

Frailty and perioperative patient-reported disability in patients undergoing cardiac surgery: a pilot study

Benjamin Milne^{1,†}, Joshua Lucas de Carvalho^{1,†}, Salma Ayis², Sanjay Chaubey³, Habib Khan³ and Gudrun Kunst^{1,4,*}

¹Department of Anaesthesia & Pain Medicine, King's College Hospital NHS Foundation Trust, London, UK, ²Department of Statistics, School of Population Health & Environmental Sciences, Faculty of Life Sciences & Medicine, King's College London, UK, ³Department of Cardiothoracic Surgery, King's College NHS Foundation Trust, London, UK and ⁴British Heart Foundation Centre of Research Excellence, School of Cardiovascular Medicine & Sciences, Faculty of Life Sciences & Medicine, King's College London, London, UK

*Corresponding author. E-mail: gudrun.kunst@kcl.ac.uk

†Contributed equally to the study and paper.

Abstract

Background: Preoperative frailty may predispose patients to poorer outcomes in cardiac surgery; however, there are limited data concerning how preoperative frailty predicts patient-centred outcomes, such as patient-reported disability. Our objective was to evaluate the association between preoperative frailty and postoperative disability.

Methods: Patients were prospectively evaluated using the Comprehensive Assessment of Frailty score, separating patients into frail and non-frail cohorts. Disability levels were quantified using the WHO Disability Assessment Schedule (WHODAS) 2.0 in percentage of the maximum disability score, with disability defined as a value $\geq 25\%$.

Results: Frail patients had increased median [inter-quartile range] disability scores of 31 [16–45]% preoperatively, 29 [9–54]% at 1 month, and 15 [3–31]% at 3 months postoperatively, compared with disability scores in non-frail patients of 10 [5–17]%, 17 [6–29]%, and 2.1 [0–12.0]%, respectively. Preoperative frailty was associated with a reduced likelihood of patients being free of disability and alive at 3 months; adjusted odds ratio 0.51 (for age, European System for Cardiac Operative Risk Evaluation II, and WHODAS 2.0: 12-Part Questionnaire score); $P=0.045$. The trajectory of disability scores, assessed in percentage change from the preoperative baseline, showed non-frail patients had increased disability burden at 1 month, whereas frail patients had reduced disability burden (+4.2% vs –2.1%; $P=0.04$). Although the disability burden decreased for both groups at 3 months, this was most marked for frail patients (–6.3% vs –10.4%; $P=0.02$).

Conclusions: Disability burden in frail patients improves continuously postoperatively, whereas in non-frail patients, it worsens at 1 month before improving at 3 months postoperatively. This positive trajectory of patient-centred outcomes in frail patients should be considered in preoperative decision-making.

Keywords: cardiac surgery; disability; frailty; patient-centred outcome; postoperative outcome

Received: 5 June 2021; Accepted: 4 March 2022

© 2022 The Authors. Published by Elsevier Ltd on behalf of British Journal of Anaesthesia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

For Permissions, please email: permissions@elsevier.com

Editor's key points

- Frailty is an increasingly recognised risk factor for surgery.
- The extent of frailty and how this may affect postoperative recovery profiles are unclear.
- This study found that disability transiently increased at 1 month after surgery in non-frail patients, but continuously decreased in frail patients.
- Frailty seems to be associated with a relatively positive recovery trajectory of disability after cardiac surgery.

Frailty is a clinical syndrome characterised by vulnerability for the development of increased dependency and mortality when exposed to a stressor.¹ Often described clinically as a lack of physiological reserve, it manifests as an impaired ability to maintain or restore homeostasis after a destabilising event,^{2,3} leading to increased mortality and morbidity.^{4,5} Cardiac surgery represents a profoundly destabilising event, particularly for the 20–50% of patients with preoperative frailty.^{6–8}

Clinical frailty is defined in terms of recognition by an identifiable phenotype⁹ or by the accumulation of specific deficits.¹⁰ Despite clinical discourse often using the terms interchangeably, disability is a separate concept, defined by the development of difficulty or dependency in completing activities of daily living (ADL), a potential adverse outcome of the frail patient being exposed to a stressor.^{11–13}

In noncardiac surgery, a recent study demonstrated that frail patients undergoing surgery had a significantly improved disability score 1 yr after surgery compared with the preoperative disability baseline score, which was in contrast to non-frail patients, whose disability scores remained unchanged at 1 yr.¹⁴ Relatively high rates of frailty before cardiac surgery are in contrast to relatively low rates of preoperative disability,¹⁵ indicating that either the latter is used to guide surgical candidate selection,^{3,13} or that frailty is an important precursor of disability and should be treated as such. This relationship has not been fully investigated in cardiac surgery, particularly regarding disability, a patient-centred outcome. Traditional scoring models for operative risk, including the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, may miss vital information regarding physiological status, which frailty assessment may supply.^{16,17} Therefore, assessment of frailty may inform surgical decision-making and help contextualise surgical consent with a patient-centred outcome, such as disability scores reflecting the burden of disability and the number of patients free of disability and alive (disability-free survival [DFS]).¹⁸

The Comprehensive Assessment of Frailty (CAF) incorporates both specific deficit and phenotypical evaluation for frailty, and assignment as frail is associated with increased 30 day and 1 yr mortality.^{7,19} The WHO Disability Assessment Schedule 2.0 (WHODAS) can serve as a disability score, ranging from 0 (no disability) to 48 (maximal disability), with significant disability defined at a disability score ≥ 12 .^{20,21} Disability scores and the fraction of patients free of disability and alive have been suggested as fitting key criteria for use as patient-centred outcome measures after cardiac surgery.^{20–22}

We hypothesised that preoperative frailty would be associated with being free of disability and alive at 3 months in

adult patients undergoing elective cardiac surgery, and we sought to further explore the association of preoperative frailty and perioperative disability scores.

Methods

This study received ethical (West London & GTAC Research Ethics Committee; 16/LO/0215) and institutional (King's College Hospital Research & Innovation Department; KCH16-012) approval. All adult patients at our tertiary referral centre, who are undergoing elective cardiac surgery, such as coronary artery bypass graft, valvular replacement/repair, or combination procedure surgeries, were approached for written informed consent. The exclusion criteria were inability to provide informed consent, emergency surgery, and severe concurrent CNS disease.

The primary outcome was the association of preoperative frailty with postoperative DFS at 3 months. Secondary outcomes included patient-reported disability scores preoperatively, and 1 and 3 months after surgery.

At preoperative assessment, alongside routine anaesthetic and surgical evaluation, all consenting participants underwent CAF evaluation by two investigators, and also collection of baseline characteristics (Table 1). The CAF has been described elsewhere¹⁹ and involves evaluation of biological markers, patient-reported levels of exhaustion and activity, physical tests of strength and stability, and subjective investigator assessment using the Canadian Clinical Frailty Scale (the mean of two scores by two independent scorers, each blinded to the other's evaluation). Assessment gives a value out of 35, with patients scoring ≥ 11 being assigned frail and < 11 non-frail.¹⁹ The simplified form (frailty predicts death one year after cardiac surgery test [FORECAST] score) was also calculated.⁷ The 12-question self-reporting version of WHODAS 2.0 (WHODAS-12) was calculated at this point to establish preoperative linear WHODAS-12 values (in percentage of the maximum disability score, which is 48) and the binary outcome DFS (with disability defined as a value $\geq 25\%$).^{21,22}

Deceased patients were assigned a maximal WHODAS disability score of 48 (i.e. 100%) at all postoperative time points, and their disability scores were included in the results. A minimal clinically important difference assessment was used to evaluate patients, where a change in WHODAS-12 values was $\geq 5\%$ (minimum significant change).²³ Clinicians involved in patients' perioperative care were blinded to the results of these assessments.

Conduct of anaesthesia was according to consensus-based locally approved institutional methods, with use of standard cardiac monitoring. Institutional protocol was followed for cardiac surgical care, with patients requiring cardiopulmonary bypass receiving intermittent cold blood St Thomas's cardioplegia. Patients were cared for in a cardiac ICU postoperatively, following institutional protocols with evidence-based best practice for the routine care of patients undergoing elective cardiac surgery.

Postoperatively, operative characteristics and outcome data (Table 1; Supplementary Table 1, respectively) were collected by research team members, who were blinded to preoperative CAF and WHODAS-12 values (Table 2). At 1 and 3 months postoperatively, telephone interviews were conducted to establish levels of DFS using WHODAS-12 values. Alternatively, mortality data were collected at this juncture as appropriate.

Table 1 Preoperative characteristics and scoring, and operative characteristics. ACE, angiotensin-converting enzyme; ASA, American Society of Anesthesiologists; AVR, aortic valve repair/replacement; CABG, coronary artery bypass graft; CAF, comprehensive assessment of frailty score; CCS, Canadian Cardiovascular Society angina grade; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; FORECAST, frailty predicts death one year after cardiac surgery test score; IDDM, insulin-dependent diabetes mellitus; IQR, inter-quartile range; LVEF, left ventricular ejection fraction; MSK, musculoskeletal; MVR, mitral valve repair/replacement; NIDDM, non-insulin-dependent diabetes mellitus; NYHA, New York Heart Association functional classification; *sd*, standard deviation; WHODAS-12, WHO Disability Assessment Schedule 2.0: 12-Part Questionnaire (% score).

	Non-frail (n=99; 67.8%)	Frail (n=47; 32.2%)	P-value
ASA physical status, n (%)			
Class 3	72 (72.7)	29 (61.7)	0.25
Class 4	27 (27.3)	18 (38.3)	
Age (yr), median [IQR]	66.0 [58.0–72.5]	71.0 [59.5–77.0]	0.10
Male sex, n (%)	77 (77.8)	30 (63.8)	0.11
BMI (kg m ⁻²) mean (<i>sd</i>)	28.4 (4.4)	28.8 (5.5)	0.67
Race, n (%)			
White	84 (84.8)	32 (68.1)	0.03
Asian	9 (9.1)	8 (17.0)	0.26
Black	6 (6.1)	7 (14.9)	0.15
Hypertension, n (%)	72 (73)	36 (77)	0.77
Hypercholesterolaemia, n (%)	64 (65)	31 (66)	1.0
Diabetes mellitus, n (%)			
NIDDM	19 (19)	10 (21)	0.94
IDDM	6 (6)	7 (15)	0.15
Previous stroke, n (%)	4 (4)	7 (15)	0.05
Significant MSK/neurological disease, n (%)	3 (3)	8 (17)	0.01
Previous myocardial infarction, n (%)	23 (23)	8 (17)	0.52
Smoking, n (%)			
Current	9 (9)	6 (13)	0.70
Previous	51 (52)	18 (38)	0.19
COPD, n (%)	11 (11)	5 (11)	1.0
Previous cardiac surgery, n (%)	4 (4)	6 (13)	0.11
LVEF, n (%)			
>55%	64 (65)	28 (60)	0.93
35–54%	30 (30)	14 (30)	1.0
<35%	5 (5)	5 (11)	0.37
Family history of ischaemic heart disease, n (%)	59 (60)	18 (38)	0.03
NYHA, modal class	2	3	0.01
Albumin (g L ⁻¹), mean (<i>sd</i>)	41 (6)	38 (6)	0.04
Aspirin use, n (%)	62 (63)	21 (45)	0.06
Beta-blocker use, n (%)	60 (61)	27 (57)	0.86
Statin use, n (%)	68 (69)	34 (72)	0.80
ACE inhibitor use, n (%)	57 (58)	36 (77)	0.04
Nitrate use, n (%)	10 (10)	7 (15)	0.57
Insulin use, n (%)	6 (6)	7 (15)	0.15
Metformin use, n (%)	15 (15)	9 (19)	0.71
CAF, median [IQR]	7.5 [5.2–9.0]	14.5 [12.5–20.8]	<0.001
FORECAST, mean (<i>sd</i>)	5.6 (2.0)	9.8 (2.7)	<0.001
WHODAS-12 (%), median [IQR]	10.4 [5.2–16.7]	31.3 [15.6–44.8]	<0.001
Preoperative disability (WHODAS-12 ≥25%), n (%)	11 (11)	31 (66)	<0.001
EuroSCORE II (%), median [IQR]	1.2 [0.9–1.9]	2.1 [1.2–3.0]	<0.001
Surgery, n (%)			
CABG	62 (63)	22 (47)	0.10
CABG+valve surgery	10 (10)	5 (11)	0.10
MVR	7 (7)	7 (15)	0.23
AVR	15 (15)	10 (21)	0.49
Other	5 (5)	3 (6)	1.0
Bypass time (min), median [IQR]	92 [67.5–114.5]	95 [67.5–119.5]	0.91
Cross-clamp time (min), median [IQR]	60 [42.5–78]	57 [46.6–76.5]	0.75
Off-pump surgery, n (%)	16 (16)	8 (17)	1.0

Statistical analysis

Descriptive statistics for patient, operative, and postoperative characteristics, were produced using mean (with standard deviation), median (with inter-quartile range [IQR]), or percentages (%). A comparison was made between the frail and non-frail cohorts with Student's *t*-test, Mann–Whitney *U*-test,

Pearson's χ^2 test, or Fisher's exact test as appropriate. Shapiro–Wilk test was used to assess for a normal distribution. Correlation between CAF, DFS, and EuroSCORE II was assessed using Spearman's rank test. Correlation coefficients (ρ) for these tests are described as weak (0.01–0.39), moderate (0.40–0.69), and strong (0.70–1.0), with the same descriptors for both positive and negative values. Differences in median

Table 2 Postoperative disability scores and disability-free survival in frail and non-frail patients. *n=134: non-frail=91; frail=43. †n=125: non-frail=86; frail=39. DFS, disability-free survival, indicated by WHODAS-12 score <25.0%; IQR, inter-quartile range; WHODAS-12, WHO Disability Assessment Schedule 2.0: 12-Part Questionnaire. Incidence compared with χ^2 test or McNemar's test, and medians with Mann–Whitney U-test.

	Preoperative frailty assessment			P-value
	Non-frail	Frail	Total	
Number of patients free of disability and alive (DFS), n (%)				
1 Month*	59 (64.8)	17 (39.5)	76 (56.7)	0.01
3 Months†	78 (90.7)	27 (69.2)	105 (84.0)	0.01
Median disability scores (%) [IQR], (WHODAS-12)				
Preoperative (n=146)	10.4 [5.2–16.7]	31.3 [15.6–44.8]	12.5 [6.3–26.6]	<0.001
1 Month*	16.7 [6.3–29.2]	29.2 [9.4–54.2]	19.8 [6.3–37.0]	0.01
3 Months†	2.1 [0.0–12.0]	14.6 [3.1–31.3]	4.2 [0.0–16.7]	<0.001
Change in median disability scores from baseline (%) [IQR]				
1 Month*	+4.2 [–4.2–{+18.8}]	–2.1 [–9.4–{+13.6}]	+2.1 [–4.2–{+18.8}]	0.04
3 Months†	–6.3 [–12.5–0.0]	–10.4 [–20.8–{–2.1}]	–8.3 [–14.6–0.0]	0.02

disability scores over time points were assessed using Kruskal–Wallis test, with differences between individual time points assessed using multiple pairwise comparisons with significant differences defined as $P < 0.05$.

The association of preoperative frailty (CAF) score with DFS at 3 months was investigated in exploratory univariate logistic models as a binary predictor. Age, WHODAS-12, and EuroSCORE II values were adjusted for in the models, and odds ratios (ORs) were calculated.

To explore the predictive ability of CAF-based frailty assessment, preoperative disability scoring, and EuroSCORE II to predict DFS, empirical receiver operating characteristic (ROC) curves were constructed. The Hosmer–Lemeshow goodness-of-fit test was performed to exclude markedly poorly fitting models (P -value ≤ 0.05).

Secondary outcomes were investigated in a similar fashion. Imputation of missing values was not considered appropriate, and there were no significant differences between complete and missing cases for key characteristics.

Shulman and colleagues²² demonstrated that DFS occurs in 72% of all ASA 3 patients at 6 months after surgery. An *a priori* power calculation to detect an association of preoperative frailty with half the incidence of DFS, when compared with non-frail patients (i.e. an OR of 0.5 for DFS) demonstrated a sample size of 120 patients, with a power of 85% and an alpha error of 0.05. Age has been taken into account using squared multiple correlation of 0.1 (G*Power 3.1).²⁴

Statistical analysis was performed with R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria, 2020), and RStudio v1.3.1093 (2020) (RStudio, Inc. Boston, MA, USA).

Results

From January to May 2016, 146 patients gave informed consent and underwent preoperative frailty and disability assessments. In addition, 134 patients completed follow-up at 1 month and 125 patients completed follow-up at 3 months (Fig 1).

Patients and perioperative variables

Forty-seven patients (32.2%) were considered frail by CAF evaluation (CAF score ≥ 11) and 99 (67.8%) as non-frail (CAF

score < 11). Preoperative patient characteristics and risk scores (including CAF, WHODAS-12, EuroSCORE II, and FORECAST) in frail and non-frail patients are shown in Table 1. Frail patients in this cohort were not significantly older when compared with non-frail patients. Operative details and postoperative outcomes of frail and non-frail patients are shown in Table 1 and Supplementary Table 1, respectively. There were no significant differences in operative characteristics between the two groups. Mortality was significantly higher in frail patients than in non-frail patients, in-hospital and at 3 months (8.5% [$n=4$] vs 0%; $P=0.016$).

Perioperative disability burden and postoperative number of patients free of disability and alive (DFS)

Table 2 shows perioperative disability scores and fractions of patients free of disability and alive in frail and non-frail patient groups. Frail patients had significantly higher perioperative median [IQR] disability scores of 31.3 [15.6–44.8]% preoperatively, 29.2 [9.4–54.2]% at 1 month, and 14.6 [3.1–31.3]% at 3 months postoperatively, when compared with non-frail patients, who had median [IQR] disability scores of 10.4 [5.2–16.7]% preoperatively, 16.7 [6.3–29.2]% at 1 month, and 2.1 [0–12.0]% at 3 months postoperatively. The fraction of patients who were free of disability and who were alive (i.e. who presented with DFS) was higher in the non-frail patient group, with 64.8% ($n=59$) and 90.7% ($n=78$) at 1 and 3 months, respectively, when compared with frail patients, with only 39.5% ($n=17$) and 69.2% ($n=27$) at 1 and 3 months, respectively.

The ORs for associations of preoperative frailty and being free of disability and alive (DFS) at 1 and 3 months postoperatively are shown in Table 3. Assignment as frail was associated with an OR of 0.23 for being free of disability and alive at 3 months ($P=0.004$), and an adjusted OR (for age, preoperative disability level, and EuroSCORE II value) of 0.51 ($P=0.045$).

Postoperative trajectory of disability scores in frail and non-frail patients

Median disability scores in frail patients were non-significantly reduced from baseline to 1 month ($P=0.72$), but significantly from baseline to 3 months ($P=0.02$), whereas non-

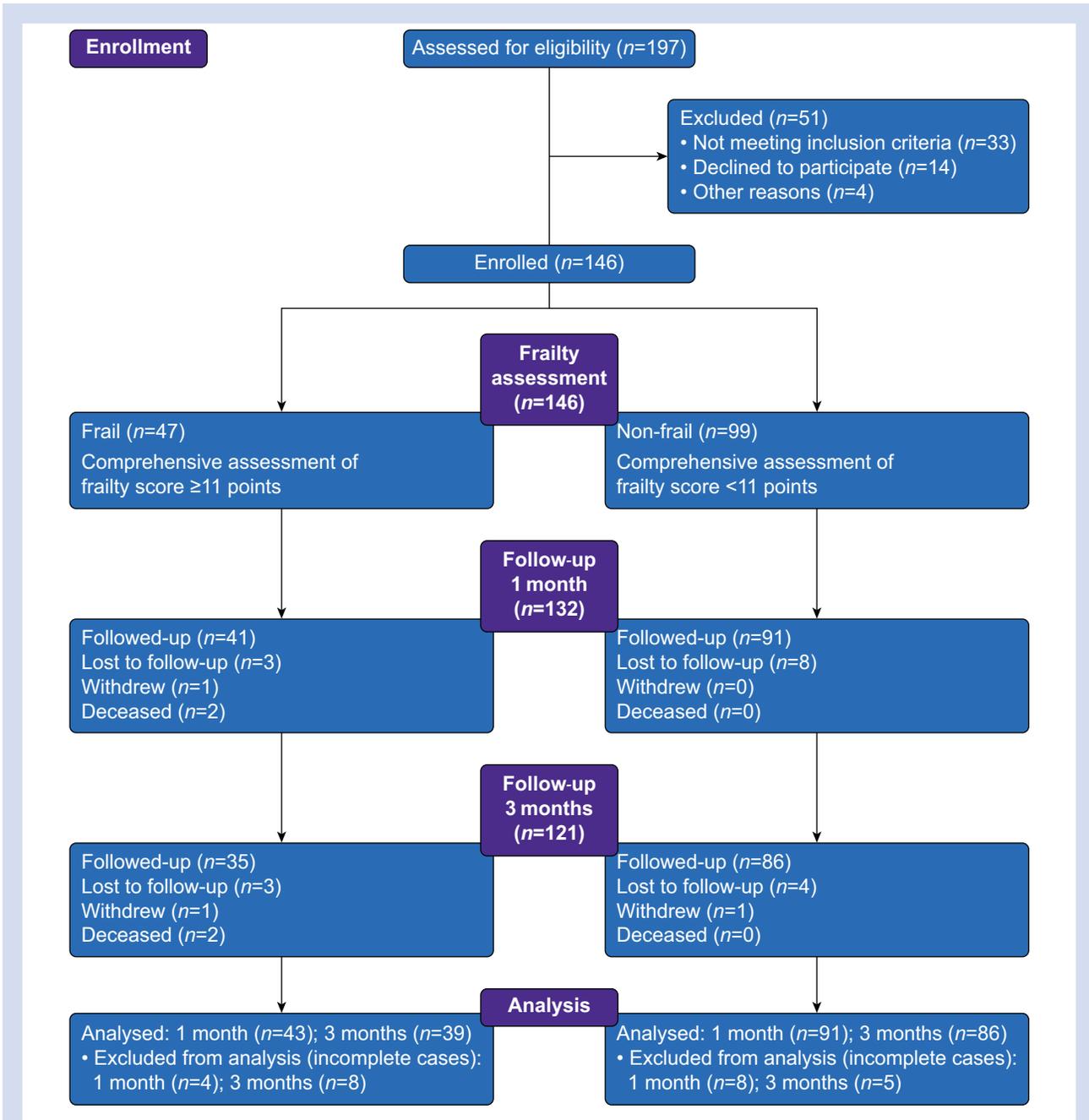


Fig 1. Consolidated Standards of Reporting Trials diagram.

Table 3 Odds ratios for the association between preoperative CAF-based frailty and disability-free survival at 1 and 3 months. *Estimates adjusted for age and EuroSCORE II values for each patient in logistic model. CAF, comprehensive assessment of frailty; DFS, disability-free survival; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II. Odds ratios (ORs) and 95% confidence intervals (CIs) based on univariate logistic regression models.

Preoperative frailty	Postoperative free of disability and alive (DFS)	Unadjusted estimates			Adjusted estimates*		
		OR	95% CI	P-value	OR	95% CI	P-value
CAF score ≥ 11	1 Month	0.33	0.15–0.72	0.006	0.64	0.29–1.09	0.177
	3 Months	0.23	0.08–0.62	0.004	0.51	0.24–0.89	0.045

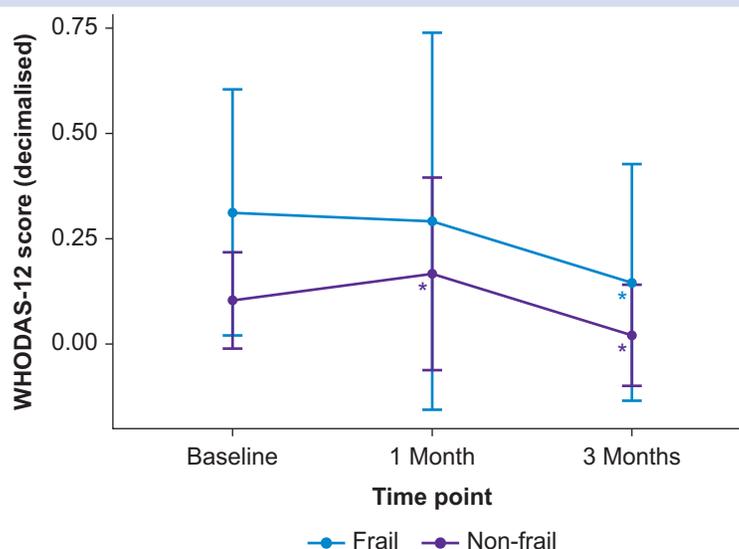


Fig 2. Frailty group assignment and median disability (WHODAS-12) score (%; inter-quartile range) at baseline ($n=146$), 1 month ($n=134$), and 3 months ($n=125$). Frail patients: change from preoperative to 1 month ($P=0.72$) and 3 months ($P=0.02$). Non-frail patients: change from preoperative to 1 month ($P=0.002$) and 3 months ($P<0.001$). Asterisk (*) denotes significant change from preoperative value ($P<0.05$). WHODAS-12, WHO Disability Assessment Schedule 2.0: 12-Part Questionnaire score.

frail patients had a significant increase in disability scores at 1 month ($P<0.001$), before a significant decline in disability scores at 3 months ($P<0.001$) (Fig 2) when compared with preoperative disability scores.

The median disability score, assessed in percentage change, showed a different trajectory for non-frail and frail patients postoperatively. At 1 month, non-frail patients had an increased burden of disability, whereas frail patients had a reduced disability burden (+4.2% vs -2.1%; $P=0.04$). At 3 months, disability burden had reduced for both groups, and this reduction was significantly greater in the frail patients (-6.3% vs -10.4%; $P=0.02$) (Table 2).

Considering disability scores only in patients with a minimum significant change in disability (i.e. a change $\geq 5\%$), median change from baseline demonstrated similar trajectories as for the change across all patients (Supplementary Table S2). Frail patients showed an improving trajectory, with reduced minimum significant change in disability scores at 1 and 3 months (-6.3% [-10.4%–{+20.3%}] and -13.5% [-29.7%–{-10.4%}], median [IQR], respectively), whereas the minimum significant change in disability scores in non-frail patients showed an initial increase towards higher disability at 1 month and an improvement at 3 months (+14.3% [-6.3%–{+22.4%}] and -9.4% [-14.6%–{+6.3%}], median [IQR], respectively).

Predictability of postoperative DFS by preoperative EuroSCORE, frailty, and disability scores

Empirical ROC analyses demonstrated that frailty and disability scores predict being free of disability and alive (DFS) at 3 months postoperatively more reliably, with areas under the curves (AUCs) of 0.76 and 0.77 (adjusted) (0.72 and 0.79 unadjusted), respectively, when compared with the EuroSCORE, which had an AUC of 0.61 (unadjusted 0.62) (Fig 3; Supplementary Fig 3).

Association of frailty scores and perioperative disability scores

When treated as a continuous variable, the frailty (CAF) score shows a moderate correlation with preoperative disability (WHODAS-12) scores, a weak correlation with 1 month disability scores, and a moderate correlation with 3 month postoperative disability scores (Supplementary Fig. 1a–c). Correlations between CAF score and 3 month postoperative disability scores were moderate for frail patients and weak for non-frail patients (Supplementary Fig. 1e and 1f). The preoperative disability scores were moderately correlated with both 1 and 3 month postoperative disability scores, and moderately negative correlated with the difference in disability scores from baseline to 3 months (Supplementary Fig. 1g–i).

Preoperative frailty, postoperative DFS, and EuroSCORE II

The EuroSCORE II demonstrated only a weak correlation with preoperative CAF scores ($\rho=0.31$; $P<0.001$), preoperative WHODAS-12 scores ($\rho=0.25$; $P=0.002$), and 3 month WHODAS-12 scores ($\rho=0.23$; $P=0.01$) (Supplementary Fig 2).

Discussion

This study demonstrates that preoperative frailty (as determined by the CAF score) is associated with a reduced likelihood of being free of disability and alive compared with non-frail patients, with the odds for this outcome reduced by half. Furthermore, frailty was associated with a significantly lower fraction of patients who were free of disability and alive at 1 and 3 months, when compared with patients deemed not frail, and the average degree of disability faced by individual patients was also greater in this group. However, whereas the

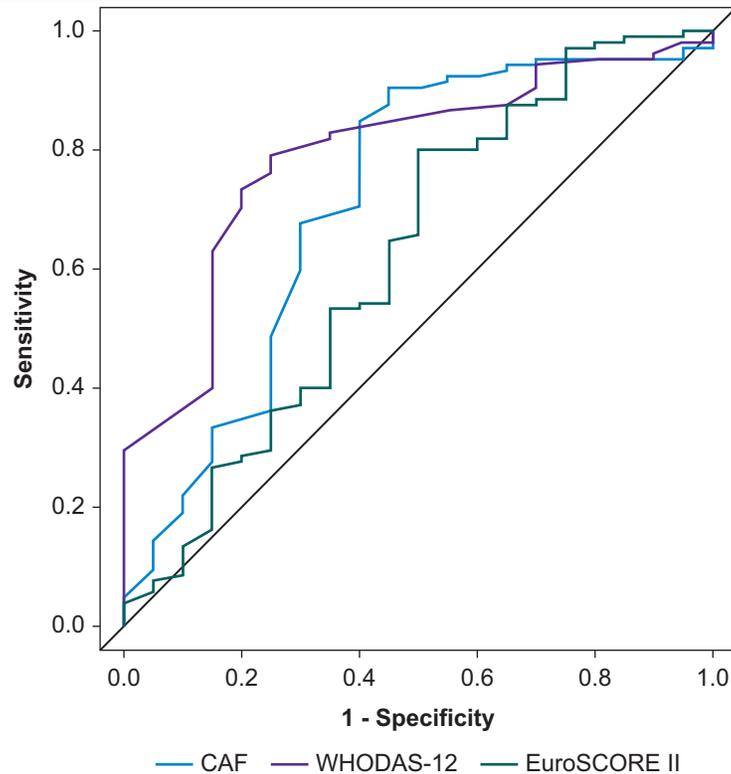


Fig 3. Empirical receiver operating characteristic (ROC) curves for the performance of unadjusted models of the CAF score, WHODAS-12 score, and EuroSCORE II to predict patients being free of disability and alive (DFS) at 3 months. Unadjusted (continuous) CAF score: AUC 0.72 [95% CI: 0.57–0.86] and optimal cut-off score 13.8 (sensitivity 91%; specificity 55%; accuracy 85%; NPV 52%; PPV 91%). (HL P-value: 0.2421). Unadjusted WHODAS-12 score: AUC 0.79 [95% CI: 0.69–0.90] and optimal cut-off score 24.0% (sensitivity 79%; specificity 75%; accuracy 78%; NPV 41%; PPV 94%). (HL P-value: 0.24). Unadjusted EuroSCORE II: AUC 0.62 [95% CI: 0.47–0.77] and optimal cut-off score 2.4% (sensitivity 80%; specificity 50%; accuracy 75%; NPV 32%; PPV 89.4%). (HL P-value: 0.9064). AUC, area under the curve; CAF, comprehensive assessment of frailty; CI, confidence interval; DFS, disability-free survival; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; HL P-value, Hosmer–Lemeshow goodness-of-fit test P-value; NPV, negative predictive value; PPV, positive predictive value; WHODAS-12, WHO Disability Assessment Schedule 2.0: 12-Part Questionnaire score (in % of the maximum disability score).

disability burden in non-frail patients was increased at 1 month compared with preoperative disability, it continuously decreased in frail patients postoperatively, demonstrating a positive trajectory of this patient-centred outcome.

The most important addition to our knowledge is the observation that non-frail patients experienced a degree of bidirectionality with regard to the incidence of significant disability, with levels highest at 1 month postoperatively, before reaching their lowest levels at 3 months. Whereas frail patients have a greater degree of disability at baseline, they display a very different trajectory, with reduced disability scores (i.e. a decreased disability burden), from baseline through each time point. Long-term improvement in disability, and thus a recovery trajectory, in patients initially deemed frail has been described in older patients undergoing noncardiac surgery.¹⁴ However, the trajectory of a decreased burden of disability in frail patients after cardiac surgery is a novel and important observation, as several other studies have failed to assess post-surgical change in disability. Thus, whereas frailty is associated with increased mortality,^{7,19} surviving frail patients are more likely to see continuous

improvements of their disability burden after cardiac surgery when compared with non-frail patients.

The CAF incorporates both specific deficit and phenotypical evaluation for frailty, and assignment as frail is associated with increased 30 day and 1 yr mortality.^{7,19} The incidence of frailty (32.2%) was in keeping with the established incidence of 20–50% in patients undergoing cardiac surgery.^{6,7} Incidence of CAF-defined frailty was previously found to be higher (53.5%), but notably in a cohort of older patients, with higher median CAF scores and higher mortality amongst frail patients.^{7,19} Previous studies have used frailty assessments to detect, and thus risk stratify according to, physiological differences not well accounted for by more traditional risk scoring systems. The results presented here add weight to this argument, as both the frail and non-frail cohorts were largely similar with regard to patient characteristics, age, comorbidities, and medication use. In contrast, there were significant differences in incidence and average degree of preoperative disability, and also, for example, functional classification of cardiac performance, such as New York Heart Association class. Similarly, a statistically significant difference exists between groups with

respect to EuroSCORE II value. Other studies have also suggested that the EuroSCORE II may overestimate perioperative risk,²⁵ with an overdependency on chronological age and comorbidity,^{7,26,27} lacking the dynamic nature of some frailty assessments, which aim to capture biological age.²⁸

Being free of disability and alive is a patient-centred outcome, which has been used as an endpoint in a study of patients undergoing surgery, with disability measured with WHODAS-12.²² This study demonstrated a similar level of preoperative disability as we have, and in addition, we have shown moderate correlation between preoperative frailty and preoperative WHODAS-12 scores. Mortality is a more commonly used primary endpoint, alongside composite cardiac or procedural outcomes,^{4,6,19,26,29} with patient-centred outcomes being more commonplace in studies involving minimally invasive cardiac procedures.^{30–32} Disability has also been investigated as part of a composite secondary outcome³³ and as part of the concept of ‘functional decline’ or the inability to complete ADL,^{34–37} and these outcomes have been investigated in the context of preoperative frailty.^{38,39} However, being free of disability and alive provides an outcome that incorporates functional performance alongside survival and, similar to the concept of ‘days alive at home’,⁴⁰ it is likely to have greater relevance to the preoperative patient. Underlying this complex relationship is the likelihood that the underlying cardiac pathology impinges upon performance during frailty assessment preoperatively. Our results make clear the requirement to isolate the manifestations of frailty, as opposed to those of the primary cardiac disease.³⁰ The CAF is a multi-domain assessment, and as such should reduce, but not remove entirely, the confounding effect of the underlying primary pathology and may improve the predictive ability of the component assessments.³⁰ Furthermore, whilst preoperative frailty may make the deleterious early manifestations and complications of major surgery more severe, the improved postoperative cardiac performance will be of greatest benefit to those most seriously affected (i.e. the frail cohort) and potentially explains why disability is markedly reduced over the longer term.⁴¹

We present OR adjusted for EuroSCORE II values, and also age, despite lack of clear association between the former and the frailty score for individual patients. Although the findings here cannot quantify the additional discriminatory ability of the frailty score, we find further support for the notion that the EuroSCORE II is poorly predictive of patient-centred outcomes, such as disability burden. The ROC analysis clearly shows that frailty and preoperative disability scores predict postoperative disability burden more reliably than the EuroSCORE. As such, the addition of frailty measures, specifically the CAF,⁴² to more traditional perioperative risk scoring systems may improve predictive ability for relevant patient-related clinical outcomes.^{17,38}

Future studies

In the future, it will be important to address the perioperative trajectory of disability in patients undergoing cardiac surgery in relation to preoperative frailty in a larger multicentre cohort of patients. If the observations from this single-centre study can be confirmed, then the improved trajectory of postoperative disability burden, a patient-centred outcome, will need to be considered strongly in the decision-making regarding frail patients undergoing cardiac surgery. Frailty as a predictor for postoperative disability, assessed by disability

for basic ADL, has been observed in older patients undergoing aortic transcatheter and surgical valve replacements.³³ These results demonstrating that preoperative frailty is associated with postoperative worsening disability are in strong contrast to our findings, and future studies will need to reassess these diverging findings in this specific surgical cohort. Particularly, more thorough investigations using a comprehensive frailty assessment tool and perioperative disability scores, such as the WHODAS score, may assist in identifying patients likely to benefit from an invasive or noninvasive type of cardiac surgical intervention for aortic valve disease.³²

Acknowledging that the frailty state is the result of numerous, potentially interacting, physiological insults, and the relationship between preoperative frailty and postoperative disability does not appear to be either simple or linear, this area has been confirmed as one requiring further study. The crucial next step will be to investigate individual elements of the frailty assessment, and their relationship with frailty and vulnerability to disability, and their association with cardiac disease, to enable bedside prediction of the utility of surgery. Our results confirm the feasibility of assessing frailty before operation and disability throughout the perioperative period for patients undergoing cardiac surgery. Furthermore, our exploratory ROC analysis of the predictive ability of frailty and disability scores to predict disability has yielded potentially clinically useful threshold values, which should be investigated in a larger study.

The results of this investigation should prompt perioperative teams to consider that frail preoperative patients may experience an improvement in their disability level after cardiac surgery.

Strengths and limitations

The strengths of this study are the use of a well-described frailty assessment and a relevant patient-centred outcome, and what we believe to be the first use of WHODAS-12 in patients undergoing cardiac surgery. This validated measure can be easily completed over the phone for further follow-up, increasing its applicability to further research and clinical practice. Finally, the collection of preoperative and postoperative disability levels allowed frailty and disability, and transitions of both, to be considered throughout the study period, providing insight into the shortcomings of current assessment models.

This single-centre study used the CAF score, which incorporates a subjective investigator’s score, introducing a risk of observer bias, although this should be minimised by the multimodal nature of the assessment. Use of the WHODAS-12 questionnaire invites potential for recall bias; however, it remains of considerable value as a pragmatic, reproducible, and genuinely patient-oriented measure of outcome. Initial assessment of CAF could be prohibitively time-consuming in a busy pre-assessment clinic, thus limiting general uptake, although this was not our finding.

WHODAS-12 was used as the primary follow-up tool, and the CAF was only performed at baseline. Although evaluation of ongoing postoperative frailty could be of considerable value, our intention was to focus upon a patient-centred outcome (such as DFS), rather than assessing ongoing vulnerability to physiological deterioration, which will be less easily modifiable, and of less consequence to the perioperative physician. Furthermore, postoperative CAF follow-up would have mandated in-person follow-up. A limited number of patients were lost to follow-

up, and given sample size and the nature of the study, data imputation was felt to be inappropriate. Deceased patients were assigned a maximum disability score to enable them to be included in the final analysis. This results in a conservative assessment of patients' improving disability trajectory in the frail group, which would be even more pronounced if deceased patients were not included as maximal disabled.

We believe that the chosen cut-off value below 25% for disability-free patients serves as a reasonable threshold in cardiac patients, which of course may be refined with future investigations, as indeed Shulman and colleagues²³ have done over the past 5 or so years. We acknowledge that the term 'disability-free' at this cut-off value may include patients with mild disability; however, based on the best available evidence, it is unlikely to include more patients with moderate disabilities.

Conclusions

Patients deemed to be frail by a comprehensive preoperative assessment had higher disability scores postoperatively than patients deemed to be non-frail before cardiac surgery. However, within the group of frail patients, disability scores were continuously improving postoperatively, whereas a more complex relationship existed for non-frail patients. This suggests an important interplay between either frailty or frailty assessment measures underlying pathology and existing disability, which should be included in preoperative decision-making of frail patients. This study adds yet further weight to the concept that traditional cardiac perioperative risk scores are poor predictors of patient-centred outcomes.

Authors' contributions

Data acquisition: JLC, HK, SC, GK
 Data analysis: SA, BM, GK
 Data interpretation: BM, JLC, GK
 Drafting of paper: BM, JLC, SA, GK
 Revising and approving of final paper: all authors

Acknowledgements

The authors would like to thank Weihong Du, Jacopo Berti, Rachel McNulty, and Lloyd Kwanten for their contributions to the data collection. The views expressed are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health.

Declarations of interest

The authors declare that they have no conflicts of interest.

Funding

National Institute for Health Research to BM; National Institute of Academic Anaesthesia John Snow Anaesthesia Inter-calated 2016 award to JLC; National Institute for Health Research Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London to SA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2022.03.015>.

References

1. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc* 2013; **14**: 392–7
2. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American geriatrics society/national institute on aging research conference on frailty in older adults. *J Am Geriatr Soc* 2006; **54**: 991–1001
3. Graham A, Brown CH. Frailty, aging, and cardiovascular surgery. *Anesth Analg* 2017; **124**: 1053–60
4. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation* 2010; **121**: 973–8
5. Afilalo J, Eisenberg MJ, Morin JF, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *J Am Coll Cardiol* 2010; **56**: 1668–76
6. Afilalo J, Mottillo S, Eisenberg MJ, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. *Circ Cardiovasc Qual Outcome*. 2012; **5**: 222–8
7. Sündermann S, Dademasch A, Rastan A, et al. One-year follow-up of patients undergoing elective cardiac surgery assessed with the comprehensive assessment of frailty test and its simplified form. *Interact Cardiovasc Thorac Surg* 2011; **13**: 119–23. discussion 123
8. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg* 2010; **210**: 901–8
9. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; **56**: M146–56
10. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci* 2007; **62**: 738–43
11. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med* 1995; **332**: 556–61
12. Vermeulen J, Neyens JC, van Rossum E, Spreeuwenberg MD, de Witte LP. Predicting ADL disability in community-dwelling elderly people using physical frailty indicators: a systematic review. *BMC Geriatr* 2011; **11**: 33
13. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014; **63**: 747–62
14. McIsaac DI, Taljaard M, Bryson GL, et al. Frailty and long-term postoperative disability trajectories: a prospective multicentre cohort study. *Br J Anaesth* 2020; **125**: 704–11
15. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: an independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc* 2010; **58**: 643–9
16. Thalji NM, Suri RM, Greason KL, Schaff HV. Risk assessment methods for cardiac surgery and intervention. *Nat Rev Cardiol* 2014; **11**: 704–14
17. Sepeshri A, Beggs T, Hassan A, et al. The impact of frailty on outcomes after cardiac surgery: a systematic review. *J Thorac Cardiovasc Surg* 2014; **148**: 3110–7
18. Mohanty S, Rosenthal RA, Russell MM, Neuman MD, Ko CY, Esnaola NF. Optimal perioperative management of the geriatric patient: a best practices guideline from the

- American College of Surgeons NSQIP and the American Geriatrics Society. *J Am Coll Surg* 2016; **222**: 930–47
19. Sündermann S, Dademasch A, Praetorius J, et al. Comprehensive assessment of frailty for elderly high-risk patients undergoing cardiac surgery. *Eur J Cardiothorac Surg* 2011; **39**: 33–7
 20. Myles PS. Meaningful outcome measures in cardiac surgery. *J Extra Corpor Technol* 2014; **46**: 23–7
 21. Ustun TB, Kostnjeseck N, Chatterji S, Rehm J. *Measuring Health and disability: manual for WHO disability assessment Schedule (WHODAS 2.0)*. Geneva: World Health Organization; 2010
 22. Shulman MA, Myles PS, Chan MT, McIlroy DR, Wallace S, Ponsford J. Measurement of disability-free survival after surgery. *Anesthesiology* 2015; **122**: 524–36
 23. Shulman MA, Kasza J, Myles PS. Defining the minimal clinically important difference and patient-acceptable symptom state score for disability assessment in surgical patients. *Anesthesiology* 2020; **132**: 1362–70
 24. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods* 2009; **41**: 1149–60. 24
 25. Barili F, Pacini D, Capoa A, et al. Does EuroSCORE II perform better than its original versions? A multicentre validation study. *Eur Heart J* 2013; **34**: 22–9
 26. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. *JACC Cardiovasc Interv* 2012; **5**: 974–81
 27. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. *BMC Geriatr* 2002; **2**: 1
 28. Kim S, Jazwinski SM. Quantitative measures of healthy aging and biological age. *Healthy Aging Res* 2015; **4**: 26
 29. Stortecky S, Schoenenberger AW, Moser A, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2012; **5**: 489–96
 30. Green P, Arnold SV, Cohen DJ, et al. Relation of frailty to outcomes after transcatheter aortic valve replacement (from the PARTNER trial). *Am J Cardiol* 2015; **116**: 264–9
 31. Osnabrugge RL, Arnold SV, Reynolds MR, et al. Health status after transcatheter aortic valve replacement in patients at extreme surgical risk: results from the CoreValve U.S. trial. *JACC Cardiovasc Interv* 2015; **8**: 315–23
 32. Arnold SV, Reynolds MR, Lei Y, et al. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. *Circulation* 2014; **129**: 2682–90
 33. 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
 34. 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
 35. Henry L, Halpin L, Barnett SD, Pritchard G, Sarin E, Speir AM. Frailty in the cardiac surgical patient: comparison of frailty tools and associated outcomes. *Ann Thorac Surg* 2019; **108**: 16–22
 36. Kim DH, Afilalo J, Shi SM, et al. Evaluation of changes in functional status in the year after aortic valve replacement. *JAMA Intern Med* 2019; **179**: 383–91
 37. Nomura Y, Nakano M, Bush B, et al. Observational study examining the association of baseline frailty and post-cardiac surgery delirium and cognitive change. *Anesth Analg* 2019; **129**: 507–14
 38. 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
 39. Kimber DE, Kehler DS, Lytwyn J, et al. Pre-operative frailty status is associated with cardiac rehabilitation completion: a retrospective cohort study. *J Clin Med* 2018; **7**: 560
 40. McIsaac DI, Föttinger A, Sucha E, McDonald B. Association of frailty with days alive at home after cardiac surgery: a population-based cohort study. *Br J Anaesth* 2021; **126**: 1103–10
 41. McAdams-DeMarco MA, Isaacs K, Darko L, et al. Changes in frailty after kidney transplantation. *J Am Geriatr Soc* 2015; **63**: 2152–7
 42. Bäck C, Hornum M, Jørgensen MB, Lorenzen US, Olsen PS, Møller CH. Comprehensive assessment of frailty score supplements the existing cardiac surgical risk scores. *Eur J Cardiothorac Surg* 2021; **60**: 710–6

Handling editor: Paul Myles