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ORIGINAL ARTICLE

A novel geriatric assessment frailty score predicts 2-year mortality after transcatheter aortic valve implantation

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Aims Established surgical scores have limitations in delineating risk among candidates for transcatheter aortic valve implantation (TAVI). Assessment of frailty might help to estimate the mortality risk and identify patients likely to benefit from treatment. The aim of the study was to develop a frailty score to guide the decision for TAVI.

Methods and results We conducted a prospective observational study in patients ≥70 years referred for TAVI during 2011–15. A Heart Team had declined the patients for open heart surgery due to high risk but accepted them for TAVI. Prior to the procedure, a geriatric assessment (GA) was performed. Based on this, an 8-element frailty score with a 0–9 (least frail–most frail) scale was developed. A total of 142 patients, 54% women, mean age 83 (standard deviation 4) years, with severe and symptomatic aortic stenosis were assessed. All-cause 2 year mortality was 11%. The novel GA frailty score predicted 2-year mortality in Cox analyses, also when adjusted for age, gender, and logistic EuroSCORE [hazard ratio (HR) 1.75, 95% confidence interval (CI): 1.28–2.42, P < 0.001]. A receiver operating characteristic (ROC) curve analysis indicated that a GA frailty score cut-off at ≥4 predicted 2-year mortality with a specificity of 80% (95% CI: 73–86%) and a sensitivity of 60% (95% CI: 36–80%). The area under the curve was 0.81 (95% CI 0.71–0.90).

Conclusion A novel 8-element GA frailty score identified gradations in survival in patients declined for open heart surgery. Patients with higher GA frailty scores had significantly higher 2-year mortality after TAVI.

Keywords TAVI • Decision-making • Frailty • Ageing • Prognosis

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Introduction

The population of older adults is growing, and intrinsic susceptibility to aortic stenosis is high with this new demographic scenery. Improved decision making is necessary for the expanding population of those eligible for transcatheter aortic valve implantation (TAVI).[1]

Commonly used risk scores for mortality and morbidity in coronary heart surgery, like the Society of Thoracic Surgeons risk score (STS score) and European System for Cardiac Operative Risk Evaluation (EuroSCORE), are based on age and comorbidity.[2,3] However, by omitting frailty, sensitivity of these scores to predict adverse events in the oldest population is limited.[4–6] Frailty, a condition frequent in older adults, is defined as a state of impaired physiologic reserve and decreased resistance to stressors which increase the risk of an adverse outcome.[7,8] Frailty status enhances prognostic sensitivity for patients with multiple heart conditions including acute coronary disease, stable angina, heart failure, [9–11] and TAVI.[12,13] A recent systematic review confirmed the relationship between frailty and mortality in the TAVI population, with a more than doubled risk [hazard ratio (HR) 2.35] of early (≤30 days) death in frail patients, and a 1.63 HR of later death.[14] Although TAVI has been assessed to be cost-effective compared with medical treatment,[15] this is undermined by early mortality after TAVI. As the population of older adults expands, it is important to select patients who will benefit most from the intervention to best justify its expense.[16]

Both US and European guidelines recommend the use of a Heart Team in decision making prior to treatment for severe, symptomatic aortic stenosis.[17,18] In addition to the assessments by the interventional cardiologist, cardiac surgeons and imaging specialists, the guidelines recommend a frailty assessment to evaluate cognition and physical function using validated checklists.[17] However, it is not described in detail who should perform and evaluate the frailty assessment and which tools to use.[1,17,19] Recently, Afilalo *et al.*[20] demonstrated that the essential frailty toolset (EFT) outperformed other frailty scores in predicting 1-year mortality in TAVI patients. Nonetheless the authors emphasized that the EFT is primary a screen for frailty. Once patients are identified by the EFT, further geriatric assessment (GA) is recommended. This demands a more thorough clinical evaluation. We developed a novel frailty score that provides additional information, based on a comprehensive GA. In this study, we show the utility of this novel GA frailty score to predict 2-year mortality, showcasing its powerful prognostic value.

Methods

Study design

A prospective, observational cohort study with 2-year follow-up and inclusion of elective TAVI patients from 2011 to 2015. The study was approved by the Regional Committee for Medical Research Ethics (REK 2010/2936-6 and 2013/1310). All participants signed an informed consent before assessment.

Participants

Patients with severe and symptomatic aortic stenosis accepted for TAVI were recruited from a tertiary university hospital in Western Norway serving a population of 1.1 million. All patients were recruited the day before the procedure and were assessed by a Heart Team consisting of a cardiac surgeon, an interventional cardiologist and an imaging specialist. Based on the evaluation, patients were all turned down for open heart surgery due to comorbidity and/or high EuroSCORE. The recruitment period lasted from February 2011 to April 2015. From February 2011 to September 2013, 65 patients ≥80 years also participating in a concomitant study of delirium were included.[21] From October 2013 to April 2015, 82 patients ≥70 years were included (*Figure 1*). Age was then adjusted to 70 years as frailty was assessed to be important also in this younger group. Exclusion criteria were declined consent or inability to understand and/or speak Norwegian.

Severe aortic stenosis was defined as maximal Doppler velocity across the aortic valve ≥4 m/s, a mean gradient ≥40 mmHg or an aortic valve area <1 cm^2 (indexed area <0.6 cm^2/m^2) and concomitant clinical symptoms indicating severe aortic stenosis.

Development of a novel frailty score

The GA frailty score was developed based on a comprehensive GA which includes cognition, instrumental activity of daily living, nutrition, physical frailty, comorbidity, and psychological health.[22,23] The method for developing this score is described by Harrell.[24] In this method expert clinicians assign severity points to each condition and sum the points in a total score. Three geriatricians (A.W.S., A.H.R., and E.S.) and one cardiologist (J.E.N.) independently ranked the clinical severity of signs within each potentially important domain. The suggestions were sent to the first author who developed a combined frailty score based on the different proposals.[24] All cut-off values in this combined score were based on previous studies.[13,22] The researchers then agreed on the GA frailty score, a 0–9 point numeric scale with 8 validated geriatric variables (*Table 1*). The score was finalized before the statistical analysis were performed.

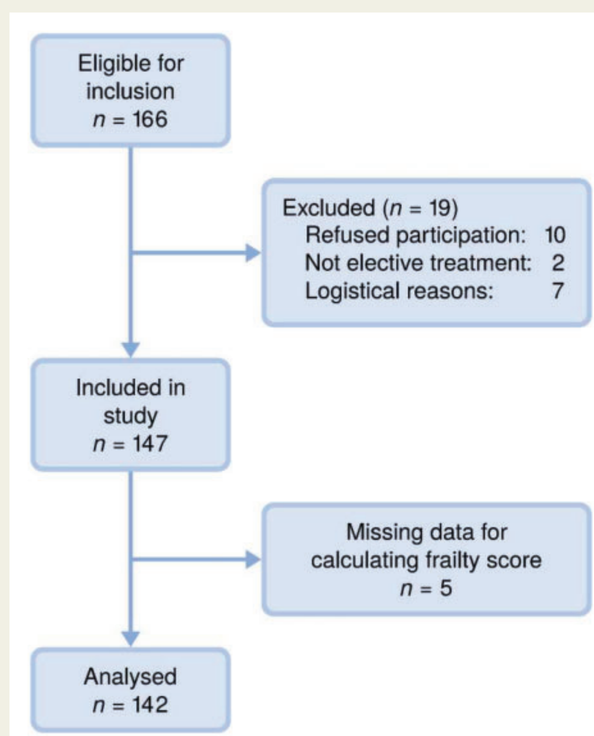

Figure 1 Patient recruitment flowchart.

Table 1 Geriatric assessment tools used in the novel frailty score, along with the corresponding scoring scheme

Domain	Cut-off	Points
Cognition	MMSE ≥27	0
	MMSE 20–26	1
	MMSE <20	2
Instrumental activity of living	NEADL ≤43	1
Nutrition	BMI <20.5	1
Energy level SOF index	Low energy	1
Weight loss SOF index[a]	Weight loss	1
Limb strength SOF index	Chair stand (not able)	1
Comorbidity	Charlson comorbidity index ≥3	1
Psychological factors	HADS (total score) ≥ 15	1
Total	Maximum score	9

The total score is calculated by adding the different domain scores.
BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini Mental Status Examination; NEADL, Nottingham Extended Activity of Daily Living Scale; SOF Study of Osteoporotic Fractures index.
[a]Modified from the original SOF; see 'Measurements' section for details.

Measurements

Novel frailty score

Baseline data were collected by L.S.P.E. and E.S. All baseline examinations were performed the day before the procedure. Cognition was assessed by the Mini Mental Status Examination (MMSE).[25] It has a range from 0 to 30, with higher scores indicating better cognition. Different cut-offs are reported, and we chose a weighted score with one point for possible cognitive impairment/mild dementia and two points for probable dementia.[13,26]

Instrumental activities of daily living was measured by Nottingham Extended Activities of Daily Living scale (NEADL),[27] a 22-item questionnaire assessing mobility, kitchen, domestic, and leisure activities. Each item has a score from 0 to 3, and the items are added to a total score from 0 to 66, with a higher score indicating better functioning. A cut-off ≤43 suggests that the patient is dependent, and studies have shown that this predicts complications and mortality after elective surgery in older patients.[28,29]

Nutrition was assessed by the body mass index (BMI) and the weight question of modified Study of Osteoporotic Fractures index. The cut-off value for BMI was based on the nutritional risk screening 2002, a screening instrument for nutritional risk.[30]

Physical frailty was assessed by a modified version (patients self-reported weight loss past year, not measured as in the original index) of the Study of Osteoporotic Fractures Index (mSOF index).[31] This validated index has a maximum of three points: (i) One point if the patient has >5% weight loss the previous year (Since, we only had baseline characteristics, the patients were given one point if answering yes to the question 'have you lost weight during the past year'), (ii) one point if the patient is unable to rise from a chair without using their arms (This was tested by L.S.P.E./E.S., not reported by the patients.), and (iii) one point if the patient answers no to the question 'Do you feel full of energy?'.

Comorbidity was assessed by Charlson comorbidity index. This is a weighted index based both on the numbers of diseases and the seriousness of each disease. A score of 1 is assigned for myocardial infarction, congestive heart failure, dementia, etc., while the highest score of 6 is given to metastatic solid tumours and AIDS. In the original paper describing the index, Charlson *et al.*[32] recommends a high cut-off of 2 or 3 if the mortality in the disease under study is high, and we chose a cut-off ≥3.

Psychological health was assessed by the Hospital Anxiety and Depression Scale (HADS),[33] with seven questions on anxiety and seven on depression. Each question ranges from 0 to 3. Summing up the anxiety and depression subscales, we get total HADS, of which a cut-off ≥15 was used to identify symptoms of anxiety and/or depression.[33,34]

The modified essential frailty toolset

The Essential Frailty Toolset (EFT) is a brief four-item (chair rise, cognition, haemoglobin, and serum albumin) frailty scale that predicts morbidity and mortality after TAVI.[20] Afilalo recommends applying this scale as a screening tool.[20] In this study, we aimed to compare the GA frailty score to the EFT.

However, for the first 62 patients in our study, we only had information on success/failure of chair rise, not on the number of seconds it took to complete the chair rises. Therefore, when calculating the EFT for these patients, we assigned 0 points if they completed five sit-to-stand repetitions without using arms (chair rises) and 2 points if they failed to complete all five chair rises. We refer to this modified methodology for the EFT as the modified Essential Frailty Toolset (mEFT). This might give some patients one point lower total score (i.e. the patients who used ≥15 s to perform chair rise). For three patients, we missed serum albumin values, and the mEFT was thus calculated for 139 patients.

Follow-up measurements

Two-year all-cause mortality has been stated as a clinically relevant outcome for TAVI candidates and was the primary outcome of this study.[1] The Valve Academic Research Consortium-2 (VARC 2) consensus document[6] recommends the use of composite endpoints after TAVI, and we report this for the first 6 months.

Power analysis

The initial power analysis was based on categorizing the patients into three groups, a fit group, an intermediate group and a frail group, with 25% in the frail group.[22,35,36] To achieve a power of 80% with a 5% level of significance, power calculations showed that we needed a total of 140 patients. To account for dropouts, we included 5% more, a total of 147 patients. In order to make the frailty score more applicable in clinical practice, we ultimately dichotomized it into frail and non-frail (fit and intermediate). In addition, we analysed frailty as a continuous score, which increases the statistical power.

Statistical analyses

We present the data as means and standard deviations (SDs), counts and percentages, or proportions and Hazard Ratios (HRs) with 95% confidence intervals (CIs), as appropriate. To assess whether the new frailty score could predict mortality within 2 years, and also when adjusted for other common predictors, we fitted Cox regression models with Firth's correction. Firth's correction provides reduced bias when there are few events (deaths) compared with the number of predictors. The regression models included frailty score as a continuous predictor (unadjusted model/trend test), or frailty score, age, gender, and logistic EuroSCORE as predictors (adjusted model). We also fit a similar adjusted model with frailty score as a dichotomized variable. We present time to death stratified by frailty score (continuous or dichotomized) using Kaplan–Meier plots.

The Receiver Operating Characteristic (ROC) curve[37] was examined to find cut-off values for the dichotomized GA frailty score. We reported the Area Under the Curve (AUC) as a summary measure. We found two cut-off values with an estimated high sensitivity and specificity, and chose the one (≥4) emphasizing specificity over sensitivity. Confidence intervals for the sensitivity and specificity were calculated using the Wilson (score) method.[38]

Some patients had missing data for a few of the questions in the HADS and NEADL questionnaires. Where it was unambiguous on which side of the cut-off the total score would fall on, we used the data for these patients; otherwise, the patients were excluded. For one secondary analysis (based on the mEFT frailty scale), there were additional missing data. For all analyses, we report the number of observations used.

Statistical analyses were performed using IBM SPSS Statistics 24 and R version 3.5.0.[39] Cox regression with Firth's correction was performed using R 'coxphf' package[40] version 1.13, and the ROC and AUC calculations were performed using the R 'pROC' package version 1.12.1.[41]

Results

Baseline data

General characteristics

A total of 147 patients with severe and symptomatic aortic stenosis were included. Of these, 142 patients had enough data so that the frailty score could be computed (*Figure 1*). Of the 142 patients, 54% were women, mean age was 83 years (SD 4), five patients were less than 75 years old and three patients were 90 years or older. The oldest patient in the study was 95 years old. More than half of the patients lived with their spouse.

Geriatric characteristics

More than half of the patients (56%) did not have significant cognitive disturbance, a MMSE of 27 or higher. The others (44%) had possible cognitive impairment, but for most of them (89%) probably mild cognitive impairment or mild dementia (MMSE 20–26). Most patients (82%) had a NEADL score above 43, suggesting they were independent in activities of daily living. Few patients (13%) had low BMI (below 20.5 kg/m^2); however, 52 (37%) patients had a reported weight loss during the last year. Sixty-one (43%) of the patients had a high score of ≥3 on the Charlson comorbidity scale.

Cardiovascular characteristics

Almost all patients 127/135 (missing data on seven patients) had an indexed aortic valve area below 0.6 cm^2/m^2. Logistic EuroSCORE was below 10 in 18% and over 20 in 30% of the patients. Half of the patients had New York Heart Association III or IV at the time of the procedure (*Table 2*).

Follow-up

No patients were lost to follow-up.

Mortality and morbidity

Fifteen patients (11%) had died within 2 years, 11 of cardiovascular causes and four of non-cardiovascular causes. There was a high degree of early device success, with 141/142 (99.3%) valves in the correct position with good valve function. Early (≤30 days) mortality was seen in four patients (2.8%). Moderate to severe prosthetic valve regurgitation and stroke occurred within 6 months in 12.7% and 4.8% of the patients, respectively (*Table 3*).

Table 2 Patient baseline characteristics (*n* = 142)

	Mean or count	SD or (proportion)
Characteristics		
Age, years	83.4	4.0
Women	76	(54%)
Living alone	60	(42%)
Education		
Primary school	88	(62%)
High school	33	(23%)
University	21	(15%)
Geriatric characteristics		
Cognition		
MMSE	26.3	3.3
MMSE ≥27	80	(56%)
MMSE 20–26	55	(39%)
MMSE <20	7	(5%)
Activities of daily living		
NEADL ≤43	121	(82%)
Nutrition		
BMI	25.0	3.9
BMI <20.5	19	(13%)
SOF index		
Weight loss[a]	52	(37%)
Low energy	58	(41%)
Unable to chair stand	42	(30%)
Comorbidity		
Charlson comorbidity index	2.53	1.3
Charlson comorbidity index ≥3	61	(43%)
Psychological factors		
HADS ≥15	17	(12%)
Cardiovascular characteristics		
Logistic EuroSCORE	17	8.7
Aortic valve area index, cm^2/m^2 [b]	0.4	0.12
Mean aortic valve gradient, mmHg[c]	47.6	14.4
Left ventricular ejection fraction	56.4	11
NYHA ≥III	67/134	(50%)
Previous myocardial infarction	34	(24%)
CABG	31	(22%)
Permanent pacemaker	12	(9%)
Atrial fibrillation	45	(32%)
Pulmonary hypertension	45/139	(32%)
Cerebral vascular disease	16	(11%)
Comorbidity		
COPD	31	(22%)
Kidney failure; creatinine >177 μmol/L[d]	5	(4%)

MMSE, Mini Mental Status Examination; NEADL, Nottingham Extended Activities of Daily Living Scale; BMI, Body Mass Index; SOF Index, Study of Osteoporotic Fractures Index; HADS, Hospital Anxiety and Depression Scale; NYHA, New York Heart Association Functional Classification of Heart Failure, Range From I-IV, Most Severe Symptoms at IV; CABG, Coronary Artery Bypass Grafting; COPD, Chronic Obstructive Pulmonary Disease.
[a]Modified from the original SOF index; see 'Measurements' section for details.
[b]Missing data on seven patients.
[c]Missing data on two patients.
[d]As reported in the PARTNER study; creatinine >2 mg/dL (177 μmol/L).[1]

Table 3 **Composite endpoints according to Valve Academic Research Consortium-2 consensus document[a] criteria**

	Total (N = 142)	Percent
Device success		
Absence of immediate procedural mortality[b]	142	100
Correct positioning	141	99.3
Intended performance of the prosthetic heart valve[c]	141	99.3
No moderate or severe prosthetic valve regurgitation[d]	135	95.1
Early safety(at 30 days)		
All-cause mortality	4	2.8
All stroke(disabling or non-disabling) in hospital[e]	4	2.8
Life-threatening or disabling bleeding	8	5.6
Acute kidney injury Stage 2 or 3[f]	3	2.1
Coronary artery obstruction requiring intervention	1	0.7
Major vascular complication	6	4.2
Valve-related dysfunction requiring intervention	1	0.7
Clinical efficacy(30 days–6 months)		
All-cause mortality	6	4.2
All stroke(disabling or non-disabling)	3	2.1
Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure	15	10.6
NYHA class III or IV[g]	9/136	6.6
Time-related valve safety		
Structural valve deterioration		
Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg) and/ or moderate or severe prosthetic valve regurgitation[h]	18/141	12.7
Requiring repeat procedure (TAVI or SAVR)	1	0.7
Prosthetic valve endocarditis	1	0.7
Trombo-embolic events (e.g. stroke)	7	4.8
VARC bleeding (life threatening/disabling bleeding or major bleeding) and unless clearly unrelated to valve therapy (e.g. trauma)	28	19.7

SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; NYHA New York Heart Association.
[a]The Valve Academic Research Consortium (VARC)-2 consensus document (see references).
[b]Immediate or consequent death ≤72 h post-procedure.
[c]No prosthesis patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s.
[d]After TAVI procedure at index hospitalization.
[e]Assessment of stroke at index. All strokes verified by imaging (CT or MRI).
[f]Evaluation of acute kidney injury is based on serum creatinine, we miss data on urine output.
[g]New York Heart Association (NYHA), missing data on six patients.
[h]Follow-up at 6 months, missing data on one patient.

Frailty and mortality

The distribution of frailty scores and the corresponding 2-year mortality is shown in *Table 5*. Based on the dichotomized GA frailty score, 34 patients (24%) were characterized as frail (score ≥4).

The Cox analyses showed that the continuous GA frailty score predicted mortality within 2 years, with an estimated HR of 1.79 (95% CI: 1.34–2.36, $P < 0.001$), i.e. an estimated 79% increase in hazard for a unit increase in GA frailty score. This predictive power also remained (HR = 1.75, 95% CI: 1.28–2.42, $P < 0.001$) when adjusting for age, gender, and logistic EuroSCORE (*Table 4*). A test of the proportional hazard assumption did not find any problems with the model ($P = 0.77$).

The corresponding results for the dichotomous GA frailty score were HR = 5.35 (95% CI: 1.99–15.3, $P = 0.001$) (unadjusted) and HR = 4.91 (95% CI: 1.79–14.2, $P = 0.002$) (adjusted).

The ROC curve (*Figure 2*) illustrates that a frailty score cut-off at ≥4 predicts 2 year mortality with a specificity of 80% (95% CI: 73–86%) and a sensitivity of 60% (95% CI: 36–80%). The AUC was 0.81 (95% CI: 0.71–0.90).

None of the patients with a frailty score of 0 or 1 were dead after 2 years, and none of the patients had a frailty score of 8 or 9. In general, the higher the frailty score, the higher the risk of dying within 2 years (*Table 5*).

When adjusting for mEFT along with age, gender, and logistic EuroSCORE, the continuous GA frailty score were no longer a statistically significant predictor (HR = 1.36, 95% CI: 0.87–2.21, $P = 0.18$, $n = 139$), and neither were any of the other variables (including mEFT).

Discussion

In this prospective observational study, we found that a novel GA frailty score could predict 2-year all-cause mortality in TAVI

Table 4 Cox regression (with Firth's correction) (*n* = 142)

	Unadjusted			Adjusted		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age, years	1.16	1.00–1.37	0.04	1.16	1.01–1.37	0.04
Male gender	1.01	0.37–2.71	0.99	2.14	0.68–6.93	0.19
Logistic EuroSCORE	1.06	1.01–1.11	0.02	1.04	0.99–1.08	0.13
GA frailty score	1.79	1.34–2.36	0.001	1.75	1.28–2.42	<0.001

CI, confidence interval; HR, hazard ratio.
Hazard ratio estimates (with 95% confidence intervals) for death within 2 years of transcatheter aortic valve implantation. The hazard ratios show the increase in hazard for a unit increase in age (years), logistic EuroSCORE and/or GA frailty score, and for males compared with females.

Table 5 Distribution of geriatric assessment frailty score and mortality within each frailty score (*n* = 142)

Frailty score	Count	Prop. (%)	Cum. prop. (%)	Deaths[a]	Mortality[a] (%)
0	15	11	11	0	0
1	26	18	29	0	0
2	39	27	56	2	5
3	28	20	76	4	14
4	20	14	90	4	20
5	10	7	97	3	30
6	2	1	99	2	100
7	2	1	100	0	0
8	0	0	100	—	—
9	0	0	100	—	—

Cum., cumulative; Prop., proportion.
[a]Deaths within 2 years after TAVI.

patients declined for open heart surgery by a Heart Team. After 2 years, there were no deaths in the cohort with very low (0 or 1) frailty score.

Standard risk scores like EuroSCORE and STS score are insufficient for predicting adverse events in the older adult,[11,13,42] and a frailty assessment adds information which increases predictability. There is an ongoing discussion regarding the definition of frailty and whether to include cognition, psychological factors, and comorbidity.[43] The GA frailty score was developed to provide information for a better decision making prior to TAVI. This study adds to previous work highlighting the need for a more thorough evaluation of the individual patient based on a comprehensive GA. This can provide significant decision-making support for the interventional cardiologist or surgeon. The purpose of the score is not to screen all TAVI candidates, as this will be too time-consuming. Rather it should be used in patients in whom a simpler screening[44] has revealed potential obstacles for TAVI. In this setting, an assessment solely on physical frailty would not be sufficient, in part due to decline in physical

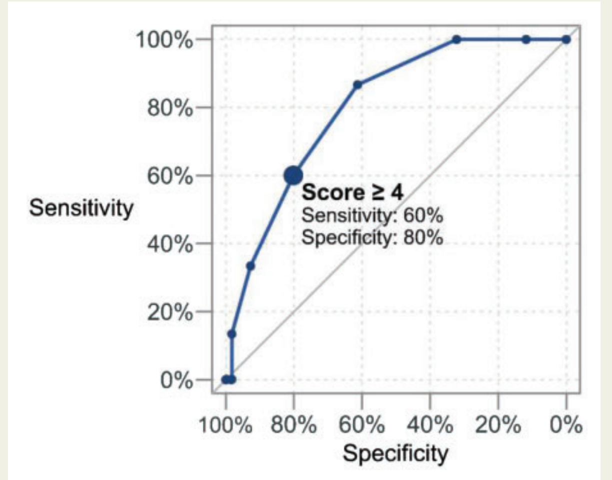

Figure 2 Receiver operator characteristics curve for geriatric assessment frailty score (0–9) and 2 year mortality (*n* = 142). The area under the curve is 0.81 (95% confidence interval: 0.71–0.90).

performance related to severe aortic stenosis. An approach with an initial basic screening for frailty and a selective thorough assessment by a geriatrician has been advocated.[44,45]

Patients categorized as frail might still be eligible for TAVI. All patients should be involved in a shared decision process regarding their treatment, but for patients where there is doubt whether the procedure is beneficial, it is especially important. Previous studies have underlined the importance of exploring patients' perspectives.[46,47] Asking the question 'What do you hope to accomplish by having your valve repaired?' might capture what is most important to patients.[48] The decision to offer TAVI should in the end be made by the interventional cardiologist or cardiac surgeon performing TAVI, based on an analysis of benefit vs. risk, taking into account symptoms, comorbidity, patient perspective, procedural risk, and frailty. We suggest the geriatrician to be an important collaborator in this analysis. If TAVI is offered despite frailty, the treatment team should be prepared for a higher risk of complications, including delirium.[21] Ideally, detecting frailty should lead to additional pre-, per-, and post-operative support.[11] The GA frailty score provides delineation of specific aspects of frailty that can be addressed (e.g. nutritional supply if undernourished, treatment for depression).[49,50] We do not have enough evidence to recommend specific exercise before TAVI in order to improve frailty status.

This study confirms the clinical relevance of frailty assessment prior to TAVI.[12,13,17] The GA frailty score evaluating cognition, independence in daily life, nutrition, physical frailty, comorbidity, and psychological health, give a thorough and comprehensive assessment of the patient. A high GA frailty score ≥4 indicates a reduced 2-year survival (*Figure 3*). However, we do not advocate a strict cut-off where TAVI is not offered. Knowledge of the (0–9 based) GA frailty score should lead to a careful final evaluation by the TAVI team, and should involve weighting frailty, technical challenges, exploring patient preferences, and symptom burden before offering TAVI. The geriatrician can contribute to the heart team as a frailty expert.

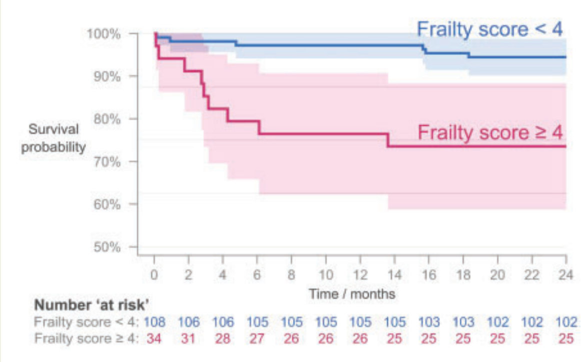

Figure 3 Kaplan–Meier plot of 2 years survival after transcatheter aortic valve implantation (n = 142). The coloured bands indicate 95% confidence intervals.

Strengths of the study

This is a prospective study, with potentially fewer sources of bias and higher quality of data than a retrospective study would have. In Norway, deaths of all patients are automatically registered in the patients' electronic journal. Our primary outcome is therefore complete. We also have high completeness in the rest of our data, and importantly, no patients are lost to follow-up for the primary endpoint. The variables included in the GA frailty score were determined before the statistical analysis, eliminating the risks associated with a purely data-driven analysis. Finally, our risk score was reliable in patients already excluded from surgery due to comorbidity.

Limitations of the study

Survival with benefit after 2 years is advocated as a relevant clinical endpoint, and it would have strengthened the study if we also assessed quality of life in the patient 2 years after the procedure.[1] However, there are limitations to soft endpoints, and in order to simplify the interpretation of the frailty score, we chose to focus mainly on prediction of mortality. Some items were self-reported and not performance based, introducing some subjectivity to the index; however, previous studies have showed for all the selected self-report items to be markers of frailty.[7,31] This is a single-centre study, and the results might not be transferable to any other centre, although they are probably comparable to other European centres of the same size. The study population changed during the study. Initially, inclusion consisted of patients ≥80 years, but was later expanded to include all patients ≥70 years. This was partly due to a shift in the general TAVI population, but also a growing awareness that frailty is a complex phenomenon where age is only one contributing factor.[7] The partial lack of data used in calculating the EFT score reduces the precision of the score somewhat. And finally, the small sample size (especially the few number of deaths) is a limitation, particularly for calculating the sensitivity of the dichotomized frailty score in predicting 2-year mortality. Before recommending the GA frailty scale, it needs to be validated in an independent population.

Conclusions

In patients declined for open heart surgery, an 8-element frailty score based upon GA can identify patients less likely to benefit from TAVI. Patients with a frailty score ≥4 had significantly higher 2-year mortality. We believe the novel GA frailty score has clinical relevance and may be a useful tool for heart teams in decision making for TAVI.

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References

1. Otto CM, Kumbhani DJ, Alexander KP, Calhoon JH, Desai MY, Kaul S *et al.* 2017 ACC expert consensus decision pathway for transcatheter aortic valve replacement in the management of adults with aortic stenosis: a report of the American College of Cardiology task force on clinical expert consensus documents. *J Am Coll Cardiol* 2017;**69**:1313–1346.
2. Clark RE. The STS cardiac surgery national database: an update. *Ann Thorac Surg* 1995;**59**:1376–1380; discussion 1380–1.
3. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;**16**:9–13.
4. Mack M. Frailty and aortic valve disease. *J Thorac Cardiovasc Surg* 2013;**145**:S7–S10.
5. Forman DE, Rich MW, Alexander KP, Zieman S, Maurer MS, Najjar SS *et al.* Cardiac care for older adults. Time for a new paradigm. *J Am Coll Cardiol* 2011;**57**:1801–1810.
6. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH *et al.* Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Thorac Cardiovasc Surg* 2013;**145**:6–23.
7. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J *et al.* Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M146–M156.
8. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013;**381**:752–762.
9. Rodriguez-Pascual C, Paredes-Galan E, Ferrero-Martinez AI, Gonzalez-Guerrero JL, Hornillos-Calvo M, Menendez-Colino R *et al.* The frailty syndrome is associated with adverse health outcomes in very old patients with stable heart failure: a prospective study in six Spanish hospitals. *Int J Cardiol* 2017;**236**:296–303.
10. Ekerstad N, Swahn E, Janzon M, Alfredsson J, Lofmark R, Lindenberger M *et al.* Frailty is independently associated with short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction. *Circulation* 2011;**124**:2397–2404.
11. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA *et al.* Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014;**63**:747–762.
12. Sepehri A, Beggs T, Hassan A, Rigatto C, Shaw-Daigle C, Tangri N *et al.* The impact of frailty on outcomes after cardiac surgery: a systematic review. *J Thorac Cardiovasc Surg* 2014;**148**:3110–3117.
13. Stortecky S, Schoenenberger AW, Moser A, Kalesan B, Juni P, Carrel T *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**:489–496.
14. Anand A, Harley C, Visvanathan A, Shah ASV, Cowell J, MacLullich A *et al.* The relationship between preoperative frailty and outcomes following transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes* 2017;**3**:123–132.
15. Watt M, Mealing S, Eaton J, Piazza N, Moat N, Brasseur P *et al.* Cost-effectiveness of transcatheter aortic valve replacement in patients ineligible for conventional aortic valve replacement. *Heart* 2012;**98**:370–376.

16. Puri R, Iung B, Cohen DJ, Rodes-Cabau J. TAVI or No TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. *Eur Heart J* 2016;**37**:2217–2225.
17. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ *et al*. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.
18. Mascherbauer J. The 2014 AHA/ACC valve disease guideline: new stages of disease, new treatment options, and a call for earlier intervention. *Wien Klin Wochenschr* 2014;**126**:458–459.
19. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA *et al*. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;**70**:252–289.
20. Afilalo J, Lauck S, Kim DH, Lefevre T, Piazza N, Lachapelle K *et al*. Frailty in older adults undergoing aortic valve replacement: the FRAILTY-AVR study. *J Am Coll Cardiol* 2017;**70**:689–700.
21. Eide LS, Ranhoff AH, Fridlund B, Haaverstad R, Hufthammer KO, Kuiper KK *et al*. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. *Am J Cardiol* 2015;**115**:802–809.
22. Kristjansson SR, Nesbakken A, Jordhoy MS, Skovlund E, Audisio RA, Johannessen HO *et al*. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study. *Crit Rev Oncol Hematol* 2010;**76**:208–217.
23. Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist* 2000;**5**:224–237.
24. Harrell FE. *Regression Modeling Strategies, with Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*, 2nd edn. Swizerland: Springer International Publishing; 2015. pp. 79–80, 330–333.
25. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189–198.
26. Perneczky R, Wagenpfeil S, Komossa K, Grimmer T, Diehl J, Kurz A. Mapping scores onto stages: mini-mental state examination and clinical dementia rating. *Am J Geriatr Psychiatry* 2006;**14**:139–144.
27. Lincoln NB, Gladman JR. The extended activities of daily living scale: a further validation. *Disabil Rehabil* 1992;**14**:41–43.
28. Kristjansson SR, Jordhoy MS, Nesbakken A, Skovlund E, Bakka A, Johannessen HO *et al*. Which elements of a comprehensive geriatric assessment (CGA) predict post-operative complications and early mortality after colorectal cancer surgery? *J Geriatr Oncol* 2010;**1**:57–65.
29. Ommundsen N, Wyller TB, Nesbakken A, Jordhoy MS, Bakka A, Skovlund E *et al*. Frailty is an independent predictor of survival in older patients with colorectal cancer. *Oncologist* 2014;**19**:1268–1275.
30. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc EWG. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr* 2003;**22**:321–336.
31. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA *et al*. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci* 2007;**62**:744–751.
32. Charlson ME, Pompei P, Ales KL, MacKenzie cR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987;**40**:373–383.
33. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–370.
34. Gustad LT, Laugsand LE, Janszky I, Dalen H, Bjerkeset O. Symptoms of anxiety and depression and risk of heart failure: the HUNT Study. *Eur J Heart Fail* 2014;**16**:861–870.
35. Purser JL, Kuchibhatla MN, Fillenbaum GG, Harding T, Peterson ED, Alexander KP. Identifying frailty in hospitalized older adults with significant coronary artery disease. *J Am Geriatr Soc* 2006;**54**:1674–1681.
36. Afilalo J. Frailty in patients with cardiovascular disease: why, when, and how to measure. *Curr Cardiovasc Risk Rep* 2011;**5**:467–472.
37. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;**143**:29–36.
38. Wilson E. Probable interference, the Law of Succession, and Statistical Interference. *J Am Stat Assoc* 1927;**22**:209–2012.
39. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna. 2018, https://www.R-project.org (31 January 2018).
40. Heinze G, Plo M. Cox Regression with Firth's Penalized Likelihood. R. 2018. https://CRAN.R-project.org/package=coxphf (31 January 2018).
41. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC *et al*. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011;**12**:77.
42. Schoenenberger AW, Stortecky S, Neumann S, Moser A, Juni P, Carrel T *et al*. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). *Eur Heart J* 2013;**34**:684–692.
43. Forman DE, Alexander KP. Frailty: a vital sign for older adults with cardiovascular disease. *Can J Cardiol* 2016;**32**:1082–1087.
44. Lilamand M, Dumonteil N, Nourhashemi F, Hanon O, Marcheix B, Toulza O *et al*. Gait speed and comprehensive geriatric assessment: two keys to improve the management of older persons with aortic stenosis. *Int J Cardiol* 2014;**173**:580–582.
45. Noble S, Frangos E, Samaras N, Ellenberger C, Frangos C, Cikirikcioglu M *et al*. Transcatheter aortic valve implantation in nonagenarians: effective and safe. *Eur J Intern Med* 2013;**24**:750–755.
46. Lauck SB, Baumbusch J, Achtem L, Forman JM, Carroll SL, Cheung A *et al*. Factors influencing the decision of older adults to be assessed for transcatheter aortic valve implantation: an exploratory study. *Eur J Cardiovasc Nurs* 2016;**15**:486–494.
47. Skaar E, Ranhoff AH, Nordrehaug JE, Forman DE, Schaufel MA. Conditions for autonomous choice: a qualitative study of older adults' experience of decision-making in TAVR. *J Geriatr Cardiol* 2017;**14**:42–48.
48. Coylewright M, Palmer R, O'Neill ES, Robb JF, Fried TR. Patient-defined goals for the treatment of severe aortic stenosis: a qualitative analysis. *Health Expect* 2016;**19**:1036–1043.
49. Milne AC, Potter J, Vivanti A, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database Syst Rev* 2009;**2**:CD003288.
50. Wilson K, Mottram P, Sivanranthan A, Nightingale A. Antidepressant versus placebo for depressed elderly. *Cochrane Database Syst Rev* 2001;**2**:CD000561.