group. We categorised clinical outcomes and reported the frequency at each time point. Heterogeneity across studies was assessed using the I^2 statistic.[12]

For adverse clinical outcomes, we pooled proportions using the inverse-variance weighted DerSimonian and Laird model and incorporated the Freeman-Tukey double arcsine transformation.[13 14] A funnel plot was used to plot the effect estimates from individual studies against the SE of each study. In the absence of bias and heterogeneity, the funnel plot will be symmetrical.[15] For the length of hospitalisation, we pooled the values, estimating the mean and SD using the random effects model for continuous variables.[16] For studies presenting Kaplan-Meier curves with time to death, we collected the information on numbers at risk and total number of events, and then created a single pooled Kaplan-Meier curve. We pooled time to death data from individual studies to obtain an overall estimate of survival, based on an algorithm developed by Guyot *et al*.[17] All analyses were conducted using R software (V.3.5.0). A two-sided p value of 0.05 or less was considered statistically significant.

Subgroup analysis

We conducted a subgroup analysis to see if the estimates of mortality rates differed for studies that used the Fried phenotype, the most common multidimensional measure, compared with studies that did not use the Fried phenotype.

Grading of Recommendations, Assessment, Development and Evaluation assessment

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system to conduct an evaluation of the overall estimates based on considerations of risk of bias, consistency, precision, directness and publication bias.[18] Given that cohort studies of prognosis exclude randomised controlled trial study designs, we did not downgrade the certainty of evidence due to observational study design.

Patient and public involvement

No patient involved.

RESULTS

Characteristics of included studies

Our search identified 4944 records with 2635 articles remaining after removing duplicates. After screening, 49 studies[19–67] were identified as eligible for inclusion in the review (figure 1).

The characteristics of the included studies are summarised in online supplemental appendix B. Three studies[40 43 53] enrolled patients from the Placement of Aortic Transcatheter Valves trial reporting separately on outcomes of frail patients; the remaining studies reported on patients from a single cohort or registry. Most studies collected patient data

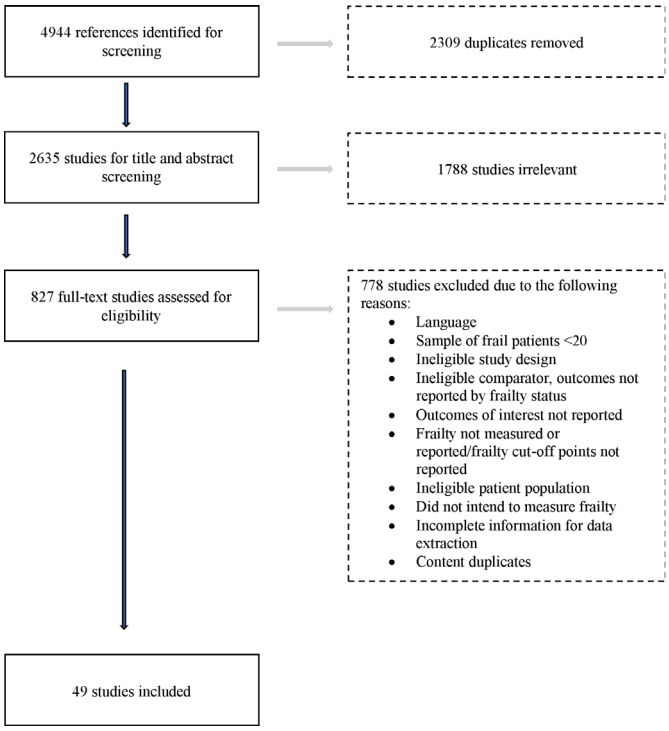

Figure 1 PRISMA flow diagram of included studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

prospectively; 17 studies[21 23 24 26 32 35 38 41 43 45 46 48 57 60–62 65] were conducted retrospectively.

Online supplemental appendix C summarises the risk of bias assessment of individual studies. Of the 49 studies, 21[25 26 28 29 31 33 37 39 40 47 49 52 55 58–60 62–66] were rated at overall low risk of bias, 21,[19–24 32 35 36 42–45 48 50 51 53 54 56 61] at moderate risk and 7[27 38 41 46 50 57 67] at high risk of bias.

Measurement of frailty in patients undergoing TAVI

Table 1 summarises frailty assessment in patients undergoing TAVI. Twenty-one studies[19–33 54–59] used single-dimension measures, 3 studies[60–62] used administrative data-based measures and 25 studies[34–53 63–67] used multidimensional measures. The prevalence of frailty varied widely among studies that assessed frailty with single dimension measures, ranging from 5.67% to 90.07%. Albumin, body mass index, and Katz Activity of Daily Living were the three most commonly used single-dimension measures when assessing frailty in TAVI patients. However, even with the same measure, different cut-points or definitions of frailty were used. For example, four studies[21 23 24 59] used albumin to assess frailty; two[21 23] defined frailty as albumin level below 4 g/dL, and two[24 59] as albumin level below 3.5 g/dL.

Among studies that used frailty indices based on administrative data, the prevalence of frailty ranged from 5.54% to 47.64%. Two studies[60 62] used the Hospital Frailty Risk Score, a frailty algorithm calculated based on a list of predefined International Statistical Classification of Diseases and Related Health Problems, Tenth Revision diagnostic codes. Frailty prevalence reported among the two studies was 41.06% and 47.64%, respectively. One study[61] used the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnosis indicator that was based on 10 clusters of frailty-defining diagnoses.

The prevalence of frailty reported by studies that assessed frailty using multidimensional measures ranged from 15.23% to 84.67%. Most of these studies assessed frailty based on the Fried frailty phenotype; one study[34] assessed frailty based on the accumulated deficits frailty index. Of the 25 studies reporting multidimensional measures, four[46–48 51] used the original Fried frailty phenotype and eight[35 38–41 43 44 53] modified the Fried frailty phenotype by examining fewer dimensions, altering cut-off values or measuring the same domains with different criteria. Among the eight studies[35 38–41 43 44 53] reporting the modified Fried frailty phenotype, measures used to assess mobility and disability were identical. Measures used to assess nutrition were different; seven studies[35 38–40 43 44 53] measured serum albumin and one study[41] measured weight loss.

Prognosis of frail TAVI recipients

Online supplemental appendix D summarises prognosis of frail TAVI recipients reported for each study. Twenty studies[19 21 27–31 34–36 40 41 43 50 53 56 58 62 65 66] reported 30-day mortality, which ranged from 2.83% to 25%; the combined 30-day mortality estimate was 7.32% (95% CI 5.66% to 9.42%, table 2, figure 2). Combining three studies[35 40 41] that measured frailty using the modified Fried frailty phenotype, we estimated a 30-day mortality of 7.86% (5.20% to 11.70%, table 2, figure 2).

Fifteen studies[25 30 31 34 35 37 40 43 46 49 50 53 56 58 62] reported 1 year mortality, ranging from 14.8% to 37.5%. The combined 1 year mortality estimate was 23.98% (20.71% to 27.58%, table 2, figure 3).When pooling two studies[35 46] that used the Fried or modified Fried frailty phenotype to assess frailty, the estimated 1-year mortality was 26.91% (21.50% to 33.11%, table 2, figure 3). Subgroup analyses of studies reporting frailty measurement using the Fried phenotype compared with non-Fried phenotype did not find statistical differences in effect estimates on 30-day and 1-year mortality (online supplemental appendix E).

Seventeen studies[22 23 25–29 31 33 34 40 41 47 48 52 56 58 60 62] reported survival of frail patients after TAVI using a Kaplan-Meier curve. The combined survival estimates at 1, 2 and 3 years were 75.6% (95% CI 75.2% to 76.0%, table 2), 65.0% (95% CI 63.3% to 66.7%, table 2) and 48.7% (95% CI 43.3% to 54.7%, table 2), respectively. Combining the studies that used the Fried or modified Fried phenotype, we found survival estimates at 1, 2 and 3 years were 73% (95% CI 68.8% to 77.5%, table 2), 64.5% (95% CI 56.4% to 73.9%, table 2) and 58.9% (95% CI 49% to 70.9%, table 2), respectively. Details of survival are provided in online supplemental appendix F.

Five studies[42 44 63 65 67] measured health-related quality of life (online supplemental appendix G). Three studies[44 65 67] assessed quality of life preoperatively using the 12-item Kansas City Cardiomyopathy Questionnaire

Table 1 Frailty assessment in patients undergoing TAVI

Studies that used a single dimension to assess frailty

Study, year	Measure	Dimensions	Definition	Total N	Frail n (%)
Alfredsson *et al*, 2016[19]*	Gait speed (5 m)	Mobility	<0.83 m/s or >6 s	8039	6100 (75.88%)
Bagienski *et al*, 2017[20]†	Katz ADL	Disability	<6 points	141	127 (90.07%)
Bogdan *et al*, 2016[21]	Albumin	Nutrition	≤4 g/dL	150	79 (52.67%)
Cockburn *et al*, 2015[22]	Brighton Mobility Index	Mobility	Poor mobility	312	65 (20.83%)
Grossman *et al*, 2017[23]	Albumin	Nutrition	<4 g/dL	426	192 (45.07%)
Koifman *et al*, 2015[24]‡	Albumin	Nutrition	<3.5 g/dL	476	238 (50%)
Kleczynski *et al*, 2017[25]	ISAR	Unclear	≥2 points	101	53 (52.48%)
Mok *et al*, 2016[26]	Sarcopenia	Nutrition	skeletal muscle mass index 2 SDs less than the mean SMM of young, healthy gender-specific reference ranges	460	293 (63.70%)
Martin *et al*, 2018[27]	CSHA score (1–7)	Physical function	Scores 5–7	2624	1043 (39.75%)
Puls *et al*, 2014[28]	Katz ADL	Disability	<6 points	300	144 (48%)
Rodés-cabau *et al*, 2010[29]	Clinical judgement	Subjective	Unclear	339	85 (25.07%)
Stortecky *et al*, 2012[30]	BMI	nutrition	<20 kg/m^2	256	24 (9.38%)
Shimura *et al*, 2017[31]§	CFS	Subjective	≥5 points (score ranges 0–9)	1215	353 (29.05%)
Traynor *et al*, 2017[32]	Assisted care	Unclear	Need assisted care	597	60 (10.05%)
Yamamoto *et al*, 2015[33]	BMI	Nutrition	<20 kg/m^2	777	56 (7.21%)
Welle *et al*, 2020[54]	Gait speed (5 m)	Mobility	≥6 s	723	483 (66.8%)
Mach *et al*, 2020[55]	Fitness-tracker assisted frailty score	Unclear	≥1 point	50	39 (78%)
Kiani *et al*, 2020[56]*	Gait speed (5 m)	Mobility	<0.83 m/s or >6 s (including unable to perform the test)	56 500	11 316 (20.03%)
Gharibeh *et al*, 2019[57]	Clinical judgement	Subjective	Indicators for limited self-dependence	461	186 (40.35%)
Voigtländer *et al*, 2020[58]	BMI	Nutrition	<20 kg/m^2	16 865	956 (5.67%)
Shimura *et al*, 2020[59]§	Albumin	Nutrition	<3.5 g/dL	1524	284 (18.64%)

Studies that used administrative database algorithms to assess frailty

Study, year	Measure	Definition/cut-off points	Total N	Frail n (%)
Malik *et al*, 2020[60]	Hospital Frailty Risk Score	Hospital Frailty Risk Score ≥5 points	20 504	8419 (41.06%)
Sami *et al*, 2020[61]	Johns-Hopkins Adjusted Clinical Groups frailty indicator	A dichotomous indicator defined based on 10 clusters of frailty-defining diagnoses	51 685	2865 (5.54%)
Kundi *et al*, 2019[62]	Hospital Frailty Risk Score	Hospital Frailty Risk Score ≥5 points	28 531	13 593 (47.64%)

Studies that used multiple dimensions to assess frailty

Study, year	Name	Measures	Dimensions	Definition	Total N	Frail n (%)
Bureau, 2017[34]	Multidimentional prognostic index	ADL	Disability	MPI ≥0.34 (the sum of all domain values is divided by eight to obtain the MPI score between 0 and 1)	116	71 (61.21)
		IADL	Disability			
		SPMSQ	Cognition			
		CIRS-CI	Medical			
		MNA-SF	Nutrition			
		ESS	Medical			
		No of medications	Medical			
		Social support network	Living status			

Continued

Table 1 Continued

Studies that used multiple dimensions to assess frailty						
Study, year	**Name**	**Measures**	**Dimensions**	**Definition**	**Total N**	**Frail n (%)**
Chauhan *et al*, 2016[35]¶	Modified Fried phenotype	ADL	Disability	Presence of 2 or more criteria	343	233 (67.93)
		Hand strength	Muscle strength			
		Gait speed	Mobility			
		Albumin	Nutrition			
Capodanno *et al*, 2014[36]	GSS	Not reported	Not reported	Value of 2 or 3	1256	306 (24.36)
Eichler *et al*, 2017[37]	FI	MMSE	Cognition	≥3 points (score ranges 0–7)	333	152 (45.65)
		MNA	Nutrition			
		ADL	Disability			
		IADL	Disability			
		Time up and go test	Mobility			
		Subjective mobility disability	Mobility			
Ghatak *et al*, 2012[38]	Modified Fried phenotype	Albumin	Nutrition	Presence of 3 or more criteria	45	22 (48.89)
		Katz ADL	Disability			
		5MWT	Mobility			
		Grip strength	Muscle strength			
Green *et al*, 2015[39]	Modified Fried phenotype	Gait speed	Mobility	Frailty score ≥6	244	110 (45.08)
		Grip strength	Muscle strength			
		Albumin	Nutrition			
		ADL	Disability			
Green *et al*, 2012[40]	Modified Fried phenotype	Gait speed	Mobility	Frailty score ≥5 points	159	76 (47.80)
		Grip strength	Muscle strength			
		Albumin	Nutrition			
		ADL	Disability			
Huded *et al*, 2016[41]	Modified Fried phenotype	Unintentional weight loss	Nutrition	Presence of 3 or more criteria	191	64 (33.51)
		Grip strength	Muscle strength			
		5MWT	Mobility			
		Katz ADL	Disability			
Kobe *et al*, 2016[42]	FORCAST	Chair rise	Muscle strength	≥4 points (score ranges 0–12)	130	71 (54.62)
		Weakness	Muscle strength			
		Stair	Mobility			
		CFS	Subjective			
		Creatinine level	Medical			
Maniar *et al*, 2016[43]	Modified Fried phenotype	Serum albumin	Nutrition	≥6 points (score ranges 0–12)	219	73 (33.3)
		Gait speed	Mobility			
		Grip strength	Muscle strength			
		Katz ADL	Disability			
Okoh *et al*, 2017[44]¶	Modified Fried phenotype	Hand grip strength	Muscle strength	FI ≥3/4	75	30 (40)
		Gait speed	Mobility			
		Serum albumin	Nutrition			
		ADL	Disability			
Patel *et al*, 2016[45]	NA	Gait speed	Mobility	Gait speed ≥6 s or/and albumin <3.5 g/dL	117	31 (26.50)
		Albumin	Nutrition			
Rabinovitz *et al*, 2016[46]	Fried phenotype	Unintentional weight loss	Nutrition	Presence of 3 or more criteria	302	46 (15.23)
		Exhaustion	Exhaustion			

Continued

Table 1 Continued

Studies that used multiple dimensions to assess frailty

Study, year	Name	Measures	Dimensions	Definition	Total N	Frail n (%)
		Weakness	Muscle strength			
		Walk speed	Mobility			
		Low physical activity	Physical activity			
Rodríguez-Pascual *et al*, 2016[47]	Fried phenotype	Unintentional weight loss	Nutrition	Presence of 3 or more criteria	109	68 (62.39)
		Exhaustion	Exhaustion			
		Weakness	Muscle strength			
		Walk speed	Mobility			
		Low physical activity	Physical activity			
Rogers *et al*, 2018[48]	Fried phenotype	Unintentional weight loss	Nutrition	Presence of 3 or more criteria	544	242 (44.49)
		Exhaustion	Exhaustion			
		Weakness	Muscle strength			
		Walk speed	Mobility			
		Low physical activity	Disability			
Schoenenberger *et al*, 2018[49]	NA	MMSE	Cognition	≥3 points (score ranges 0–7)	330	169 (51.21)
		Time up and go	Mobility			
		MNA	Nutrition			
		Basic ADL	Disability			
		Incremental ADL	Disability			
Steinvil *et al*, 2018[50]	NA	BMI	Nutrition	Presence of 3 or more criteria	498	232 (46.59)
		Albumin	Nutrition			
		Katz ADL	Disability			
		Grip strength	Muscle strength			
		Walk test	Mobility			
Shi *et al*, 2018[51]	Fried phenotype	Weight loss	Nutrition	Presence of 3 or more criteria	137	116 (84.67)
		Exhaustion	Exhaustion			
		Minnesota leisure time activity	Physical activity			
		5 m walk test	Mobility			
		Grip strength	Muscle strength			
Skaar *et al*, 2018[52]	Geriatric assessment tool (0–9)	MMSE	Cognition	Scores ≥4	142	34 (23.94)
		Nottingham extended ADL	Disability			
		BMI <20.5	Nutrition			
		Low energy	Exhaustion			
		Weight loss	Nutrition			
		Chair stand	Muscle strength			
		Charlson Comorbidity Index	Comorbidity			
		Hospital anxiety and depression scale	Psychological			
Zajarias *et al*, 2016[53]	Modified Fried phenotype	Albumin	Nutrition	≥6 points (score ranges 0–12)	553	265 (47.92)
		Gait speed	Mobility			
		Grip strength	Muscle strength			
		Katz ADL	Disability			
Goudzwaard, 2020[63]	Erasmus Frailty Score	MMSE	Cognition	Presence of 3 or more criteria	330	97 (29.50)
		Hand grip test	Muscle strength			

Continued

Table 1 Continued

Studies that used multiple dimensions to assess frailty						
Study, year	**Name**	**Measures**	**Dimensions**	**Definition**	**Total N**	**Frail n (%)**
		Malnutrition universal screening tool	Nutrition			
		Katz ADL	Inactivity in basic activities of daily living			
		Lawton and Brody index	Inactivity in instrumental activities of daily living			
Goudzwaard, 2020[64]	Erasmus Frailty Score	MMSE	Cognition	Presence of 3 or more criteria	239	70 (29.3)
		Hand grip test	Muscle strength			
		Malnutrition universal screening tool	Nutrition			
		Katz ADL	Inactivity in basic activities of daily living			
		Lawton and Brody index	Inactivity in instrumental activities of daily living			
Patel, 2020[65]	A composite of two frailty markers	Gait speed	Mobility	Presence of both criteria	407	74 (18.18)
		Serum albumin	Nutrition			
Drudi, 2018[66]	Essential frailty toolset	Muscle weakness	Muscle strength	≥3 scores (out of 5)	723	254 (35.13)
		Cognitive impairment	Cognition			
		Anaemia	Nutrition			
		Hypoalbuminaemia	Nutrition			
Morris, 2020[67]	Essential frailty toolset	Muscle weakness	Muscle strength	≥3 scores (out of 5)	559	234 (41.86)
		Cognitive impairment	Cognition			
		Anaemia	Nutrition			
		Hypoalbuminaemia	Nutrition			

*Alfredsson (2016) and Kiani (2020) enrolled patient populations from the STS/ACC registry. Chauhan (2016), Green (2012), Green (2015), Huded (2016), Okoh (2017), Rogers (2018), Steinvil (2018), Traynor (2017) and Bagienski (2017) enrolled patients from the participating centres of STS/ACC registry.
†Bagienski (2017) and Kleczynski (2017) enrolled patients from the same medical centre but used different frailty definitions.
‡Koifman (2015), Rogers (2018) and Steinvil (2018) enrolled patients from the same medical centre but used different frailty definitions.
§Shimura (2020) and Shimura (2017) enrolled patients from the same registry but used different frailty definitions.
¶Chauhan (2016) and Okoh (2017) enrolled patients from the same medical centre but used different frailty definitions.
ADL, activities of daily living; BMI, body mass index; CFS, Clinical Frailty Scale; CIRS-CI, Cumulative Illness Rating Scale Comorbidity Index; CSHA, Canadian Study of Health and Ageing; ESS, Exton Smith Scale; FI, Frailty Index; FORCAST, Frailty Predicts Death 1 year after Elective Cardiac Surgery Test; GSS, Geriatric Status Scale; IADL, Instrumental Activities of Daily Living; ISAR, Identification of Seniors at Risk; MMSE, Mini-Mental State Examination; MNA-SF, Mini-Nutritional Assessment Short Form; MPI, Multidimensional Prognostic Index; 5MWT, 5 m walk test; NA, not applicable; SMM, skeletal muscle mass; SPMSQ, Short Portable Mental Status Questionnaire; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

(KCCQ). Two studies[65 67] assessed quality of life post-TAVI; both studies found improved quality of life overall. Okoh *et al*[44] assessed quality of life at 30 days following TAVI, and found that at 30 days, frail patients reported worsening in two domains, KCCQ-symptoms and KCCQ physical limitation, but quality of life improved slightly overall. Kobe *et al*[42] assessed quality of life before and 30 days after TAVI using the Short Form-36 questionnaire; they found that at 30-day follow-up, the mean scores of all but role physical and social functioning were significantly lower for frail patients. Goudzwaard *et al*[63] assessed quality of life using the Euro-QoL-5-dimension (EQ-5D) scale; they found that at 12 months follow-up, the mean EQ-5D decreased while the mean EQ-Visual Analogue Scale increased.

Other commonly reported outcomes measuring the prognosis of frail TAVI recipients include procedural acute kidney injury (ranging from 3.95% to 20.51%), conversion to open heart surgery (ranging from 0% to 9.9%), life-threatening bleeding (ranging from 4.86% to 16.7%), major bleeding (ranging from 2.56% to 21.81%), permanent pacemaker implantation (ranging from 2% to 12.82%) and stroke (ranging from 0% to 8.3%). Eight studies[32 33 38 39 41 44 45 56]

Table 2 Results of meta-analysis and GRADE assessment*

Effects					GRADE assessment						
# included study	Frailty measures†	# individuals	# events	Estimate (95% CI)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty
Procedural death											
6	All	9586	654	7.60% (4.41% to 12.79%)	Observational	Not serious	Strongly serious	Strongly serious	Not serious	None	Very low
30-day mortality											
13	All	23 628	1236	7.32% (5.66% to 9.42%)	Observational	Serious	Strongly serious	Strongly serious	Not serious	None	Very low
8	Multi	1352	113	8.58% (7.18% to 10.22%)	Observational	Serious	Serious	Strongly serious	Not serious	None	Very low
3	Modified Fried	407	31	7.86% (5.20% to 11.70%)	Observational	Serious	Not serious	Strongly serious	Serious	None	Very low
Cardiovascular death at 30 days											
2	Single	6453	259	3.37% (1.93% to 5.81%)	Observational	Serious	Serious	Strongly serious	Not serious	None	Very low
6-month mortality											
2	Multi	187	30	16.12% (11.50% to 22.13%)	Observational	Serious	Serious	Strongly serious	Strongly serious	None	Very low
1-year mortality											
10	All	15 471	3151	23.98% (20.71% to 27.58%)	Observational	Serious	Strongly serious	Strongly serious	Not serious	None	Very low
6	Multi	845	191	22.75% (20.03% to 25.71%)	Observational	Serious	Serious	Strongly serious	Serious	None	Very low
2	Fried and modified Fried	223	60	26.91% (21.50% to 33.11%)	Observational	Serious	Serious	Strongly serious	Strongly serious	None	Very low
Survival											
17	All	48 258	NA	1-year survival: 75.6% (75.2% to 76.0%) 2-year survival: 65.0% (63.3% to 66.7%) 3-year survival: 48.7% (43.3% to 54.7%)	Observational	Serious	Strongly serious	Strongly serious	Not serious	None	Very low
4	Fried and modified Fried	484	NA	1-year survival: 73% (68.8% to 77.5%) 2-year survival: 64.5% (56.4% to 73.9%) 3-year survival: 58.9% (49% to 70.9%)	Observational	Serious	Serious	Strongly serious	Strongly serious	None	Very low
Procedural acute kidney injury											

Continued

Table 2 Continued

Effects					GRADE assessment						
# included study	Frailty measures†	# individuals	# events	Estimate (95% CI)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty
4	Single	6548	458	11.34% (6.43% to 19.22%)	Observational	Not serious	Strongly serious	Strongly serious	Not serious	None	Very low
Procedural cardiac tamponade											
3	Single	553	17	3.19% (1.99% to 5.07%)	Observational	Not serious	Serious	Strongly serious	Not serious	None	Very low
Convert to open heart surgery											
2	All	4259	300	2.29% (0.49% to 9.91%)	Observational	Not serious	Strongly serious	Strongly serious	Not serious	None	Very low
Procedural life-threatening bleeding											
5	All	653	63	9.75% (7.69% to 12.29%)	Observational	Not serious	Serious	Strongly serious	Not serious	None	Very low
Procedural major bleeding											
5	Single	830	104	8.53% (3.53% to 19.19%)	Observational	Not serious	Strongly serious	Strongly serious	Not serious	None	Very low
Procedural minor bleeding											
4	Single	774	147	18.34% (10.66% to 29.73%)	Observational	Not serious	Strongly serious	Strongly serious	Serious	None	Very low
Procedural major vascular complications											
3	Single	647	63	10.49% (4.76% to 21.54%)	Observational	Serious	Strongly serious	Strongly serious	Not serious	None	Very low
30-day major vascular complications											
2	All	189	7	2.97% (0.34% to 21.67%)	Observational	Serious	Serious	Strongly serious	Not serious	None	Very low
Procedural minor vascular complications											
2	Single	591	43	7.37% (3.24% to 15.93%)	Observational	Serious	Strongly serious	Strongly serious	Not serious	None	Very low
Procedural major access-site complications											
3	Single	148	15	9.44% (4.04% to 20.51%)	Observational	Serious	Serious	Strongly serious	Strongly serious	None	Very low
Procedural permanent pacemaker											
7	All	3660	365	8.12% (5.79% to 11.26%)	Observational	Serious	Serious	Strongly serious	Not serious	None	Very low
Readmission within 30 days											
3	Multi	248	27	10.37% (3.75% to 25.59%)	Observational	Serious	Strongly serious	Strongly serious	Strongly serious	None	Very low
Procedural stroke											

Continued

Table 2 Continued

Effects					GRADE assessment						
# included study	Frailty measures†	# individuals	# events	Estimate (95% CI)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty
8	All	1756	39	2.94% (1.76% to 4.88%)	Observational	Strongly serious	Serious	Strongly serious	Not serious	None	Very low
Stroke within 30 days											
2	Single	6185	132	2.14% (1.81% to 2.53%)	Observational	Serious	Serious	Strongly serious	Not serious	None	Very low
Transfusion											
3	All	458	191	41.01% (34.02% to 48.39%)	Observational	Serious	Serious	Strongly serious	Strongly serious	None	Very low
2-valve implantation											
2	Single	409	10	2.46% (1.33% to 4.51%)	Observational	Not serious	Serious	Strongly serious	Not serious	None	Very low
Length of hospitalisation											
6	All	308	NA	8.25 (6.62 to 10.27)	Observational	Strongly serious	Strongly serious	Strongly serious	Strongly serious	None	Very low

Single indicates single measures.
Multi indicates multimeasures.
Fried indicates the Fried phenotype.
Modified Fried indicates the modified Fried phenotype.
Fried and modified Fried includes the Fried phenotype and modified Fried phenotype.
All includes all single and multimeasures, including administrative database algorithms.
*Meta-analyses conducted using random-ffects model.
†Frailty measures are categorised as single, multimeasures, administrative data based, Fried, modified Fried and all.
GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

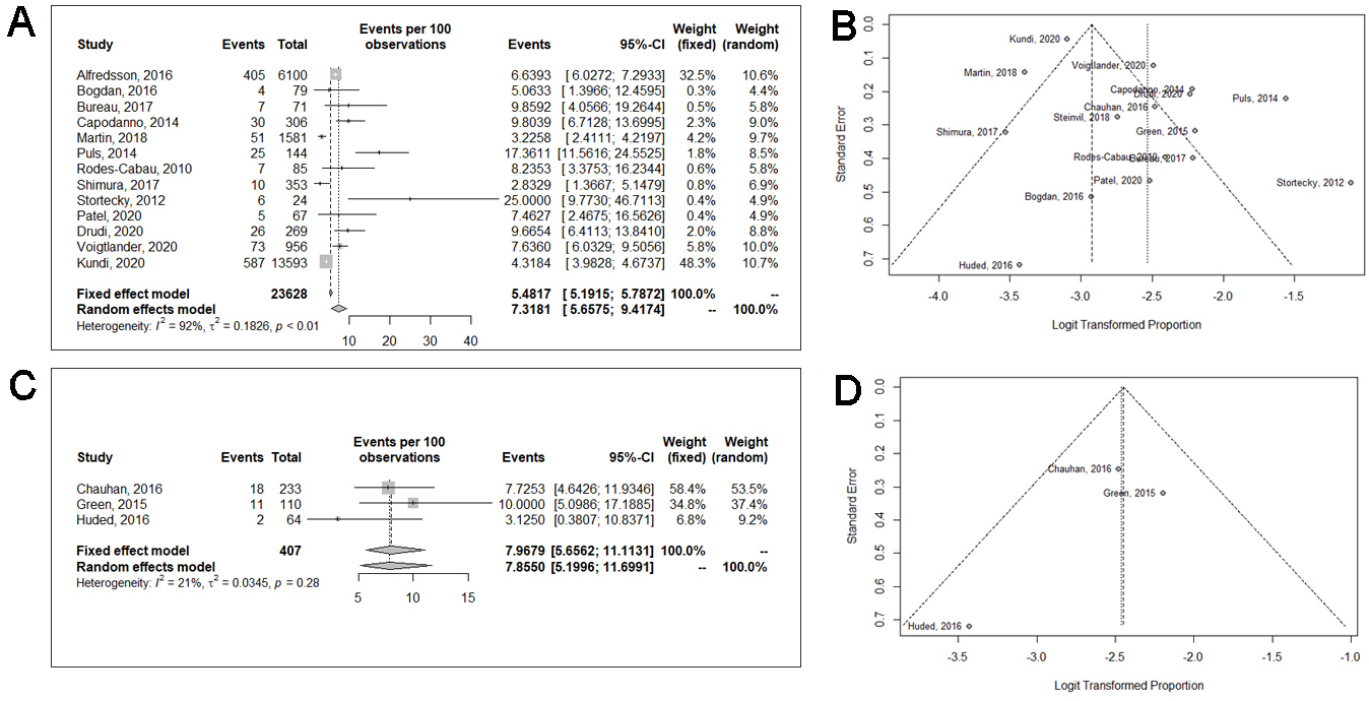

Figure 2 (A) Meta-analysis of 30-day mortality in frail patients after TAVI. Frailty was measured using sing and multidimensional measures, including administrative database algorithms. The squares indicate the 30-day mortality reported by each study. The horizontal lines indicate the magnitude of the CI. The diamond indicates the pooled estimate for 30-day mortality. (B) Funnel plots, using data from all studies that reported 30-day mortality. The y-axis is the SE of the 30-day mortality. The x-axis is the logit of 30-day mortality. (C) Meta-analysis of 30-day mortality in frail patients after TAVI. Frailty was measured using modified Fried frailty phenotype. The squares indicate the 30-day mortality reported by each study. The horizontal lines indicate the magnitude of the CI. The diamond indicates the pooled estimate for 30-day mortality. (D) Funnel plots, using data from studies that frailty was measured using modified Fried frailty phenotype. The y-axis is the SE of the 30-day mortality. The x-axis is the logit of 30-day mortality. CI, confidence interval; SE, standard error; TAVI, transcatheter aortic valve implantation.

reported the mean length of hospitalisation, ranging from 5 days to 12.1 days.

GRADE assessment

The GRADE certainty assessment per outcome, together with the pooled effects, is provided in table 2. Due to inconsistency as influenced by heterogeneity of estimates and indirectness of frailty measures as influenced by lack of homogeneity across the TAVI populations, confidence in the overall estimates was very low.

DISCUSSION

Principal findings

We found that multidimensional measures are more commonly used than single-dimension measures. Even with the same frailty measure, different definitions or cut-offs were used. The most frequently used frailty measure in the studies we identified was the modified Fried phenotype, in which disability, muscle strength, mobility and nutrition were assessed. Approaches to modifying the Fried phenotype included measuring fewer domains, using different cut-offs or using different tools to assess the same domain.

Greater heterogeneity of meta-analyses that included single measures suggests single measures did not measure the same frailty construct and did not reliably measure frailty. Single measures included a mix of biological variables (albumin and BMI) or single performance measures (gait speed or activities of daily living), which address only a single component of the frailty construct. Thus, our study suggests that frailty is a multidimensional phenomenon that cannot be captured by a single construct.

The variety of frailty definitions and the diversity of TAVI populations in the studies contribute to the wide range and substantial heterogeneity of patient outcomes after TAVI.

Using GRADE to assess confidence in prognosis estimates from the meta-analyses, we found very low confidence in the overall estimates, mainly due to inconsistency as influenced by heterogeneity of estimates and indirectness of frailty measures as influenced by lack of homogeneity across the TAVI populations identified in the studies.

Comparison with other studies

Previous studies demonstrated that the assessment of frailty significantly enhances prediction of mortality after TAVI when combined with the European system for cardiac operative risk evaluation (EuroSCORE) or the Society of Thoracic Surgeons (STS) score.[49] There

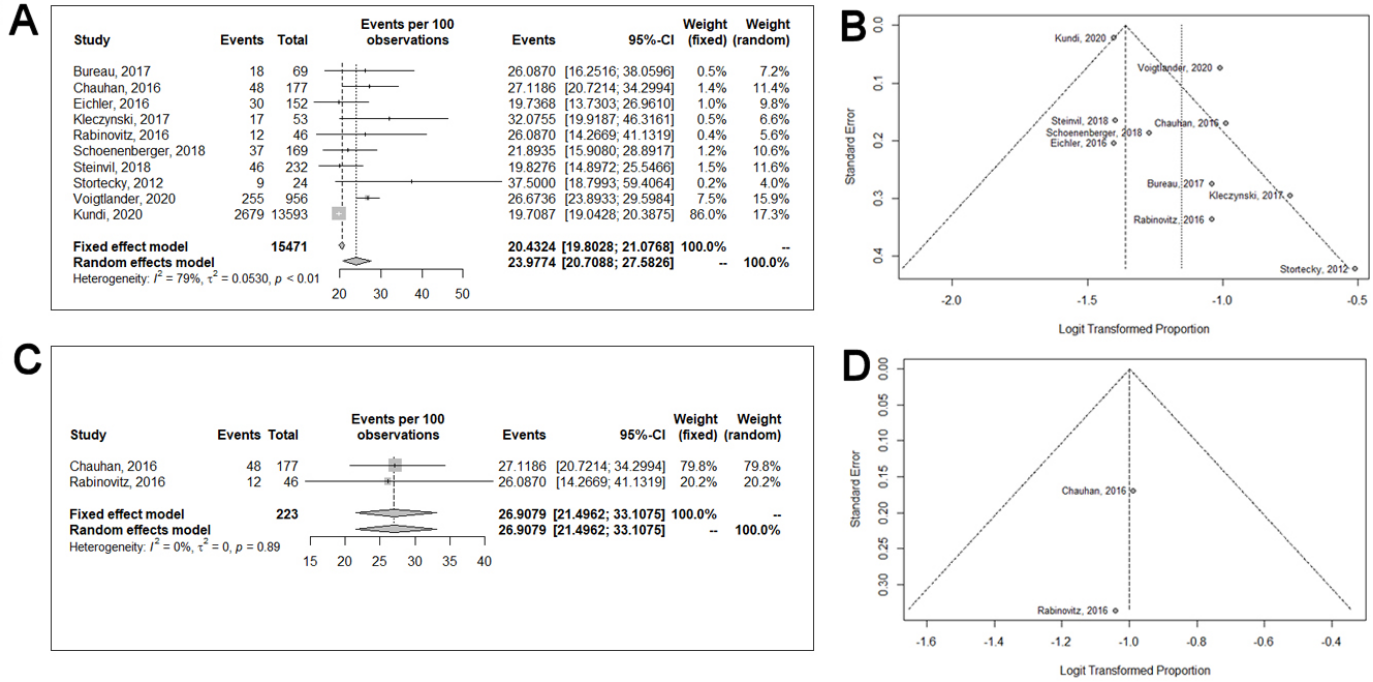

Figure 3 (A) Meta-analysis of 1-year mortality in frail patients after TAVI. Frailty was measured using single and multidimensional measures, including administrative database algorithms. The squares indicate the 1-year mortality reported by each study. The horizontal lines indicate the magnitude of the CI. The diamond indicates the pooled estimate for 1-year mortality. (B) Funnel plots, using data from all studies that reported 30-day mortality. The y-axis is the SE of the 1-year mortality. The x-axis is the logit of 1-year mortality. (C) Meta-analysis of 1-year mortality in frail patients after TAVI. Frailty was measured using the Fried frailty phenotype. The squares indicate the 1-year mortality reported by each study. The horizontal lines indicate the magnitude of the CI. The diamond indicates the pooled estimate for 1-year mortality. (D) Funnel plots, using data from studies that frailty was measured using modified Fried frailty phenotype. The y-axis is the SE of the 1-year mortality. The x-axis is the logit of 1-year mortality. CI, confidence interval; SE, standard error; TAVI, transcatheter aortic valve implantation.

have been several studies reviewing frailty in cardiac surgical populations. Kim *et al*[5] conducted a systematic review of frailty instruments in older adults undergoing cardiac surgical procedures. Kim *et al*[5] found high-quality evidence that used mobility assessment as a single frailty measure and found mobility to be the most frequently assessed domain. Sepehri *et al*[68] performed a systematic review to demonstrate the association of frailty with negative postoperative outcomes in patients undergoing cardiac surgery. Our study adds to the existing literature as we investigate the frequency of adverse outcomes and pool estimates of survival after TAVI in frail patients from multiple studies.

The FRAILTY-AVR study[69] examined the validity of frailty measures in predicting mortality among TAVI recipients. The study added value to the literature by selecting frailty elements with the greatest predictive value, finding that the Essential Frailty Toolset (EFT) consisting of chair rise, cognition measured by the Mini-Mental State Examination, haemoglobin and serum albumin, performed best for predicting 1-year mortality.[69] Due to the focus on predictive validity, the FRAILTY-AVR study[69] did not report outcomes separately for frail patients. As a result, the study[69] did not meet the inclusion criteria for our systematic review, which was focused on prognostic information among frail patients only. The FRAILTY-AVR study[69] makes important efforts to define a standard frailty assessment tool. Although the Fried and modified Fried were the most commonly used instruments among studies included in our meta-analysis, the FRAILTY-AVR showed the Fried did not perform as well as the EFT in predicting mortality among TAVI patients.[69] We suggest the use of a standard measure, such as the EFT, can enhance the quality of frailty research in the TAVI patient population. We also recognise that use of a standard frailty measure is unlikely as researchers and clinicians may value use of diverse measures which reflect different aspects of frailty. If the EFT emerges as a standard, it may be used by clinicians to exclude frail patients from treatment, due to concerns about increased mortality. This would limit the opportunity to better understand the prognosis of frail patients undergoing TAVI, which was the primary goal of our study.

Strengths and limitations

This review has several unique strengths. We performed a comprehensive literature search to identify both published and unpublished studies, in addition to searching citations from previous reviews. We included prognostic data from randomised controlled trials and observational studies. Using the QUIPS tool, two reviewers independently assessed the risk of bias, and the use of the GRADE system to assess the certainty of evidence offers a structured and transparent evaluation of

our findings. We systematically reviewed the operationalisation of frailty assessment in TAVI patients, and pooled clinical outcomes of frail TAVI recipients. We tested for heterogeneity and attempted to address heterogeneity by performing sensitivity analysis and subgroup analysis.

This review has some important limitations. Given the limited data reported by the included studies, we were unable to perform meta-regression to further investigate the potential sources of heterogeneity and to determine the influence of mean age on outcomes. We, therefore, explored the causes and types of heterogeneity relying on the investigation of the I^2 statistic, which may be imprecise when the number of studies is small.[70] When extracting data, we encountered several studies that applied multiple frailty instruments in the same patient group, and in this situation, we only extracted data from the most commonly used frailty instrument, and this may introduce selection bias. Some studies defined an intermediate 'prefrail' group, but we did not find sufficient data to synthesise outcomes for this important sub-group. Though less vulnerable than the frail group, prefrail patients may be at higher risk than robust patients for experiencing adverse outcomes.[71 72] Individual-patient level data were not available, precluding adjustment for any study level differences in clinical or procedural variables that may have influenced prognosis across the cohorts. Therefore, clinical heterogeneity could not be ruled out and along with high levels of heterogeneity, resulted in lower GRADE evaluations. The aim of this study was to characterise prognosis for frail patients undergoing TAVI, therefore, we did not directly compare prognosis to other groups of patients or to frail patients undergoing different therapies, nor were we able to determine which frailty measures perform best as prognostic tools for TAVI recipients.

Implications

When selecting candidates to undergo TAVI, several multivariate risk scores have been widely used to estimate operative mortality based on patient characteristics. The STS score and the EuroSCORE are the most commonly used scoring systems.[73 74] However, a disadvantage of both scores is that the main variables for scoring perioperative risk are medical diagnoses and comorbidities, which may not reflect the true 'biological status' of the patient.[73 74] When considering valve procedures for patients, clinical practice guidelines recommend assessing frailty as one component of risk.[5 7] Although a large number of frailty measures exist, there is currently little consensus on the optimal approach to assessing frailty in patients undergoing TAVI.[2] Frailty has consistently been shown to significantly predict mortality[68] and postoperative delirium,[75] even after controlling for other risk factors, suggesting that use of any frailty assessment is better than none when selecting patients for TAVI. Systematically reviewing the operationalisation of frailty assessment in TAVI patients and pooling clinical outcomes of frail TAVI recipients will help better understand how frailty is assessed among TAVI patients, provide information on the prognosis of frail patients after TAVI, and can ultimately improve decisions related to treatment of AS.

To help achieve consensus on frailty measures to be applied in TAVI recipients, future studies should evaluate the prognostic value of frailty measures in TAVI recipients and determine the additional prognostic value of frailty measurement in addition to these established risk scores. Future studies should also compare prognosis of frail patients undergoing TAVI to frail patients undergoing surgical intervention or medical therapy. Few studies reported quality of life measures. In order to address the gaps in the literature future studies should measure quality of life before and after TAVI with use of standardised quality of life measurement tools such as the Short-Form 36.

CONCLUSION

In conclusion, frailty instruments for TAVI recipients varied across studies, leading to a range of frailty prevalence estimates and substantial heterogeneity. The results of this systematic review provide clinicians, patients and healthcare administrators, with potentially useful evidence on the prognosis of frail patients.

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