openheart

Clinical Frailty Scale as a predictor of adverse outcomes following aortic valve replacement: a systematic review and meta-analysis

Tadhg Prendiville ,[1] Aoife Leahy,[2] Ahmed Gabr,[2] Fayeza Ahmad,[3] Jonathan Afilalo,[3] Glen Philip Martin ,[4] Mamas Mamas ,[5] Ivan P Casserly,[6] Abdirahman Mohamed,[2] Anastasia Saleh,[2] Elaine Shanahan,[2] Margaret O'Connor,[2] Rose Galvin[7]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/openhrt-2023-002354).

To cite: Prendiville T, Leahy A, Gabr A, *et al*. Clinical Frailty Scale as a predictor of adverse outcomes following aortic valve replacement: a systematic review and meta-analysis. *Open Heart* 2023;**10**:e002354. doi:10.1136/openhrt-2023-002354

Received 24 April 2023
Accepted 3 July 2023

For numbered affiliations see end of article.

Correspondence to
Dr Tadhg Prendiville; prendivilletadhg@gmail.com

ABSTRACT

Objectives Assessment of frailty prior to aortic valve intervention is recommended in European and North American valvular heart disease guidelines. However, there is a lack of consensus on how it is best measured. The Clinical Frailty Scale (CFS) is a well-validated measure of frailty that is relatively quick to calculate. This meta-analysis sought to examine whether the CFS predicts mortality and morbidity following either transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR).

Methods Nine electronic databases were searched systematically for data on clinical outcomes post-TAVI/SAVR, where patients had undergone preoperative frailty assessment using the CFS. The primary endpoint was 12-month mortality. TAVI and SAVR data were assessed and reported separately. For each individual study, the incidence of adverse outcomes was extracted according to a CFS score of 5–9 (ie, frail) versus 1–4 (ie, non-frail), with meta-analysis performed using a random effects model.

Results Of 2612 records screened, nine were included in the review (five TAVI, three SAVR and one which included both interventions). Among 4923 TAVI patients, meta-analysis showed 12-month mortality rates of 19.1% for the frail cohort versus 9.8% for the non-frail cohort (RR 2.53 (1.63 to 3.95), p<0.001, I^2=83%). For the smaller cohort of SAVR patients (n=454), mortality rates were 20.3% versus 3.9% for the frail and non-frail cohorts, respectively (RR 5.08 (2.31 to 11.15), p<0.001, I^2=5%).

Conclusions Frailty, as determined by the CFS, was associated with an increased mortality risk in the 12 months following either TAVI or SAVR. These data would support its use in the preoperative assessment of elderly patients undergoing aortic valve interventions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Frailty is associated with increased mortality after aortic valve replacement. There is a lack of consensus surrounding which measure of frailty is most suitable in this setting.

WHAT THIS STUDY ADDS

⇒ The Clinical Frailty Scale is predictive of increased mortality in the first 12 months following transcatheter or open aortic valve replacement.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This data supports the use of the Clinical Frailty Scale to aid in preoperative risk stratification of patients with aortic stenosis.

INTRODUCTION

Frailty has been recognised as an important preoperative determinant of outcomes following aortic valve replacement (AVR), described as 'perhaps the most important patient characteristic not included in current risk models' by the Valve Academic Research Consortium (VARC).[1] The development of transcatheter aortic valve implantation (TAVI) has extended the suitability of aortic valve intervention to patients who would have been deemed unsuitable for traditional surgical aortic valve replacement (SAVR), many of whom would be considered frail. TAVI registry data show up to 60% of valve recipients have at least one marker of frailty, which is associated with increased mortality.[2 3]

The performance of traditional mortality risk estimation scores has been suboptimal, including newer registry-based scores which showed only moderate discrimination when externally validated.[4 5] There is the potential for risk estimation to be improved with the addition of dedicated frailty scoring. Furthermore, recent European and North American valvular heart disease guidelines recommend an assessment of frailty to inform the Heart Team discussion regarding fitness for an aortic valve procedure.[6 7] There is, however, a lack of consensus as to which measure of frailty is most suitable in this context.

The Rockwood Clinical Frailty Scale (CFS) is a commonly used frailty screening instrument which has been validated across several different hospital settings.[8 9] This semiquantitative tool relies on an assessment of mobility and independence derived from a brief history and physical examination, following which a patient is allocated a score of 1–9. Frailty is diagnosed with a score of 5 or greater. The principal advantage of the CFS is that it is quick and easy to calculate compared with other frailty measures,[10] which might make it more applicable in clinical practice.

We sought to examine the association of frailty (as determined by the CFS) with adverse outcomes following either TAVI or SAVR.

METHODS

The protocol for this study has been reported previously.[11] Our study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[12] and is registered with the PROSPERO database for systematic reviews (registration number CRD42020213757).

Search strategy, study eligibility and data extraction

We conducted a systematic search of nine electronic databases (Ovid, PubMed, CINAHL, PsycINFO, Web of Science, Cochrane Library, WHOLIS Virtual Health Library, Science Direct and SCOPUS) from January 2005 to December 2021 using a pre-specified search strategy (online supplemental file 1). Studies which reported complication rates following TAVI or SAVR were included if a preoperative assessment of frailty using the CFS was performed. Eligibility for inclusion was assessed independently by two reviewers (TP and MOC), with disagreements resolved by a third reviewer (RG). A data extraction form was then compiled for eligible studies, comprising details regarding study type, year of publication, procedure type and which clinician had performed the frailty assessment, together with baseline and clinical characteristics of their patient cohorts. Authors were contacted if additional data not published in their original peer-reviewed article were required, with these data also included in the results.

Primary and secondary outcomes

Our primary endpoint was all-cause mortality at 12 months following either TAVI or SAVR. Several secondary endpoints were assessed also, including 30-day mortality, 6-month mortality, stroke, acute kidney injury (AKI), bleeding rates and the composite outcome of early safety at 30 days (as defined by the VARC).[1] The full list of secondary endpoints is described in table 1.

Table 1 Secondary endpoints

Procedure	Endpoint
TAVI	In-hospital mortality
	30-day mortality
	3-month mortality
	6-month mortality
	Early safety[1]
	Coronary obstruction
	Myocardial infarction
	Stroke
	Acute kidney injury
	Major vascular complications[1]
	Minor vascular complications[1]
	Life-threatening bleeding[1]
	Major bleeding[1]
	Minor bleeding[1]
	Two-valve implantation
	Permanent pacemaker requirement
	Cardiac tamponade
	Conversion to open surgery
SAVR	In-hospital mortality
	30-day mortality
	6-month mortality
	Myocardial infarction
	Stroke
	Acute kidney injury
	Permanent pacemaker requirement
	Cardiac tamponade

SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Statistical analysis

Patients were dichotomised into frail (CFS ≥5) and non-frail (CFS <5) cohorts, with the incidence of adverse outcomes compared between the two groups. Outcome data were plotted on forest plots to calculate unadjusted pooled relative risk ratios with 95% CIs, with meta-analyses conducted using inverse variance and a random effects model to account for between-study heterogeneity. The presence of heterogeneity was determined by a large χ^2 result relative to its degree of freedom (df), together with a low p value for heterogeneity. The I^2 statistic was also reported, to denote the percentage of variability observed that was due to between-study heterogeneity. Post hoc subgroup analysis was used to investigate sources of heterogeneity. Statistical significance was set at a p value of ≤0.05. All analyses were performed using Review Manager V.5.4.1.

Study quality and certainty of evidence

Methodological quality was assessed using the Quality of Diagnostic Accuracy Studies-2 method, with each included study graded on its applicability and risk of selection, outcome or attrition bias.[13] Judgements on methodological quality were made by two reviewers independently

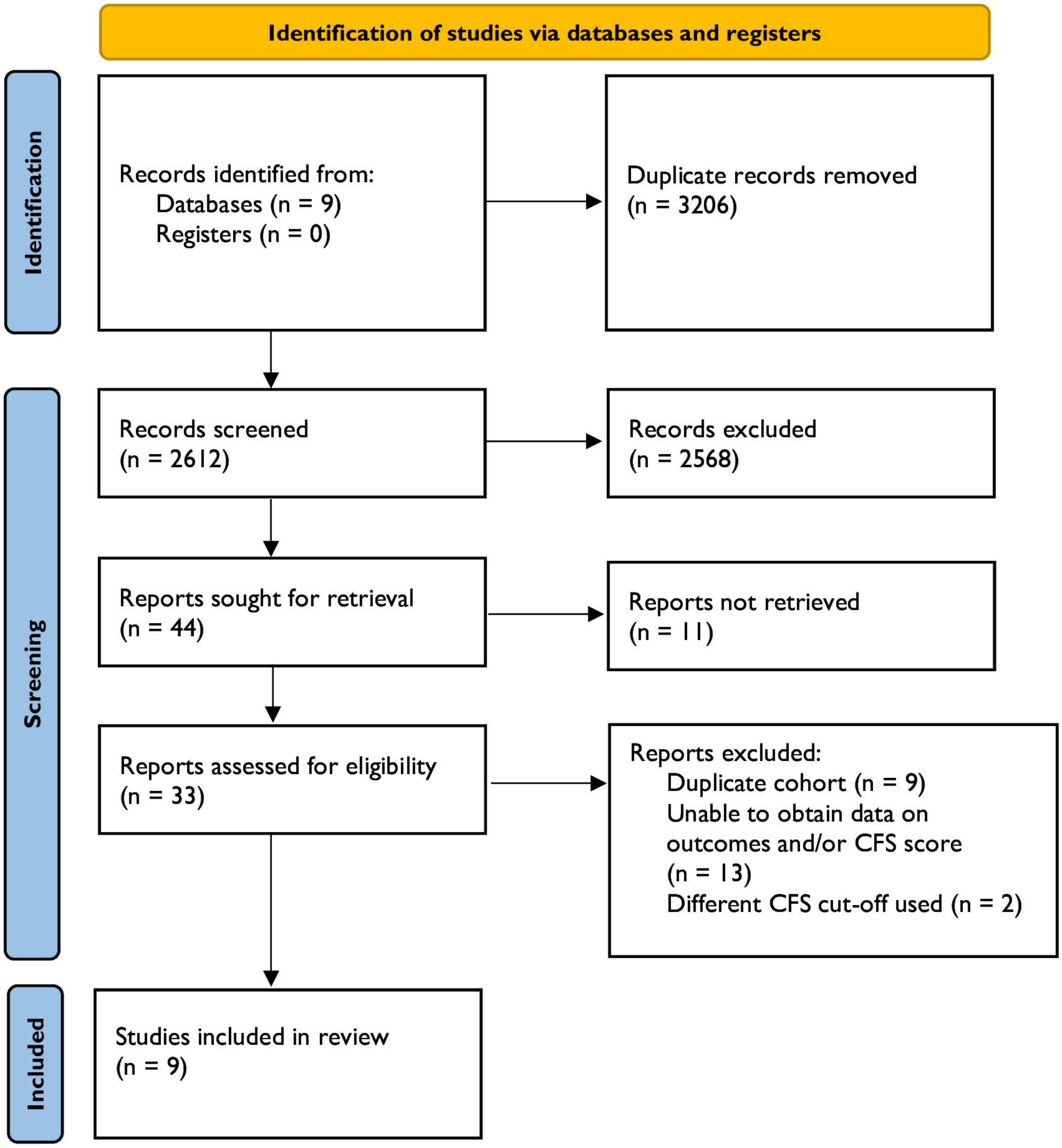

Figure 1 PRISMA flow diagram of study inclusion. CFS, Clinical Frailty Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(TP and MOC), with disagreements resolved by discussion with a third reviewer (RG). The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was used to determine overall confidence in our findings, with each endpoint assessed for inconsistency, indirectness, imprecision and risk of bias.[14]

Patient and public involvement

Patients and the general public were not involved in the design, conduct or reporting of our meta-analysis but will be involved in the dissemination of our results, and will help to inform the discussion surrounding our findings.

RESULTS

Characteristics of included studies

Our search identified 2612 records once duplicates were removed. After reviewing 33 full-text papers, nine were included in the review (figure 1). Characteristics of included studies are detailed in table 2. TAVI outcomes were reported in six studies with SAVR outcomes reported in four studies (a study by Afilalo *et al*[15] reported on both interventions). There was an equal gender balance among TAVI participants (50.8% women), with mean or median age of 81–85 reported across the six included studies. Valve interventions were performed between 2008 and 2019, with transfemoral access in 82.2% of cases. Mean/median Society of Thoracic Surgeons (STS) mortality risk scores ranged from 3.6% to 12.0%. There was significant (>10%) loss to follow-up in two TAVI studies at 12 months. A subset of patients from the Cockburn study[16] was also included in that by Martin *et al*,[2] therefore where an outcome was reported in both studies, this subset was excluded from the Cockburn data.

Table 2 Data extraction form

Author	Year	Procedure	Study type	Patient cohort	Sample size, n	Male gender, %	Age, years*	EF, %*	TF-TAVI, %	STS-PROM, %*	CFS screening clinician	Lost to follow-up at 1 year, n (%)
Afilalo *et al*[15]	2017	TAVI/SAVR	Prospective cohort, multicentre	Symptomatic AS USA/Canada/ France	845 (646 TAVI, 199 isolated SAVR)	58.7	82 (77–86)	60 (50–65)	77.2	4.3 (2.7–6.8) TAVI 5.4 (3.6–8.1) SAVR 2.4 (1.7–3.7)	Trained research assistants	TAVI: 53 (8.2) SAVR: 0
Cockburn *et al*[16]	2015	TAVI	Prospective cohort, single centre	90.7% AS 6.3% AR 3.2% mixed Brighton, UK	312	53.2	81.2±7	NR	88.1	4.6±2.8	Determined at heart team meeting	6 (1.9)
Kleczynski *et al*[21]	2017	TAVI	Prospective cohort, single centre	Symptomatic severe AS Krakow, Poland	101	39.6	81 (76–84)	60.0 (47.5–65.0)	77.2	12.0 (4.0–24.0)	NR	0
Martin *et al*[2]	2018	TAVI	Prospective cohort, multicentre	TAVIs performed in England/Wales 2013–2014 (data from UK TAVI registry)	2624	54.6	81.2±7.58	948 patients (36.1%) with EF <50%	81.1	4.95±4.29	Cardiologist	0
Quine *et al*[19]	2020	TAVI	Prospective cohort, multicentre	Symptomatic severe AS Melbourne, Australia	633	53.9	82.7	Normal BMI 56.8±11.7 Overweight 57.4±11.1 Obese 57.8±10.2	94.5	3.6 (2.7–5.6)	Cardiologist or TAVI research nurse	288 (45.5)
Shimura *et al*[20]	2017	TAVI	Prospective cohort, multicentre	Symptomatic severe AS OCEAN registry, Japan	1215	29.7	CFS 1–3 83.8±5.08 CFS 4 84.5±4.98 CFS 5 85.1±4.62 CFS 6 85.4±4.59 CFS ≥7 850.1±5.73	CFS 1–3 62.0±12.9 CFS 4 62.7±11.7 CFS 5 61.9±14.5 CFS 6 60.8±13.9 CFS ≥7 590.2±12.8	79.8	CFS 1–3 7.37 (4.2–8.6) CFS 4 7.84 (4.79–9.22) CFS 5 10.3 (5.48–11.1) CFS 6 10.4 (5.56–11.1) CFS ≥7 110.7 (6.0–15.1)	Trained medical professional (as per CSHA criteria)	186 (15.3)
Lytwyn *et al*[36]	2017	SAVR	Prospective cohort, single centre	Elective or urgent CABG or valve replacement (isolated AVR cohort extracted) Winnipeg, Canada	36 isolated AVR	70.7	71 (66–76)	NR	NA	1.72 (0.84–2.96)	Research assistant	0

Continued

Table 2 Continued

Author	Year	Procedure	Study type	Patient cohort	Sample size, n	Male gender, %	Age, years*	EF, %*	TF-TAVI, %	STS-PROM, %*	CFS screening clinician	Lost to follow-up at 1 year, n (%)
Miguelena-Hycka *et al*[17]	2019	SAVR	Prospective cohort, multicentre	Elective cardiac surgery (isolated AVR cohort extracted) Spain	71 isolated AVR	52.1	78.6±4.4	NR	NA	2.99±2.0	Cardiac surgeon (trained by a geriatrician specialised in frailty evaluation)	71 (100)
Naganuma *et al*[18]	2021	SAVR	Retrospective cohort, single centre	Severe AS Aomori, Japan	219	44.7	74 (69–79)	64.0 (52.6–71.1)	NA	NR	Trained medical professional (as per CSHA criteria)	0

*Data are presented as mean±SD or median (IQR).
AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; BMI, body mass index; CABG, coronary artery bypass graft; CFS, Clinical Frailty Scale; CSHA, Canadian Study of Health and Ageing; EF, ejection fraction; NA, not applicable; NR, not recorded; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons Procedural Risk of Mortality; TAVI, transcatheter aortic valve implantation; TF-TAVI, transfemoral TAVI.

The SAVR cohort was also gender-balanced (52.8% men) with a younger participant group compared with TAVI (mean/median age 71–82). STS scores were collected in three out of four studies, with mean/median scores of 1.72%–2.99%. Data published by Miguelena were only collected up to 6 months postprocedure.[17] Isolated SAVR patients alone are included in three out of four SAVR studies (56% of patients in the study by Naganuma *et al* underwent a concomitant valve or coronary bypass procedure[18]).

Risk of bias

Our risk of bias assessment for the primary outcome is presented in table 3 (the Miguelena study was omitted from this assessment as it did not contain any primary outcome data). Concerns regarding patient loss to follow-up affected three TAVI studies,[15 19 20] though only the Quine cohort had attrition of greater than 20%. Applicability concerns were raised for studies by Kleczynski (due to the median STS score of 12% indicating a higher baseline risk in this group) and Naganuma (due to greater than 50% of patients undergoing an additional procedure at the time of AVR).[18 21] It was also noted that a high number of SAVR patients (879/1253) screened as part of the Afilalo study were not enrolled, most commonly due to patient and/or researcher unavailability for a preprocedure interview, which may have predisposed to selection bias.[15]

Primary endpoint

Data on 12-month mortality were available in all six TAVI studies (4923 patients in total). This outcome occurred in 319/1666 frail patients (19.1%) and in 320/3257 non-frail patients (9.8%, RR 2.53 (1.63 to 3.95), p<0.001). Statistical heterogeneity was noted (χ^2=28.80, df=5, p value for heterogeneity <0.001, I^2=83%) (figure 2).

The primary outcome was reported in three out of four SAVR studies (454 patients), with rates of 20.3% (14/69) in the frail cohort and 3.9% (15/385) in the non-frail cohort (RR 5.08 (2.31 to 11.15), p<0.001). There was no significant heterogeneity present (χ^2=2.12, df=2, p value for heterogeneity=0.35, I^2=5%) (figure 3).

Subgroup analysis

Post hoc subgroup analysis of the primary endpoint in the TAVI group was performed with the exclusion of the study by Kleczynski due to a higher baseline surgical risk in this cohort. This yielded a reduction in statistical heterogeneity (4822 patients, RR 1.96 (1.51 to 2.54), p<0.001, χ^2=8.25, df=4, p value for heterogeneity=0.08, I^2=51%) (online supplemental data S2).

Secondary endpoints

Among the frail TAVI cohort, there was an increased risk of mortality during hospital admission and at 1, 3 and 6 months (RR 1.98, 1.80, 2.03 and 1.80 respectively, all p≤0.02). Rates of AKI (four studies, 4611 patients, 8.7% vs 5.1%, RR 1.82 (1.46 to 2.27), p<0.001, I^2=0%), major bleeding (three studies, 2104 patients, 13.9% vs 8.9%, RR

Table 3 Methodological quality of included studies

Author	Risk of bias: Patient selection	Index test	Reference standard	Flow and timing	Applicability concerns: Patient selection	Index test	Reference standard
TAVI							
Afilalo	Low	Low	Low	Unclear	Low	Low	Low
Cockburn	Low	Low	Low	Low	Low	Low	Low
Kleczynski	Low	Low	Low	Low	Unclear	Low	Low
Martin	Low	Low	Low	Low	Low	Low	Low
Quine	Low	Unclear	Low	High	Low	Low	Low
Shimura	Low	Low	Low	Unclear	Low	Low	Low
SAVR							
Afilalo	Unclear	Low	Low	Low	Low	Low	Low
Lytwyn	Low	Low	Low	Low	Low	Low	Low
Naganuma	Low	Low	Low	Low	Unclear	Low	Low

SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

1.64 (1.28 to 2.10), p<0.001, I^2=0%) and minor bleeding (three studies, 2104 patients, 13.9% vs 10.5%, RR 1.36 (1.07 to 1.74), p=0.01, I^2=0%) were also higher in the frail group, as was the VARC-defined composite endpoint of early safety (three studies, 3344 patients, 20.2% vs 14.4%, RR 1.47 (1.27 to 1.72), p<0.001, I^2=0%). Differences in stroke, myocardial infarction, cardiac tamponade, conversion to open surgery, permanent pacemaker requirement and vascular complications were not statistically significant. No difference was found between frail and non-frail SAVR cohorts with respect to any secondary outcome (online supplemental data S3).

GRADE assessment

Summary data relating to each endpoint, together with our GRADE assessment of confidence in our results, are presented in table 4. Due to the observational nature of the evidence (such that results were not controlled for potential confounders) as well as issues with inconsistency and/or imprecision, certainty for all outcomes was rated as very low.

DISCUSSION

This study represents the first systematic review and meta-analysis to examine the impact of CFS-defined frailty on outcomes following both TAVI and SAVR and found an increased risk of mortality at 12 months following either procedure. Major or minor bleeding and AKI were more common among frail TAVI recipients, as was a composite outcome combining all-cause mortality, stroke, AKI, life-threatening bleeding, coronary artery obstruction, major vascular complications and repeat valve procedures at 30 days post-TAVI.

Impact of frailty on TAVI outcomes

Several measures of frailty have been studied in relation to TAVI outcomes. Many of these were summarised in a recent systematic review by Li *et al*, which reported that multidimensional measures of frailty were more commonly used (with a modified Fried phenotype being the most common). A meta-analysis of 10 studies comprising different frailty instruments reported a crude

Study or Subgroup	CFS ≥5 Events	CFS ≥5 Total	CFS ≤4 Events	CFS ≤4 Total	Weight	Risk Ratio IV, Random, 95% CI
Afilalo 2017	42	168	44	425	20.1%	2.41 [1.65, 3.54]
Cockburn 2015	12	63	19	168	15.5%	1.68 [0.87, 3.27]
Kleczynski 2017	15	17	3	84	9.4%	24.71 [8.02, 76.07]
Martin 2018	187	1043	186	1581	22.6%	1.52 [1.26, 1.84]
Quine 2020	7	76	11	269	11.8%	2.25 [0.90, 5.61]
Shimura 2017	56	299	57	730	20.7%	2.40 [1.70, 3.38]
Total (95% CI)		**1666**		**3257**	**100.0%**	**2.53 [1.63, 3.95]**
Total events	319		320			

Heterogeneity: Tau² = 0.22; Chi² = 28.80, df = 5 (P < 0.0001); I² = 83%
Test for overall effect: Z = 4.11 (P < 0.0001)

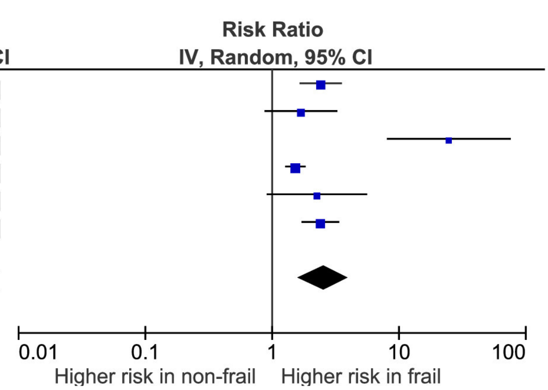

Figure 2 Meta-analysis of 12-month mortality post-TAVI comparing frail versus non-frail cohort. CFS, Clinical Frailty Scale; IV, inverse variance; TAVI, transcatheter aortic valve implantation.

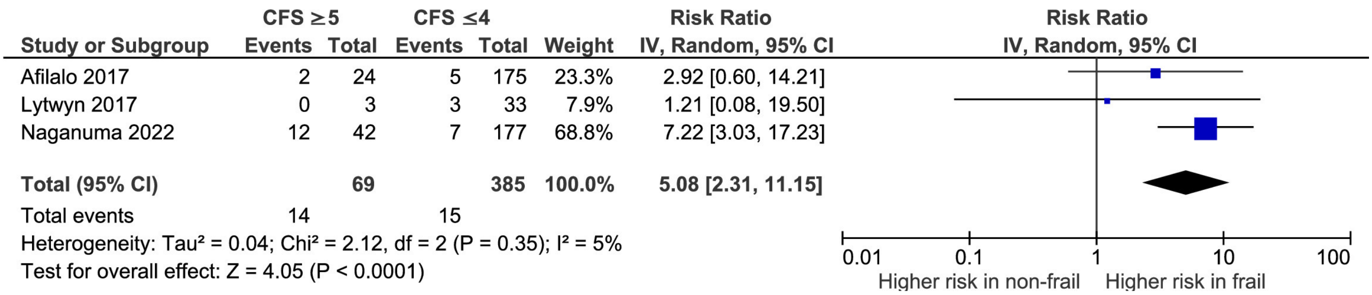

Figure 3 Meta-analysis of 12-month mortality post-SAVR comparing frail versus non-frail cohort. CFS, Clinical Frailty Scale; IV, inverse variance; SAVR, surgical aortic valve replacement.

12-month mortality rate of 20.4% postprocedure in recipients previously classified as frail (comparable to 19.1% mortality in our frail cohort).[22] A diagnosis of frailty by the Katz Index of activities of daily living has been associated with increased rates of procedural mortality, minor bleeding, severe AKI and permanent pacemaker requirement, as well as an increased length of stay.[23]

While the added mortality risk associated with frailty among TAVI recipients appears to be substantial, conservative management of severe symptomatic aortic stenosis continues to carry a very poor prognosis. Contemporary studies have reported a 12-month mortality rate postdiagnosis of 30%–60% in patients who did not undergo valve replacement due to potential medical futility, and 17%–45% in those not undergoing AVR for other reasons (most commonly due to patient refusal).[24 25] Further data from Spain cited frailty as the principal reason for opting against an invasive strategy in 44% of conservatively managed cases, with 42% mortality at 12 months in this group.[26] Defining a CFS score which would denote medical futility would be an important part of this assessment—outcome data relating to the CFS as a continuous variable was only available from two of our included studies, however, a score of ≥7 was associated with 33% and 45% 12-month mortality post-intervention.[15 20]

Research on peri-intervention strategies to potentially improve the prognosis of frail TAVI recipients is ongoing. Cardiac rehabilitation has been associated with improved functional performance and exercise capacity post-TAVI.[27 28] Meanwhile, the effect of enhanced nutritional supplementation starting 4 weeks preprocedure, coupled with a home-based exercise programme for 12 weeks postprocedure to potentially reverse frailty is currently under investigation, with the PERFORM-TAVR trial due to complete data collection later this year. It remains to be determined whether this will translate into improved survival in frail patients undergoing TAVI.

TAVI risk scoring

The addition of frailty measures (including the CFS) to existing TAVI clinical prediction models has been shown to improve their predictive performance.[2] In recent years, TAVI-specific frailty scores such as the Essential Frailty Toolset (EFT) and the Geriatric Assessment Frailty Score (GAFS) have been published.[15 29] While these scores have shown prognostic significance, they require further clinical measurements to be undertaken and are therefore more resource-intensive compared with the CFS. For example, the EFT requires a mini-mental state examination, an objective chair-rise assessment and blood tests for albumin and haemoglobin, while the GAFS requires objective assessments of cognition, mobility, nutrition, mood, comorbidities and lower limb strength. Another prognostic multidimensional assessment published by Schoenenberger requires similar objective data measurements.[30] The CFS may therefore be more accessible to non-geriatric clinicians as a means of assessing frailty, particularly where access to specialist gerontology and/or allied health support is limited. Our study adds to the growing body of evidence that frailty is an important determinant of poor TAVI outcomes and should be integrated into existing clinical models to improve risk estimates.

Impact of frailty on SAVR outcomes

Similar to TAVI, different frailty instruments have been studied in relation to outcomes following cardiac surgery. However, TAVI is the preferred method of valve intervention in frail patients, thus the effect of preoperative frailty on surgical cohorts is less well studied. For example, a 2016 systematic review by Kim *et al* contained eight studies which reported on outcomes following cardiac surgery, compared with 17 studies reporting on TAVI outcomes (or 49 studies which were reported in the aforementioned meta-analysis by Li *et al*).[22 31] In that analysis, frailty was found to be predictive of mortality at ≥6 months post-surgery, though evidence quality was low.

It is difficult to define the role of the CFS in the context of consideration for SAVR due to a paucity of outcome data. Our results would not dispute recent guidelines recommending TAVI as the first-line intervention for severe aortic stenosis where frailty is a factor,[6] though crude mortality rates among frail patients in our review cohort were similar for both procedures (19.1% TAVI mortality vs 20.3% SAVR mortality at 12 months). A Heart Team discussion remains crucial in the selection of appropriate patients for these procedures.

Inter-rater reliability

We were unable to draw any meaningful conclusions regarding the influence of the rating clinician on CFS results due to the low number of included studies and

Table 4 GRADE assessment

No. of studies	No. of patients	No. of events	RR (95% CI)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
TAVI									
12-month mortality									
6	4923	639	2.53 (1.63 to 3.95)	Observational	–1	0*	0	0	Very low
In-hospital mortality									
3	2114	57	1.98 (1.14 to 3.44)	Observational	–1	0	0	–1†	Very low
30-day mortality									
4	4663	167	1.80 (1.33 to 2.42)	Observational	–1	0	0	0	Very low
3-month mortality									
3	3448	235	2.03 (1.26 to 3.29)	Observational	–1	0*	0	0	Very low
6-month mortality									
3	3448	341	1.80 (1.20 to 2.72)	Observational	–1	0*	0	0	Very low
Early safety									
3	3344	553	1.47 (1.27 to 1.72)	Observational	–1	0	0	0	Very low
Coronary obstruction									
4	4630	35	0.69 (0.33 to 1.42)	Observational	–1	0	0	0‡	Very low
Myocardial infarction									
3	3427	17	0.69 (0.23 to 2.06)	Observational	–1	0	0	0‡	Very low
Stroke									
4	4645	104	1.59 (0.77 to 3.27)	Observational	–1	–1	0	–1†	Very low
Acute kidney injury									
4	4611	291	1.82 (1.46 to 2.27)	Observational	–1	0	0	0	Very low
Major vascular complications									
4	4618	182	1.09 (0.80 to 1.48)	Observational	–1	0	0	0‡	Very low
Minor vascular complications									
3	2099	125	1.31 (0.69 to 2.49)	Observational	–1	–1	0	–1†	Very low
Life-threatening bleeding									
3	2104	100	1.71 (1.16 to 2.51)	Observational	–1	0	0	–1†	Very low
Major bleeding									
3	2104	219	1.64 (1.28 to 2.10)	Observational	–1	0	0	–1†	Very low
Minor bleeding									
3	2104	242	1.36 (1.07 to 1.74)	Observational	–1	0	0	–1†	Very low
Two-valve implantation									
2	1521	31	1.39 (0.34 to 5.66)	Observational	–1	–1	0	–2§	Very low
Permanent pacemaker requirement									
3	3413	430	0.98 (0.76 to 1.26)	Observational	–1	0	0	–1†	Very low
Cardiac tamponade									
3	2108	31	1.64 (0.67 to 4.03)	Observational	–1	0	0	–1†	Very low
Conversion to open surgery									
3	4057	53	1.58 (0.93 to 2.70)	Observational	–1	0	0	0‡	Very low
SAVR									
12-month mortality									
3	454	29	5.08 (2.31 to 11.15)	Observational	–1	0	–1¶	0	Very low
In-hospital mortality									
2	269	10	2.75 (0.74 to 10.16)	Observational	–1	0	0	–2§	Very low
30-day mortality									

Continued

Table 4 Continued

No. of studies	No. of patients	No. of events	RR (95% CI)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
2	269	11	2.37 (0.66 to 8.54)	Observational	−1	0	0	−2§	Very low
6-month mortality									
2	266	11	2.33 (0.65 to 8.39)	Observational	−1	0	0	−2§	Very low
Myocardial infarction									
2	269	2	1.88 (0.20 to 17.54)	Observational	−1	0	0	−2§	Very low
Stroke									
2	269	7	0.71 (0.09 to 5.52)	Observational	−1	0	0	−2§	Very low
Acute kidney injury									
2	263	26	1.99 (0.93 to 4.26)	Observational	−1	0	0	−1*	Very low
Permanent pacemaker requirement									
2	266	23	1.42 (0.52 to 3.93)	Observational	−1	0	0	−2§	Very low
Cardiac tamponade									
2	268	10	1.05 (0.19 to 5.82)	Observational	−1	0	0	−2§	Very low

*Not rated down as heterogeneity not clinically significant.
†Rated down as optimal information size not met.
‡Not rated down as large sample size (<1% absolute risk difference between groups).
§Rated down two levels as unable to exclude both significant benefit and significant harm.
¶Rated down as a significant proportion of patients underwent a concomitant valve and/or bypass procedure at the time of AVR.
AVR, aortic valve replacement; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

lack of clarity in some instances regarding which clinician had applied the scale. Frailty assessment was performed by research assistants in two studies, a cardiologist or TAVI research nurse in two studies, a cardiac surgeon in one study and a 'trained medical professional' (as per Canadian Study of Health and Ageing criteria) in two studies. CFS scores were determined during the Heart Team meeting in one study, while for the remaining included study the information on which clinician had applied the CFS could not be obtained.

Good inter-rater agreement on CFS results has been reported between geriatricians and trained research assistants, as well as between primary care physicians, community nurses, general medical physicians and intensivists.[32 33] It has not yet been reported whether this remains true for cardiologists, cardiac surgeons and cardiology nurse specialists.

STRENGTHS AND LIMITATIONS

The review has several strengths. Our literature search was comprehensive, with validated tools used to assess the risk of bias and overall evidence quality. By contacting authors for additional unpublished data, we were able to provide a more complete dataset than would have been achieved using published data alone.

However, these findings should be interpreted in the context of our review's limitations. First, individual-patient level data was only available from a minority of included studies—having this data may have helped to evaluate potential causes of heterogeneity. Meta-regression was not applied in this scenario due to the low number of studies. Second, 13 studies were omitted from the review as we were unable to obtain necessary CFS and/or mortality data from the authors—the addition of this data may have influenced the overall results of the review. As mentioned previously, assessment of secondary endpoints was affected by limited outcome data, particularly in our SAVR cohort. Furthermore, this review did not compare aortic valve intervention with conservative management of aortic stenosis in the frail population to determine a clear benefit or futility of treatment.

There was substantial heterogeneity between included TAVI studies, likely explained by the Kleczynski study which was conducted in a higher risk population.[21] The study had a median 30-day estimated mortality risk according to the Society of Thoracic Surgeons Procedural Risk of Mortality score of 12%, compared with median values of 4.3%–6.2% reported in recent TAVI registry data.[34 35] However, this was a relatively small study and is unlikely to have greatly influenced the overall result, while subgroup analysis continued to show a statistically significant increased mortality risk in our frail TAVI cohort.

SAVR study results were homogenous but affected by lower patient numbers leading to an imprecise result. A lack of available data meant that secondary endpoints could not be sufficiently explored in this group. In addition, certain pre-specified secondary endpoints such as functional decline, length of hospital stay and rates of re-hospitalisation were omitted from both cohorts as these data were not collected across the majority of included studies.

CONCLUSION

Frailty, as defined by the Rockwood Clinical Frailty Scale, was predictive of 12-month mortality following either TAVI or SAVR. Our data would support the integration of the CFS into existing risk scores for TAVI to improve risk estimates of mortality. Further research is needed to determine inter-rater agreement on CFS assessments across cardiac, cardiothoracic and geriatric specialties.

Author affiliations
[1]Department of Cardiology, Cork University Hospital, Cork, Ireland
[2]Department of Ageing and Therapeutics, University Hospital Limerick, Limerick, Ireland
[3]Division of Cardiology and Centre of Clinical Epidemiology, Jewish General Hospital, McGill University, Montreal, Québec, Canada
[4]Division of Informatics, Imaging and Data Science, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
[5]Keele Cardiovascular Research Group, Centre for Prognosis Research, Keele University, Keele, UK
[6]Department of Cardiology, Mater Misericordiae University Hospital, Dublin, Ireland
[7]School of Allied Health, Faculty of Education and Health Sciences, Ageing Research Centre, Health Research Institute, University of Limerick, Limerick, Ireland

Twitter Mamas Mamas @mmamas1973

Acknowledgements We are grateful to GPM, MM, JA, James Cockburn, David Hildick-Smith, Ed Quine, Antony Walton, Brett Hiebert, Rakesh Arora and Javier Miguelena for providing additional unpublished data for the purpose of this review.

Contributors TP, AL, MOC and RG were responsible for the study concept and design. All other authors were involved in the analysis of data and drafting of the manuscript. Additionally, James Cockburn, David Hildick-Smith, Ed Quine, Antony Walton, Brett Hiebert, Rakesh Arora and Javier Miguelena contributed additional data for the meta-analysis. TP is acting guarantor and is responsible for the overall content.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available in a public, open access repository. Dataset is available from the Open Science Framework repository, DOI: [10.17605/OSF.IO/7HPVE].

ORCID iDs
Tadhg Prendiville http://orcid.org/0000-0003-1036-9859
Glen Philip Martin http://orcid.org/0000-0002-3410-9472
Mamas Mamas http://orcid.org/0000-0001-9241-8890

REFERENCES

1 Kappetein AP, Head SJ, Généreux P, *et al*. Updated standardized Endpoint definitions for Transcatheter aortic valve implantation: the valve academic research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg* 2012;42:S45–60.
2 Martin GP, Sperrin M, Ludman PF, *et al*. Do frailty measures improve prediction of mortality and morbidity following Transcatheter aortic valve implantation? an analysis of the UK TAVI Registry. *BMJ Open* 2018;8:e022543.
3 Kiani S, Stebbins A, Thourani VH, *et al*. The effect and relationship of frailty indices on survival after Transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2020;13:219–31.
4 Durand E, Borz B, Godin M, *et al*. Performance analysis of Euroscore II compared to the original logistic Euroscore and STS scores for predicting 30-day mortality after Transcatheter aortic valve replacement. *Am J Cardiol* 2013;111:891–7.
5 Martin GP, Sperrin M, Ludman PF, *et al*. Inadequacy of existing clinical prediction models for predicting mortality after Transcatheter aortic valve implantation. *Am Heart J* 2017;184:97–105.
6 Vahanian A, Beyersdorf F, Praz F, *et al*. ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2022;43:561–632.
7 Otto CM, Nishimura RA, Bonow RO, *et al*. ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American college of cardiology/American heart Association joint committee on clinical practice guidelines. *Circulation* 2021;143:e72–227.
8 Rockwood K, Song X, MacKnight C, *et al*. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489–95.
9 Church S, Rogers E, Rockwood K, *et al*. A Scoping review of the clinical frailty scale. *BMC Geriatr* 2020;20:393.
10 Elliott A, Phelps K, Regen E, *et al*. Identifying frailty in the emergency Department-feasibility study. *Age Ageing* 2017;46:840–5.
11 Prendiville T, Leahy A, Quinlan L, *et al*. Rockwood clinical frailty scale as a Predictor of adverse outcomes among older adults undergoing aortic valve replacement: a protocol for a systematic review. *BMJ Open* 2022;12:e049216.
12 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
13 Whiting PF, Rutjes AWS, Westwood ME, *et al*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
14 Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
15 Afilalo J, Lauck S, Kim DH, *et al*. Frailty in older adults undergoing aortic valve replacement: the FRAILTY-AVR study. *J Am Coll Cardiol* 2017;70:689–700.
16 Cockburn J, Singh MS, Rafi NHM, *et al*. Poor mobility predicts adverse outcome better than other frailty indices in patients undergoing Transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2015;86:1271–7.
17 Miguelena-Hycka J, Lopez-Menendez J, Prada P-C, *et al*. Influence of preoperative frailty on health-related quality of life after cardiac surgery. *Ann Thorac Surg* 2019;108:23–9.
18 Naganuma M, Kudo Y, Suzuki N, *et al*. Effect of malnutrition and frailty status on surgical aortic valve replacement. *Gen Thorac Cardiovasc Surg* 2022;70:24–32.
19 Quine EJ, Dagan M, William J, *et al*. Long-term outcomes stratified by body mass index in patients undergoing Transcatheter aortic valve implantation. *Am J Cardiol* 2020;137:77–82.
20 Shimura T, Yamamoto M, Kano S, *et al*. Impact of the clinical frailty scale on outcomes after Transcatheter aortic valve replacement. *Circulation* 2017;135:2013–24.
21 Kleczynski P, Dziewierz A, Bagienski M, *et al*. Impact of frailty on mortality after Transcatheter aortic valve implantation. *Am Heart J* 2017;185:52–8.
22 Li Z, Dawson E, Moodie J, *et al*. Measurement and prognosis of frail patients undergoing Transcatheter aortic valve implantation: a systematic review and meta-analysis. *BMJ Open* 2021;11:e040459.
23 Puls M, Sobisiak B, Bleckmann A, *et al*. Impact of frailty on Short- and long-term morbidity and mortality after Transcatheter aortic valve implantation: risk assessment by Katz index of activities of daily living. *EuroIntervention* 2014;10:609–19.
24 Ishii M, Taniguchi T, Morimoto T, *et al*. Reasons for choosing conservative management in symptomatic patients with severe aortic Stenosis- observations from the CURRENT AS Registry. *Circ J* 2019;83:1944–53.
25 Tang L, Gössl M, Ahmed A, *et al*. Contemporary reasons and clinical outcomes for patients with severe, symptomatic aortic stenosis

not undergoing aortic valve replacement. *Circ Cardiovasc Interv* 2018;11:e007220.
26 Bernal E, Ariza-Solé A, Formiga F, *et al*. Conservative management in very elderly patients with severe aortic stenosis: time to change? *J Cardiol* 2017;69:883–7.
27 Ribeiro GS, Melo RD, Deresz LF, *et al*. Cardiac rehabilitation programme after Transcatheter aortic valve implantation versus surgical aortic valve replacement: systematic review and meta-analysis. *Eur J Prev Cardiol* 2017;24:688–97.
28 Yu Z, Zhao Q, Ye Y, *et al*. Comprehensive geriatric assessment and exercise capacity in cardiac rehabilitation for patients referred to Transcatheter aortic valve implantation. *Am J Cardiol* 2021;158:98–103.
29 Skaar E, Eide LSP, Norekvål TM, *et al*. A novel geriatric assessment frailty score predicts 2-year mortality after Transcatheter aortic valve implantation. *Eur Heart J Qual Care Clin Outcomes* 2019;5:153–60.
30 Schoenenberger AW, Stortecky S, Neumann S, *et al*. Predictors of functional decline in elderly patients undergoing Transcatheter aortic valve implantation (TAVI). *Eur Heart J* 2013;34:684–92.
31 Kim DH, Kim CA, Placide S, *et al*. Preoperative frailty assessment and outcomes at 6 months or later in older adults undergoing cardiac surgical procedures: A systematic review. *Ann Intern Med* 2016;165:650–60.
32 Kaeppeli T, Rueegg M, Dreher-Hummel T, *et al*. Validation of the clinical frailty scale for prediction of thirty-day mortality in the emergency Department. *Ann Emerg Med* 2020;76:291–300.
33 Nissen SK, Fournaise A, Lauridsen JT, *et al*. Cross-Sectoral inter-Rater reliability of the clinical frailty scale - a Danish translation and validation study. *BMC Geriatr* 2020;20:443.
34 Kaneko T, Vemulapalli S, Kohsaka S, *et al*. Practice patterns and outcomes of Transcatheter aortic valve replacement in the United States and Japan: A report from joint data harmonization initiative of STS/ACC TVT and J-TVT. *J Am Heart Assoc* 2022;11:e023848.
35 Abdel-Wahab M, Fujita B, Frerker C, *et al*. Transcatheter versus rapid-deployment aortic valve replacement: A propensity-matched analysis from the German aortic valve Registry. *JACC Cardiovasc Interv* 2020;13:2642–54.
36 Lytwyn J, Stammers AN, Kehler DS, *et al*. The impact of frailty on functional survival in patients 1 year after cardiac surgery. *J Thorac Cardiovasc Surg* 2017;154:1990–9.