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. Metanalyses 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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INTRODUCTION

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

Frailty is a biological syndrome characterised by an increased vulnerability to stressors. 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. Clinical research has identified frailty as an important risk factor for mortality and morbidity following TAVI. Health economics research has shown that compared with non-frail patients, frail older adults undergoing cardiac surgery incurred substantially higher hospitalisation costs. 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.
When considering valve procedures, clinical practice guidelines recommend assessing frailty as one component of risk. 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. 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 and follows the Meta-analysis Of Observational Studies in Epidemiology guidelines.

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. 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. 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. 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.

For adverse clinical outcomes, we pooled proportions using the inverse-variance weighted DerSimonian and Laird model and incorporated the Freeman-Tukey double arcsine transformation. 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. For the length of hospitalisation, we pooled the values, estimating the mean and SD using the random effects model for continuous variables. 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. 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. 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 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 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
Table summarises frailty assessment in patients undergoing TAVI. Twenty-one studies used single-dimension measures, 3 studies used administrative data-based measures and 25 studies used multi-dimensional 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 used albumin to assess frailty, two defined frailty as albumin level below 4 g/dL, and two defined 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 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 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 assessed frailty based on the accumulated deficits frailty index. Of the 25 studies reporting multidimensional measures, four used the original Fried frailty phenotype and eight 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, reporting the modified Fried frailty phenotype, measures used to assess mobility and disability were identical. Measures used to assess nutrition were different; seven studies measured serum albumin and one study measured weight loss.

**Prognosis of frail TAVI recipients**

Online supplemental appendix D summarises prognosis of frail TAVI recipients reported for each study. Twenty studies 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 that used the Fried or modified Fried frailty phenotype, we estimated a 30-day mortality of 7.86% (5.20% to 11.70%, table 2, figure 2). Fifteen studies 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 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).

Fifteen studies 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 E.

Seventeen studies 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 E.

Five studies measured health-related quality of life (online supplemental appendix G). Three studies 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† | Gait speed (5 m) | Mobility | <0.83 m/s or >6 s | 8039 | 6100 (75.88%) |
| Bagienski et al, 2017‡† | Katz ADL | Disability | <6 points | 141 | 127 (90.07%) |
| Bogdan et al, 2018†† | Albumin | Nutrition | ≤4 g/dL | 150 | 79 (52.67%) |
| Cockburn et al, 2015‡‡ | Brighton Mobility Index | Mobility | Poor mobility | 312 | 65 (20.83%) |
| Grossman et al, 2017‡‡ | Albumin | Nutrition | <4 g/dL | 426 | 192 (45.07%) |
| Kolfman et al, 2015‡‡ †| Albumin | Nutrition | <3.5 g/dL | 476 | 238 (50%) |
| Kleczynski et al, 2013‡‡ | ISAR | Unclear | ≥2 points | 101 | 53 (52.48%) |
| Mok et al, 2016§ | 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§§ | CSHA score (1–7) | Physical function | Scores 5–7 | 2624 | 1043 (39.75%) |
| Puls et al, 2014¶ | Katz ADL | Disability | <6 points | 300 | 144 (48%) |
| Rodés-cabau et al, 2010¶¶ | Clinical judgement | Subjective | Unclear | 339 | 85 (25.07%) |
| Stortecky et al, 2012¶¶ | BMI | Nutrition | <20 kg/m² | 256 | 24 (9.38%) |
| Shimura et al, 2017‡‡ †§ | CFS | Subjective | ≥5 points (score ranges 0–9) | 1215 | 353 (29.05%) |
| Traynor et al, 2017‡‡ | Assisted care | Unclear | Need assisted care | 597 | 60 (10.05%) |
| Yamamoto et al, 2015¶§ | BMI | Nutrition | <20 kg/m² | 777 | 56 (7.21%) |
| Welle et al, 2014‡ | Gait speed (5 m) | Mobility | ≥6 s | 723 | 483 (66.8%) |
| Mach et al, 2020¶¶ | Fitness-tracker assisted frailty score | Unclear | ≥1 point | 50 | 39 (78%) |
| Kiani et al, 2020¶¶ †| Gait speed (5 m) | Mobility | <0.83 m/s or >6 s (including unable to perform the test) | 56500 | 11316 (20.03%) |
| Gharibeh et al, 2019¶¶ | Clinical judgement | Subjective | Indicators for limited self-dependence | 461 | 186 (40.35%) |
| Voigtlander et al, 2020¶¶ | BMI | Nutrition | <20 kg/m² | 16865 | 956 (5.67%) |
| Shimura et al, 2020¶¶ †§ | 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¶¶ | Hospital Frailty Risk Score | Hospital Frailty Risk Score ≥5 points | 20504 | 8419 (41.06%) |
| Sami et al, 2020¶¶ | Johns-Hopkins Adjusted Clinical Groups frailty indicator | A dichotomous indicator defined based on 10 clusters of frailty-defining diagnoses | 51685 | 2865 (5.54%) |
| Kundi et al, 2019¶¶ | Hospital Frailty Risk Score | Hospital Frailty Risk Score ≥5 points | 28531 | 13593 (47.64%) |

#### Studies that used multiple dimensions to assess frailty

| Study, year | Name | Measures | Dimensions | Definition | Total N | Frail n (%) |
|-------------|------|----------|------------|------------|---------|-------------|
| Bureau, 2017¶¶ | Multidimensional 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) |

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

Continued
### Studies that used multiple dimensions to assess frailty

| Study, year | Name | Measures | Dimensions | Definition | Total N | Frail n (%) |
|-------------|------|----------|------------|------------|---------|-------------|
| **Rodríguez-Pascual et al, 2016**<sup>12</sup> | 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**<sup>15</sup> | 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**<sup>18</sup> | 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**<sup>50</sup> | 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**<sup>51</sup> | Fried phenotype | Weight loss | Nutrition | Presence of 3 or more criteria | 137 | 116 (84.67) |
| | | Exhaustion | Exhaustion | | | |
| | | Minnesota leisure time activity | Physical activity | | | |
| | | 5m walk test | Mobility | | | |
| | | Grip strength | Muscle strength | | | |
| | | | | | | |
| **Skaar et al, 2018**<sup>52</sup> | 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**<sup>53</sup> | 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**<sup>53</sup> | Erasmus Frailty Score | MMSE | Cognition | Presence of 3 or more criteria | 330 | 97 (29.50) |
| | | Hand grip test | Muscle strength | | | |

*Table 1 Continued*
Studies that used multiple dimensions to assess frailty

| Study, year | Name | Measures | Dimensions | Definition | Total N | Frail n (%) |
|------------|------|----------|------------|------------|---------|-------------|
| Goudzwaard, 2020 | 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 | A composite of two frailty markers | Gait speed | Mobility | Presence of both criteria | 407 | 74 (18.18) |
| | | Serum albumin | Nutrition | | | |
| Drudi, 2018 | 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 | Essential frailty toolset | Muscle weakness | Muscle strength | ≥3 scores (out of 5) | 559 | 234 (41.86) |
| | | Cognitive impairment | Cognition | | | |
| | | Anaemia | Nutrition | | | |
| | | Hypoalbuminaemia | Nutrition | | | |

KCCQ) Two studies assessed quality of life post-TAVI; both studies found improved quality of life overall. Okoh et al 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 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 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 on March 12, 2021 by guest. Protected by copyright.
## Table 2  Results of meta-analysis and GRADE assessment

| Effects                              | # included study | Frailty measures† | # individuals | # events | Estimate (95%CI) | GRADE assessment | 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     | Strongly serious | Not serious    | None         | Very low             |            |
| 3                                   | Modified Fried   | 407               | 31            |          | 7.86% (5.20% to 11.70%) | Observational | 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     | Strongly serious | Not serious | None         | Very low             |            |
| **6-month mortality**                |                  |                   |               |          |                 |                   |               |              |               |              |             |                      |            |
| 2                                   | Multi            | 187               | 30            |          | 16.12% (11.50% to 22.13%) | Observational | Serious     | Strongly 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 | Not serious | None         | Very low             |            |
| 6                                   | Multi            | 845               | 191           |          | 22.75% (20.03% to 25.71%) | Observational | Serious     | Strongly serious | Serious | None         | Very low             |            |
| 2                                   | Fried and modified Fried | 223 | 60 | 26.91% (21.50% to 33.11%)) | Observational | Serious | Strongly serious | Strongly serious | Strongly serious | None | Very low             |            |
| **Survival**                         |                  |                   |               |          |                 |                   |               |              |               |              |             |                      |            |
| 17                                  | All              | 48 258            | NA            |          | 1-year survival: 75.6% (75.2% to 76.0%) | Observational | Serious | Strongly serious | Strongly serious | Not serious | None                 | Very low   |
|                                      |                  |                   |               |          | 2-year survival: 65.0% (63.3% to 66.7%) |                   |               |              |               |              |             |                      |            |
|                                      |                  |                   |               |          | 3-year survival: 48.7% (43.3% to 54.7%) |                   |               |              |               |              |             |                      |            |
| 4                                   | Fried and modified Fried | 484 | NA | 1-year survival: 73% (68.8% to 77.5%) | Observational | Serious | Strongly serious | Strongly serious | Strongly serious | None | Very low             |            |
|                                      |                  |                   |               |          | 2-year survival: 64.5% (56.4% to 73.9%) |                   |               |              |               |              |             |                      |            |
|                                      |                  |                   |               |          | 3-year survival: 58.9% (49% to 70.9%) |                   |               |              |               |              |             |                      |            |

Continued
| Effects                                      | Grading procedure | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Certainty |
|---------------------------------------------|-------------------|--------------|--------------|---------------|--------------|-------------|----------------------|-----------|
| Procedural cardiac tamponade               |                   | Observational| Not serious  | Strongly serious | Strongly serious | Not serious | None                  | Very low  |
| Convert to open heart surgery              |                   | Observational| Not serious  | Serious        | Strongly serious | Not serious | None                  | Very low  |
| Procedural life-threatening bleeding        |                   | Observational| Not serious  | Serious        | Strongly serious | Not serious | None                  | Very low  |
| Procedural major bleeding                  |                   | Observational| Not serious  | Strongly serious | Strongly serious | Not serious | None                  | Very low  |
| Procedural minor bleeding                  |                   | Observational| Not serious  | Strongly serious | Strongly serious | Not serious | None                  | Very low  |
| Procedural major vascular complications    |                   | Observational| Serious      | Strongly serious | Strongly serious | Not serious | None                  | Very low  |
| 30-day major vascular complications       |                   | Observational| Serious      | Strongly serious | Strongly serious | Not serious | None                  | Very low  |
| Procedural minor vascular complications    |                   | Observational| Serious      | Strongly serious | Strongly serious | Not serious | None                  | Very low  |
| Procedural major access-site complications |                   | Observational| Serious      | Strongly serious | Strongly serious | Not serious | None                  | Very low  |
| Procedural permanent pacemaker             |                   | Observational| Serious      | Strongly serious | Strongly serious | Not serious | None                  | Very low  |
| Readmission within 30 days                 |                   | Observational| Serious      | Strongly serious | Strongly serious | Not serious | None                  | Very low  |
| Procedural stroke                          |                   | Observational| Serious      | Strongly serious | Strongly serious | Not serious | None                  | Very low  |
### Table 2  Continued

| Effects                                      |  # included study | # individuals | # events | Estimate (95% CI)          | Study design | Risk of bias  | Inconsistency | Indirectness | Imprecision | Other considerations | Certainty |
|----------------------------------------------|-------------------|---------------|----------|---------------------------|--------------|---------------|---------------|--------------|--------------|----------------------|-----------|
| Frailty measures†                            |                   |               |          |                           |              |               |               |              |              |                      |           |
| 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 indicates the Fried phenotype and modified Fried phenotype.
All includes all single and multimeasures, including administrative database algorithms.
Meta-analyses conducted using random-effects model.
†Frailty measures are categorised as single, multimeasures, administrative data based, Fried, modified Fried and all.
GRADE, Grading of Recommendations, Assessment, Development and Evaluation.
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.19 There
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

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**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.
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 I² statistic, which may be imprecise when the number of studies is small. 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. 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. 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. When considering valve procedures for patients, clinical practice guidelines recommend assessing frailty as one component of risk. Although a large number of frailty measures exist, there is currently little consensus on the optimal approach to assessing frailty in patients undergoing TAVI. Frailty has consistently been shown to significantly predict mortality, and postoperative delirium, 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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