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Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI)

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Aims This study aimed to assess functional course in elderly patients undergoing transcatheter aortic valve implantation (TAVI) and to find predictors of functional decline.

Methods and results In this prospective cohort, functional course was assessed in patients ≥70 years using basic activities of daily living (BADL) before and 6 months after TAVI. Baseline EuroSCORE, STS score, and a frailty index (based on assessment of cognition, mobility, nutrition, instrumental and basic activities of daily living) were evaluated to predict functional decline (deterioration in BADL) using logistic regression models. Functional decline was observed in 22 (20.8%) of 106 surviving patients. EuroSCORE (OR per 10% increase 1.18, 95% CI: 0.83–1.68, $P = 0.35$) and STS score (OR per 5% increase 1.64, 95% CI: 0.87–3.09, $P = 0.13$) weakly predicted functional decline. In contrast, the frailty index strongly predicted functional decline in univariable (OR per 1 point increase 1.57, 95% CI: 1.20–2.05, $P = 0.001$) and bivariable analyses (OR: 1.56, 95% CI: 1.20–2.04, $P = 0.001$ controlled for EuroSCORE; OR: 1.53, 95% CI: 1.17–2.02, $P = 0.002$ controlled for STS score). Overall predictive performance was best for the frailty index [Nagelkerke's R^2 (NR^2) 0.135] and low for the EuroSCORE (NR^2 0.015) and STS score (NR^2 0.034). In univariable analyses, all components of the frailty index contributed to the prediction of functional decline.

Conclusion Over a 6-month period, functional status worsened only in a minority of patients surviving TAVI. The frailty index, but not established risk scores, was predictive of functional decline. Refinement of this index might help to identify patients who potentially benefit from additional geriatric interventions after TAVI.

Keywords Aortic valve stenosis • Geriatric assessment • Mortality • Activities of daily living

Introduction

Transcatheter aortic valve implantation (TAVI) is an alternative to surgical aortic valve replacement (SAVR) and medical treatment in selected patients with severe aortic stenosis. Transcatheter aortic valve implantation is considered less invasive when compared with SAVR and may therefore be performed in elderly patients at high risk for surgery with favourable effects on mortality and quality of life.[1–7] However, these outcomes reflect just one part of the clinical outcome in elderly patients. Functional outcomes are similarly important in elderly patients as the functional status of a patient will determine whether the patient is able to live independently or is dependent on the care from another person. The concept of activities of daily living (ADL) is a relevant instrument to

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measure a person's independence from another person's help.[8–10] Though ADL represent an important outcome in elderly people, no previous study reported ADL as outcome in patients undergoing TAVI.

Many established risk scores, such as EuroSCORE or Society of Thoracic Surgeons (STS) score, insufficiently assess the risk of elderly co-morbid patients undergoing surgical cardiovascular procedures.[11–23] For the prediction of mortality after TAVI, it has been previously shown that risk prediction may be improved by adding geriatric risk scores to the established scores.[23] To the best of the authors' knowledge, predictors of a poor functional outcome have not been reported previously. The present study has two objectives: (i) to investigate ADL as relevant outcome in elderly patients undergoing TAVI and (ii) to assess established risk scores as well as baseline functional status as predictors of functional decline.

Methods

Study population

Consecutive patients ≥70 years with severe symptomatic aortic stenosis and referred for evaluation for TAVI to Bern University Hospital, Switzerland, between 1 September 2009 and 31 March 2011, were eligible for this ongoing prospective cohort study. Aortic stenosis was considered severe, if the effective orifice area was $<1\ cm^2$ and/or $<0.6\ cm^2/m^2$ body surface area. An interdisciplinary team of interventional cardiologists and cardiac surgeons reviewed the individual cases and formed a consensus on treatment selection (TAVI, SAVR, or medical treatment). The consensus was based on several parameters including anatomic characteristics of the aortic root, vascular access site specifications, peri-operative risk as calculated with the logistic EuroSCORE and the STS score, underlying co-morbidities, and general clinical condition. The treatment was either selected during the in-hospital evaluation phase or in the following 2 weeks after evaluation. The following patients were excluded from the present study: (i) patients with a treatment other than TAVI (i.e. SAVR or medical treatment); (ii) patients in whom TAVI was performed as emergency procedure; (iii) patients who lived abroad and were not able to undergo follow-up evaluation. All other patients were asked for study participation. If they provided written informed consent, the geriatric baseline examination was performed. Of the patients who received the geriatric baseline examination, the following were also excluded: (i) patients awaiting a TAVI procedure after 31 March 2011; (ii) patients who died before TAVI; (iii) patients who crossed over to SAVR or medical treatment after initial allocation to TAVI; and (iv) patients in whom the time between geriatric baseline examination and TAVI was >3 months. The final study population consisted of all patients in whom TAVI and the geriatric baseline examination was performed during the study period. This study complies with the Declaration of Helsinki and was approved by the local Ethics Committee.

Baseline data

Cardiological baseline examination

All participating patients received extensive cardiological baseline examination during an in-hospital evaluation. Patient history was recorded including symptoms (e.g. NYHA class), cardiovascular risk factors, medication, prior cardiovascular events, and further co-morbidities. Physical examination included the measurement of weight, height, and blood pressure. Left-ventricular ejection fraction (LVEF), aortic valve orifice area, and transvalvular mean gradient were measured with transthoracic or transoesophageal echocardiography. All patients underwent cardiac catheterization providing information about the presence of coronary artery disease, transvalvular gradient, cardiac output, aortic valve area, and right side filling pressures. Based on the gathered information, STS score and logistic EuroSCORE were calculated. For the purpose of this analysis, both scores were dichotomized at the following cut points: STS score at ≥5% (higher risk) vs. <5% (lower risk) and EuroSCORE at ≥20% (higher risk) vs. <20% (lower risk).

Geriatric baseline examination

The geriatric baseline examination during the in-hospital evaluation consisted of the following validated instruments: Mini Mental State Exam (MMSE) for cognitive function;[24] Timed Get Up and Go Test (TUG) for gait function;[25] Mini Nutritional Assessment (MNA) for nutritional status;[26] Basic Activities of Daily Living (BADL);[9] and Instrumental Activities of Daily Living (IADL).[10] For the purpose of this analysis, the instruments were dichotomized at standard cut points which were defined a priori according to current literature: MMSE at <27 points (cognitive impairment) vs. ≥27 points (normal cognitive function), TUG at ≥20 s (mobility impairment) vs. <20 s (normal gait function), and MNA at <12 points (at risk of malnutrition) vs. ≥12 points (not at risk of malnutrition).[24–26] BADL and IADL were considered abnormal, if there was at least 1 activity with a limitation.[9,10]

Frailty index

In order to have a quantitative measure of the patient's general condition, a frailty index was defined prior to statistical analysis. According to existing literature, cognition, mobility, and nutritional status are the most commonly used components of frailty.[27,28] The frailty index of the present study was calculated as summary score from the following baseline components: 2 points were assigned, if MMSE was <21 points; 1 point was assigned for each of the following: MMSE ≥ 21 and <27 points, TUG ≥ 20 s, MNA < 12 points, BADL ≥ 1 limited activity, IADL ≥ 1 limited activity, and a pre-clinical mobility disability (defined as decreased frequency of walking 200 m and/or of climbing stairs during the preceding 6 months). Thus, the frailty index had a range from 0 to 7 points. For the purpose of this analysis, the frailty index was dichotomized prior to statistical analysis at ≥3 points (frail) vs. <3 points (non-frail).

TAVI procedure

TAVI was performed after the cardiological and geriatric baseline examination, usually within 2 weeks. Either a Medtronic CoreValve™ (Medtronic Inc., Minneapolis, MN, USA) or an Edwards Sapien XT bioprosthesis (Edwards Lifesciences, Irvine, CA, USA) was implanted. The transcatheter aortic valve was introduced transfemorally whenever feasible according to measurements based on CT scan.

Follow-up data

Follow-up was performed 6 months after the TAVI procedure. Mortality and nursing home admissions were assessed and either known from the in-hospital stay following the TAVI procedure or reported by the general practitioner. In all surviving patients, BADL and NYHA class were assessed during an office visit by a specially trained research assistant. Basic activities of daily living consisted of five daily self-care tasks, including eating and drinking, getting onto toilet, dressing, caring for personal hygiene, and moving around inside the house. Patients were scored for independence in each of the five activities using a three-step scale (patient was able to perform the activity

independently, had difficulties managing the activity, or needed help from another person for the activity). In 17 patients who were not able to undergo the geriatric follow-up examination during an office visit, specially trained interviewers assessed BADL and NYHA class by phone. Eleven phone interviews were performed with the patient and six with a proxy (e.g. close relative).

Outcomes

Functional decline was the main outcome and defined as a decrease of $\geq$1 point in the ability to perform BADL between baseline and follow-up.[29] Functional decline is particularly important in elderly people because deterioration in BADL will imperatively lead to dependence on other persons' help which often cannot be offset by an expansion of support at home and therefore often results in nursing home admission. The present study evaluated two definitions of functional outcome: (i) functional decline in survivors and (ii) functional decline or death (i.e. all-cause mortality) among all study participants.

Statistical analysis

First, mortality and functional course during follow-up were analysed. A change $\geq$1 point in the ability to perform BADL between baseline and follow-up was considered clinically relevant using the method of the minimal important difference ceiled to the next integer.[29] Secondly, the following baseline predictors of functional outcome were evaluated: logistic EuroSCORE, STS score, frailty index, and the six components of the frailty index. Uni- and bivariable associations between predictors and the endpoints were assessed by logistic regression providing odds ratios. Predictors were analysed as continuous measures and dichotomized at standard cut points. Continuous measures were either analysed as restricted cubic splines (cardiological risk scores) or as linear measures (cardiological risk scores and frailty index with its components) and were divided in subintervals for interpretational purposes. For the cardiological risk scores, no non-linear relationship was found. The MMSE was divided in subintervals of three points to obtain odds ratios for a change of three points and it was analysed reciprocally as a lower MMSE score indicates a more severe limitation. The TUG was divided in subintervals of 5 s and values >30 s were set to 30 s. The MNA was divided in subintervals of two points and it was analysed reciprocally for the same reason as for the MMSE. The association of risk predictors was assessed by Wald-statistics. In bivariable models, a global likelihood ratio χ^2-statistic was used to assess a common association of two risk scores and Nagelkerke's R-squared (NR^2) was used to quantify predictive ability.[30] Exact binomial confidence intervals were derived for proportions. All *P*-values were two-sided. Two secondary analyses were performed: (i) NYHA class at 6-month follow-up was compared in patients with and without functional decline using χ^2-statistics; (ii) the frequency of nursing home admissions during 6-month follow-up was descriptively analysed. Data were analysed using Stata 11.2 (StataCorp LP, College Station, TX, USA).

Results

Baseline data

Between 1 September 2009 and 31 March 2011, 256 patients aged at least 70 years with severe aortic stenosis were referred for TAVI evaluation (*Figure 1*). Of these, 110 patients fulfilled an exclusion criterion: 99 patients were excluded due to treatment selection other than TAVI, six patients lived abroad and were not able to participate in the follow-up, and five patients underwent TAVI as emergency procedure. Another 13 patients were excluded as they were awaiting to undergo TAVI after 31 March 2011, or because they died before TAVI, crossed-over to medical treatment or the time between geriatric baseline examination and TAVI was >3 months. Only 14 patients were not included and did not receive the geriatric baseline examination although they fulfilled the inclusion criteria (in 10 patients the geriatric baseline examination was not performed due to logistic problems and four patients refused the examination). The study population finally consisted of 119 patients undergoing TAVI. In 103 patients (86.6%), TAVI was introduced transfemorally, in 15 patients (12.6%) transapically, and in one patient (0.8%) via subclavian artery.

Baseline characteristics of the study population are shown in *Table 1*. Mean age was 83.4 $\pm$ 4.6 years (range: 71.6–93.2 years). More than half of the study participants (55.5%) were women. As patients with low risk scores were advised to undergo SAVR, the mean logistic EuroSCORE was high (25.3 $\pm$ 14.2%) and co-morbidities, such as coronary artery disease, were present in the majority of patients. At baseline, 32.8% of the patients had mild or severe cognitive impairment and 38.7% had a moderately or severely impaired gait function (*Table 1*). This high proportion of patients with functional limitations was also reflected in a high proportion of patients with a limited ability to perform BADL or IADL. Fifty-nine patients (49.6%) had a frailty index $\geq$3 and were considered to be frail.

Follow-up data

Mortality and functional course

No patient was lost to follow-up (*Figure 1*). During the 6-month follow-up, 13 patients (10.9%) died. Eight of these 13 patients died within 30 days after TAVI (early mortality 6.7%). Only two patients suffered from an additional non-fatal MACCE (stroke in both patients).

In all 106 surviving patients, 6-month follow-up information about BADL was complete. Overall, BADL improved or remained unchanged in 84 patients (79.2%), whereas functional decline was observed in 22 patients (20.8%). There were relevant individual variations in BADL between baseline and follow-up. Among surviving patients, 25 patients (23.6%) had a limitation in BADL at baseline, 81 (76.4%) were not limited in BADL at baseline. Among the 25 surviving patients with limitations in BADL at baseline, 13 patients (52.0%, 95% CI: 31.3–72.2%) improved in BADL after TAVI until follow-up, five patients (20.0%, 95% CI: 6.8–40.7%) remained unchanged, and seven patients (28.0%, 95% CI: 12.1–49.4%) experienced a functional decline. Among the 81 surviving patients without limitations in BADL at baseline, 66 patients (81.5%, 95% CI: 71.3–89.2%) preserved this ability to perform BADL independently until follow-up, whereas functional decline was observed in 15 patients (18.5%, 95% CI: 10.8–28.7%). Of the 13 patients who improved in BADL after TAVI, 11 were independent in BADL at follow-up. Together with the 66 patients who remained independent from baseline to follow-up, a total of 77 of 106 surviving patients (72.6%) had no limitation in BADL at

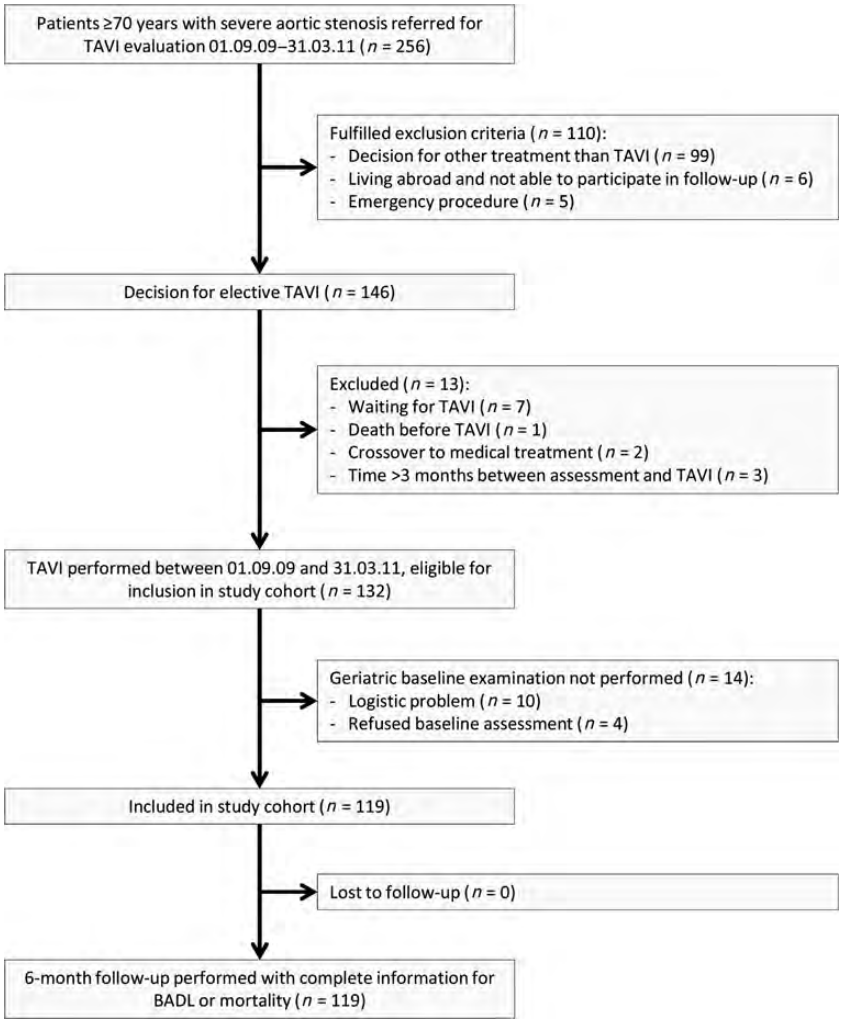

Figure 1 Flow chart. Patient flow during study. TAVI, transcatheter aortic valve implantation.

follow-up, whereas 29 patients (27.4%) were limited in at least one BADL at follow-up.

Of the 59 patients who were frail at baseline, 48 patients (81.4%) survived until 6-month follow-up. Among these survivors, 15 patients (31.3%) experienced a functional decline. Of the 60 patients who were not frail at baseline, 58 patients (96.7%) survived until 6-month follow-up. Among these survivors, functional decline was observed in seven patients (12.1%).

Prediction of functional decline among survivors

Functional decline was observed in 22 surviving patients. Univariable associations of baseline predictors with functional decline are shown in *Table 2* and *Figure 2*. The frailty index was strongly associated with a functional decline, whereas EuroSCORE or STS score showed weak evidence for an association with this outcome. All six components of the frailty index contributed to the strong association of the frailty index with the outcome.

Table 3 shows the results of bivariable regression models (frailty index in combination with logistic EuroSCORE or STS score) and their association with functional decline. The global likelihood-ratio χ^2-statistic shows evidence for a common association with the outcome. However, the combination with EuroSCORE or STS score revealed only a small increase of predictive ability in terms of NR^2 and therefore did not markedly improve the overall prediction as compared with the frailty index alone.

Prediction of functional decline and mortality

The combined outcome of functional decline or death was observed in 35 patients (22 patients with functional decline and 13 patients who died). Univariable associations of baseline predictors with functional decline or death are shown in *Table 2* and *Figure 2*. Geriatric risk scores were superior as compared with EuroSCORE or STS score for the prediction of functional decline or death with the frailty index having the highest NR^2. The bivariable associations (*Table 3*) show that EuroSCORE or STS score are no independent predictors of the outcomes, if

Table 1 Baseline characteristics

Characteristic	All study participants ($n = 119$)
Age, mean ± SD, years	83.4 ± 4.6
Female sex, *n* (%)	66 (55.5)
Body mass index, mean ± SD, kg/m^2	26.0 ± 4.7
Cardiovascular risk factors	
Hypertension, *n* (%)	102 (85.7)
Hypercholesterolaemia, *n* (%)	80 (67.2)
Current smoker, *n* (%)	5 (4.2)
Diabetes, *n* (%)	31 (26.1)
Positive family history, *n* (%)	19 (16.0)
Medical history	
CAD, *n* (%)	78 (65.5)
Previous myocardial infarction, *n* (%)	15 (12.6)
Previous stroke, *n* (%)	6 (5.0)
Chronic heart failure, *n* (%)	43 (36.1)
Symptoms	
Dyspnoea NYHA class III or IV, *n* (%)	64 (53.8)
Angina CCS III or IV, *n* (%)	29 (24.4)
Previous syncope, *n* (%)	16 (13.4)
Medication	
ACE-I/ARB, *n* (%)	60 (50.4)
Diuretic, *n* (%)	80 (67.2)
Beta-blocker, *n* (%)	62 (52.1)
Echocardiography	
LVEF, mean ± SD, %	50.8 ± 14.2
Mean gradient aortic valve, mean ± SD, mmHg	43.1 ± 15.5
Aortic valve area, mean ± SD, cm^2	0.6 ± 0.2
Risk scores	
Logistic EuroSCORE, mean ± SD, %	25.3 ± 14.2
STS score, mean ± SD, %	6.4 ± 3.5
Frailty index, mean ± SD, points	2.6 ± 1.8
Components of frailty index	
Cognitive impairment (MMSE <27 points), *n* (%)	39 (32.8)
Mobility impairment (TUG ≥ 20 s), *n* (%)	46 (38.7)
At risk of malnutrition (MNA < 12 points), *n* (%)	53 (44.5)
BADL with ≥1 activity with limitation, *n* (%)	32 (26.9)
IADL with ≥1 activity with limitation, *n* (%)	72 (60.5)
Pre-clinical mobility disability, *n* (%)	42 (35.3)

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BADL, basic activities of daily living; CAD, coronary artery disease; IADL, instrumental activities of daily living; LVEF, left-ventricular ejection fraction; MMSE, mini mental state exam; MNA, mini nutritional assessment; STS, Society of Thoracic Surgeons; TUG, timed get up and go test.

combined with the frailty index. Again, the frailty index alone explained most of the data variation and the cardiological risk scores contributed very few to the explained variance.

Secondary analyses

NYHA class

At baseline, NYHA class III or IV was present in 64 (53.8%) of 119 patients. At 6-month follow-up, this proportion decreased to 16 (15.1%) of 106 surviving patients. Five (22.7%) of 22 patients with functional decline had NYHA class III or IV at 6-month follow-up which was not significantly higher than the 11 (13.1%) of 84 patients with NYHA class III or IV among patients without functional decline ($P = 0.261$).

Nursing home admissions

At baseline, 116 patients lived in their own home, two patients in a retirement home, and only one patient lived in a nursing home. At 6-month follow-up, 95 of the 106 surviving patients (89.6%) still lived at home, five patients lived in a retirement home, and six patients in a nursing home. Of the five patients who moved to a nursing home during follow-up, three had a functional decline between baseline and follow-up and the remaining two had limitations in BADL already at baseline which persisted until 6-month follow-up.

Discussion

This prospective longitudinal cohort study documents favourable functional status in the majority of elderly patients 6 months after TAVI. Most patients continued to live independently at home. A minority of the patients experienced functional decline or death and the question arises which factors contributed to this outcome. This study provides evidence that functional limitations prior to TAVI are predictors of functional decline after TAVI with the proposed frailty index being the strongest predictor. All components of the frailty index contributed to its high association with the outcomes. Patients who are frail before TAVI are at high risk to lose their independence after TAVI. Global risk scores such as EuroSCORE or STS score that have been established for the prediction of mortality did not predict functional decline in the present study.

To our knowledge, the present study is the first study reporting functional course and predictors of functional decline after TAVI. In older patients, functional course and the ability to perform BADL are particularly important. In this study, all patients who were institutionalized after TAVI had limitations in their ability to perform BADL. Therefore, the preservation of the ability to perform BADL after TAVI and predictors of functional decline are of importance.[31] A previous analysis of the present study cohort provided evidence that both established risk scores (EuroSCORE and STS score) as well as the proposed frailty index independently predict mortality and MACCE after TAVI.[23] The present study suggests that the frailty index independently predicts functional decline of elderly patients undergoing TAVI, whereas established risk scores showed weak evidence for an association with functional decline.

This study adds to a growing evidence that geriatric measures of functional status are important outcomes and predictors of functional outcomes in elderly patients.[11–23] One recent study found a high prevalence of geriatric syndromes in older patients with acute cardiac diseases and documented a high impact of

Table 2 Univariable associations of risk scores (EuroSCORE, STS score and frailty index) and of the frailty index components for the prediction of functional decline (defined as deterioration in the ability to perform basic activities of daily living) and of functional decline or death

Predictor	Functional decline			Functional decline or death		
	OR (95% CI)	*P*-value	NR^2	OR (95% CI)	*P*-value	NR^2
Risk scores						
Logistic EuroSCORE						
Linear (OR per 10% increase)	1.18 (0.83–1.68)	0.35	0.015	1.33 (0.99–1.80)	0.06	0.050
Dichotomized (≥20 vs. <20%)	0.79 (0.31–2.02)	0.62	0.004	1.33 (0.59–3.00)	0.49	0.006
STS score						
Linear (OR per 5% increase)	1.64 (0.87–3.09)	0.13	0.034	1.95 (1.08–3.52)	0.03	0.068
Dichotomized (≥5 vs. <5%)	1.14 (0.44–2.95)	0.78	0.001	1.83 (0.80–4.16)	0.15	0.025
Frailty index						
Linear (OR per 1 point increase)	1.57 (1.20–2.05)	0.001	0.135	1.74 (1.38–2.20)	<0.001	0.236
Dichotomized (frail vs. non-frail)	3.31 (1.21–9.03)	0.02	0.085	4.46 (1.85–10.75)	0.001	0.142
Components of frailty index						
MMSE						
Linear (OR per 3 points decrease)	2.41 (1.23–4.71)	0.01	0.086	2.64 (1.55–4.50)	<0.001	0.150
Dichotomized (<27 vs. ≥27 points)	2.50 (0.94–6.65)	0.07	0.048	3.18 (1.38–7.29)	0.01	0.088
TUG						
Linear (OR per 5 s increase)	1.48 (1.13–1.94)	0.004	0.091	1.64 (1.26–2.12)	<0.001	0.161
Dichotomized (≥20 vs. <20 s)	2.50 (0.95–6.56)	0.06	0.050	4.23 (1.83–9.77)	0.001	0.138
MNA						
Linear (OR per 2 points decrease)	1.30 (0.96–1.76)	0.09	0.032	1.51 (1.09–2.10)	<0.001	0.085
Dichotomized (<12 vs. ≥12 points)	3.32 (1.24–8.87)	0.02	0.087	4.14 (1.77–9.65)	0.001	0.133
BADL						
Linear (OR per 1 point increase)	1.39 (0.86–2.25)	0.18	0.024	1.63 (1.12–2.37)	0.01	0.071
Dichotomized (≥1 limited activity)	1.71 (0.60–4.85)	0.31	0.015	2.44 (1.04–5.76)	0.04	0.049
IADL						
Linear (OR per 1 point increase)	1.45 (1.08–1.94)	0.01	0.093	1.46 (1.13–1.89)	0.004	0.109
Dichotomized (≥1 limited activity)	2.10 (0.74–5.92)	0.16	0.031	2.19 (0.91–5.27)	0.08	0.039
Pre-clinical mobility disability						
Dichotomized (disability vs. no disability)	3.23 (0.99–10.59)	0.05	0.078	3.69 (1.33–10.24)	0.01	0.108

Each predictor was assessed as linear measure and after dichotomization at standard cut points (except for pre-clinical mobility disability which can be assessed only as dichotomous measure).
BADL, basic activities of daily living; CI, confidence interval; IADL, instrumental activities of daily living; MMSE, mini mental state exam; MNA, mini nutritional assessment; NR^2, Nagelkerke's R-squared; OR, odds ratio; STS, Society of Thoracic Surgeons; TUG, timed get up and go test.

these syndromes on functional and clinical outcomes.[21] Another recent study in older patients undergoing percutaneous revascularization found a high prevalence of frailty which was associated with adverse long-term outcomes.[22] The question arises why functional measures are good predictors. These measures identify patients with diminished physiological reserves in multiple organ systems and therefore have the potential to differentiate between patients with the potential to recover and those at risk to deteriorate after an intervention.

This study has limitations. First, patients undergoing TAVI were a selection of elderly, high-risk patients with an increased EuroSCORE. Old patients with low EuroSCORE were in general allocated to SAVR, whereas elderly patients with excessive risk were sometimes assigned to medical treatment. Therefore, the predictive value of the frailty index has to be reconfirmed in patients with higher or lower risk, in case TAVI will also be performed in these populations in the future. Secondly, the findings of this study are based on data from a single centre. Therefore, confirmation in an independent sample is of importance to improve generalizability of the findings of the present study. Thirdly, the sample size was small with 119 patients. This number and the resulting number of endpoints were not sufficient to evaluate the frailty index in multivariable models involving more than two predictor variables. However, the number of 22 patients with functional decline was sufficient to avoid over-fitting in the applied univariable and bivariable models.[32] The finding that despite limited sample size the frailty index and all its subcomponents were strong predictors further supports the conclusion of

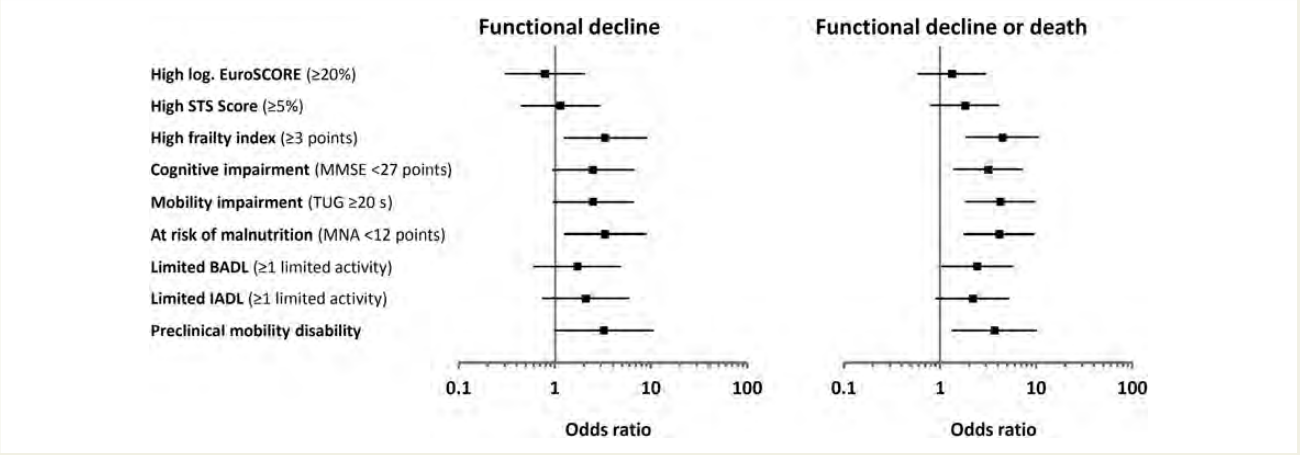

Figure 2 Odds ratios and 95% confidence intervals of univariable associations of dichotomized risk predictors with functional decline (defined as deterioration of the ability to perform basic activities of daily living) and functional decline or death in forest plots. BADL, basic activities of daily living; IADL, instrumental activities of daily living; MMSE, mini mental state exam; MNA, mini nutritional assessment; TUG, timed get up and go test.

Table 3 Bivariable associations of frailty index and EuroSCORE or STS score for the prediction of functional decline (defined as deterioration in the ability to perform basic activities of daily living) and of functional decline or death

Predictor	Functional decline			Functional decline or death		
	OR (95% CI)	*P*-value	NR^2	OR (95% CI)	*P*-value	NR^2
Combination of frailty index and EuroSCORE						
Frailty index linear	1.56 (1.20–2.04)	0.001	0.145	1.73 (1.36–2.20)	<0.001	0.262
Logistic EuroSCORE linear	1.16 (0.79–1.71)	0.46		1.28 (0.93–1.76)	0.13	
(*P*-value from global LR $\chi 2$)		0.006			<0.001	
Frailty index dichotomized	3.41 (1.24–9.33)	0.02	0.091	4.40 (1.82–10.63)	0.001	0.144
Logistic EuroSCORE dichotomized	0.71 (0.27–1.89)	0.50		1.18 (0.50–2.80)	0.70	
(*P*-value from global LR $\chi 2$)		0.04			0.002	
Combination of frailty index and STS score						
Frailty index linear	1.53 (1.17–2.02)	0.002	0.146	1.69 (1.32–2.16)	<0.001	0.251
STS score linear	1.36 (0.67–2.73)	0.39		1.45 (0.75–2.80)	0.26	
(*P*-value from global LR $\chi 2$)		0.006			<0.001	
Frailty index dichotomized	3.34 (1.18–9.43)	0.02	0.085	4.21 (1.72–10.33)	0.002	0.151
STS score dichotomized	0.95 (0.35–2.60)	0.92		1.48 (0.62–3.54)	0.37	
(*P*-value from global LR $\chi 2$)		0.05			0.001	

Each combination was assessed as linear measure and after dichotomization at standard cut points.
CI, confidence interval; NR^2, Nagelkerke's R-squared; OR, odds ratio; STS, Society of Thoracic Surgeons.

strong associations between frailty and functional outcome. Fourthly, due to the small sample size, no analyses could be conducted for the prediction of functional improvement in the small subgroup of patients with functional limitations at baseline and thus a potential to improve. Fifthly, frailty is a novel concept in geriatrics, and there is not yet a generally accepted operational definition of frailty in the literature.[27,28] In the present study, frailty was defined as an index based on validated instruments covering key subdomains related to frailty and disability in old age. The advantage of this operational definition of frailty is the inclusion of cognitive function, an aspect not covered in other operational definitions of frailty.[27] However, prior to clinical use, additional research is needed to confirm the validity of this newly proposed index.

The present study has research implications. First, studies based on larger sample sizes are needed for the derivation and validation of risk scores combining geriatric scores with other scores that have been found to be predictive of outcomes after TAVI. It is

likely that this results in further improvement of risk prediction. Secondly, larger studies are also needed to optimize the frailty index and its subcomponents for the risk prediction after TAVI. The frailty index was developed based on a priori considerations. It is likely that the frailty index performs even better, if adapted for TAVI risk prediction.

This study also has clinical implications. Early identification of patients at increased risk of functional decline is clinically relevant, because these patients might benefit from interventions designed to maintain or improve functional status. In addition to the potential benefit of the frailty index to improve risk prediction, its components used in the present study are part of geriatric assessment, a procedure developed for identification of problems amenable to targeted peri-operative interventions (e.g. malnutrition). Recent systematic analyses of randomized controlled studies demonstrate that geriatric interventions based on the principle of geriatric assessment improve functional prognosis and decrease nursing home admissions among older patients.[33,34]

In conclusion, the present study shows that functional status improved or was preserved in the majority of surviving patients after TAVI. Though not specifically developed for risk prediction, a frailty index calculated as summary score from geriatric instruments was a strong predictor of functional decline over a 6-month follow-up period. In contrast, established risk scores of mortality among cardiac patients, such as the EuroSCORE or the STS score, did not predict functional decline in this study. Given the relevance of functional status as a key component of quality of life among older persons, these findings suggest including geriatric measures in the risk assessment prior to TAVI.

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