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The Erasmus Frailty Score is associated with delirium and 1-year mortality after Transcatheter Aortic Valve Implantation in older patients. The TAVI Care & Cure program

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ABSTRACT

Background: Frailty in patients undergoing Transcatheter Aortic Valve Implantation (TAVI) has been associated with an increased 1-year mortality rate but the relation of frailty and short term outcomes yields conflicting results. This study investigated the association of a novel and self-developed Erasmus Frailty Score with both short and long term outcomes after TAVI.

Methods: TAVI Care & Cure is an observational ongoing study, which includes consecutive patients undergoing TAVI at the Erasmus University Medical Centre. Prior to the TAVI, frailty status was assessed. The Erasmus Frailty Score (EFS) was defined as follows: 1 point assigned if: MMSE was <27 points, MUST ≥2 points, grip strength <20 kg for females, <30 kg for males, KATZ index ≥1 limited activity, Lawton and Brody index ≥2 limited activity. The maximum score was 5. Patients were classified as frail when the score was ≥3. Presence of delirium was evaluated by daily clinical assessment by a geriatrician pre- and post-TAVI. Mortality data were obtained from the Dutch Civil Registry. The impact of frailty on short and long term outcomes was evaluated.

Results: 213 patients were included for analysis. Frailty was present in 28.6% ($n = 61$), (EFS ≥ 3). Baseline frailty was associated with patients developing a delirium [OR 3.3 (95% CI 1,55–7,10), $p = 0.002$] and with increased risk of 1-year mortality [HR 2.1 (95% CI 1.01–4.52), $p = 0.047$].

Conclusion: The Erasmus Frailty Score is associated with delirium and 1 year mortality in older patients after TAVI and can be used as a complement to traditional risk factors.

1. Introduction

Transcatheter Aortic Valve Implantation (TAVI) is an innovative and accepted treatment option for patients with severe aortic valve stenosis (AoS) who are frail and have high surgical risk [1,2]. Although TAVI is a less invasive procedure than a Surgical Aortic Valve Replacement (SAVR), short- and long term complications such as post-operative delirium, major vascular complications, infections and mortality [1,3–5] are still frequent and harmful. Since older patients often present the same patterns of risk factors, it is challenging to assess the individual risk of adverse outcomes when taking into account known perioperative risk factors. Therefore, there is a need for novel biomarkers in order to assess perioperative risk in this relatively novel population of patients.

The role of frailty and its possible impact on outcomes after TAVI have previously been investigated. Several studies have shown that frailty is associated with an increased 1-year mortality rate [6–8], whereas the relation of frailty and short-term outcomes yielded conflicting results [6,7,9]. The latter could be explained by the different definitions of frailty being used, but also because of the choice of short-term outcomes being studied. The aim of this study is to assess the potential independent value of a novel and self-developed frailty score, the Erasmus Frailty score, in predicting both short and long term outcomes after TAVI in older, frail patients.

2. Methods

2.1. Patient selection

The study population consists of consecutive patients with severe symptomatic AoS, and were seen in the TAVI Care & Cure program; a collaboration between the departments of geriatrics and cardiology to optimize the care for frail and older patients. Patients were referred to the interventional cardiologist for a complete cardiac assessment, followed by a consult by the geriatrician for a comprehensive geriatric assessment. There were no

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Table 1
The Erasmus Frailty Score.

Frailty domain	Risk score	Results	Interpretation	Score
Cognition	MMSE	<27 points	Cognitive impairment probable	1
Strength	Grip strength	Female: <20 kg Male: <30 kg	Diminished strength	1
Malnutrition	MUST	≥2 points	Malnutrition probable	1
Inactivity	ADL	≥1 point	At least 1 basic activity with limitation	1
Inactivity	IADL	≥2 points	At least 2 instrumental activities with limitation	1
Frailty score				Maximum of 5

The definition of the Erasmus Frailty Score. For the purpose of this study patients were divided into two groups: non-frail if the frailty score was 0–2, patients were considered frail if the frailty score was ≥3. Abbreviations: MMSE: Mini Mental State Examination, MUST: Malnutrition Universal Screening Tool, ADL: activities of daily living, IADL: instrumental activities of daily living.

specific exclusion criteria. In an interdisciplinary Heart Team, including interventional cardiologists, cardiac surgeons and geriatricians, each individual case was reviewed and a consensus was formed on a definitive treatment strategy [10]. The Medical Ethics Committee of the Erasmus Medical Center reviewed the study (MEC-2014-277) and since this study was not subjected to the Dutch Medical Research Involving Human Subjects Act no approval was required. However, the study was conducted according to the Helsinki Declaration and all patients consented to participation in this study.

2.2. Study measurements

2.2.1. Cardiology assessment

Baseline cardiology assessment included patient history including determining symptoms using the New York Heart Association (NYHA) classification and the Canadian Cardiovascular Society (CCS) grading of angina pectoris, physical examination and electrocardiogram (ECG). Further cardiologic examination included echocardiography, coronary angiography and multislice computed tomography (MSCT) to address the aortic valve and arterial tree and determine technical suitability for TAVI and access site [11,12].

2.2.2. Geriatric assessment

We performed a comprehensive geriatric assessment using validated instruments to define frailty status. The following instruments were used: Mini Mental State Examination (MMSE) [13]; Hand grip strength [14]; The Malnutrition Universal Screening Tool (MUST) [15]; Katz index was used for scoring activities of daily living (ADL) [16] and the Lawton and Brody index was used for scoring instrumental activities of daily living (iADL) [17]; 5 Meter Gait Speed test (5MGST) and Timed Up and Go Test (TUGT) [18]. For the purpose of the analysis values were dichotomized at standard cut-off points. For the definition of the Erasmus Frailty Score (EFS) we identified 5 geriatric domains relevant for this specific population. The composition of the domains within the EFS is based on previous outcomes in literature investigating the individual variables in patients undergoing TAVI or with cardiovascular disease. A comprehensive explanation of the various frailty components and composition of the EFS can be found in the supplementary material (Supplementary Material 1). The cut-off points and meaning of the used instruments and the EFS are explained in Table 1.

2.2.3. TAVI procedure

Procedures were performed either under general or local anesthesia following the decision of the heart team. The transfemoral arterial approach was the access of first choice. After TAVI, patients were admitted to the intensive care for early monitoring up to a minimum of 4 h.

2.2.4. Delirium assessment

Patients were evaluated daily by a geriatrician from the day of admission up to 4 days post-TAVI, evaluating the presence of delirium and initiation of treatment if necessary. Delirium was defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Delirium Observation Score (DOS) was also used to observe any symptoms of possible delirium. This observation scale is designed for and used by nurses to observe if a delirium is present. It is a reliable method for measuring the severity of a delirium [19]. Scores of 3 or higher were considered to be suspect for delirium.

2.2.5. Outcome measures

Short term outcomes included the onset of delirium in hospital, in-hospital life-threatening or major bleeding, major vascular complications, in-hospital stroke, infection and 30-day mortality. We investigated a composite of short-term outcomes, which are presumably patient-, more than procedure bound outcomes and are clinically relevant to this population. Life-threatening or major bleeding, major vascular complications and stroke were assessed according to the guidelines of the most recent Valve Academic Research Consortium [20]. Long-term outcome was 1-year mortality. Procedural outcomes and mortality were assessed prospectively by consulting medical files and the Dutch Civil Registry.

2.2.6. Statistical analysis

Categorical variables are presented as numbers and corresponding percentages and differences between frail and non-frail patients were compared with the chi-square or Fisher's exact test as appropriate. For all the variables used for the analysis there were no values missing exceeding 10%. Subjects with missing values of the Erasmus Frailty Score were excluded. Continuous variables are expressed as means ± SD or median values with corresponding interquartile ranges (IQR) and differences were compared using the independent *t*-test or its non-parametric equivalents, respectively. Univariate analysis was performed, and every variable with a p value <0.10 was entered in the multivariate regression models. Odds ratios (OR) and corresponding 95% confidence interval (95% CI) were computed with multivariate logistic regression analysis performed for the outcomes delirium, 30-day major vascular events and 30-day infections. For the outcome delirium, models were adjusted for age, sex, previous stroke and dyslipidemia. For the outcomes 30-day major vascular events, models were adjusted for age, sex, hypertension, peripheral artery disease and access route. For the outcome 30-day infections, models were adjusted for age, sex, diabetes mellitus.

A Cox regression analysis was performed for the outcome 1-year mortality. Hazard ratio's (HR) and corresponding 95% confidence intervals were computed. Model 1 was adjusted for age, sex and diabetes mellitus, Model 2: model 1 plus dyslipidemia, model 3: model 1 plus dyslipidemia, gait speed per second and Timed Up and Go Test.

p value of 0.05 was considered statistically significant. Data was analyzed with statistic program IBM Statistical Package for Social Science for Windows version 21 (SPSS).

Table 2
Baseline clinical and functional characteristics of total study population ($n = 213$).

Age (years)	82,03 (78,2–85,6)
Male gender (%)	46,5
BMI (kg/m^2)	26,4 (24,3–29,9)
Cardiovascular risk factors	
Hypertension (%)	82,1
Dyslipidemia (%)	67,8
Diabetes mellitus (%)	34,1
Current smoker (%)	7,8
Family history of CAD (%)	23,9
Comorbidities	
Previous myocardial infarction (%)	19,7
Previous stroke (%)	10,6
COPD (%)	23,9
Renal disease (%)	46,5
Symptoms	
NYHA Class 3 or 4 (%)	70,8
Angina CCS classification 3 or 4 (%)	13,0
Vertigo (%)	34,3
Echocardiography	
AV area (cm^2)	0,7 (0,6–0,8)
Peak AoV, (m/s)	4,1 (3,6–4,6)
LVEF (%)	54,5
Frailty indices	
Cognitive impairment probable (%)	34,7
Malnutrition probable (%)	11,7
Limitation of mobility, TUGT (%)	16,9
Limitation of mobility, 5MGS (%)	58,5
Reduced muscle strength, male (%)	30,5
Reduces muscle strength, female (%)	65,4
Limitation in ADL activity (%)	31,5
Limitation in IADL activity (%)	43,2
Frailty present (%)	28,6

BMI: body mass index, CAD: coronary artery disease, COPD: Chronic obstructive Pulmonary disease, NYHA: New York Heart Association, CCS: Canadian Cardiovascular Society, AoV: Aortic valve, LVEF: Left Ventricular Ejection Fraction, TUGT: Timed Up and Go Test, 5MGS: 5 Meter Gait Speed, ADL: activities of daily living, IADL: instrumental activities of daily living.

Table 3
Frailty components and their association with delirium and 1-year mortality after TAVI.

Risk score	Post-operative delirium[a]			1 year mortality[b]		
	OR	95% CI	*p* value	HR	95% CI	*p* value
ADL						
Continuous	1.1	(0.84–1.50)	0.44	1.5	(1.21–1.90)	<0.001
Dichotomized (≥1 point)	1.2	(0.58–2.67)	0.58	1.8	(0.85–3.70)	0.13
IADL						
Continuous	1.1	(1.02–1.29)	0.02	1.2	(1.07–1.33)	0.002
Dichotomized (≥2 points)	2.4	(1.15–4.94)	0.02	2.3	(1.06–4.90)	0.04
Gait speed per second						
Continuous	1.2	(0.79–1.83)	0.38	1.2	(0.86–1.73)	0.26
Dichotomized (>1 m/s)	1.9	(0.80–4.61)	0.14	3.3	(1.25–8.51)	0.02
TUGT						
Continuous	1.0	(0.98–1.07)	0.19	1.1	(1.02–1.09)	0.001
Dichotomized (>20 s)	1.4	(0.57–3.64)	0.45	1.8	(0.77–4.18)	0.18
Grip strength	1.9	(0.84–4.29)	0.12	1.8	(0.78–3.98)	0.18
MMSE						
Dichotomized (<27 points)	2.7	(1.27–5.58)	0.009	1.6	(0.76–3.22)	0.22
MUST						
Dichotomized (≥2 points)	2.9	(1.06–7.81)	0.04	1.5	(0.59–3.94)	0.38

Abbreviations: ADL: activities of daily living, IADL: instrumental activities of daily living, TUGT: Timed Up and Go Test, MMSE: Mini Mental State Examination, MUST: Malnutrition Universal Screening Tool, OR: odds ratio, HR: hazard ratio, CI: confidence interval.
[a] Model for post-operative delirium is a multivariable model, corrected for age, sex, previous stroke and dyslipidemia.
[b] Model for 1 year mortality is a multivariable model corrected for age, sex, diabetes mellitus and dyslipidemia.

3. Results

3.1. Patient characteristics

Between November 2013 and November 2016 a total of 356 patients were referred for evaluation of TAVI. Of these 356 patients, 287 patients were eligible for TAVI, of these, 213 patients (74%) completed a baseline frailty assessment. The baseline characteristics of the study population are shown in Table 2. Median age was 82,0 (IQR 78,2–85,6) years and 47% were male. Comorbid conditions, cardiovascular risk factors and clinical symptoms were common among these patients. Sixty-one patients were frail (Erasmus Frailty Score ≥ 3). Cognitive impairment was observed in more than a third of the patients. The gait speed showed a limitation of mobility in more than half of the patients. Impairment in i(ADL) of at least 1 basic or 2 instrumental activity was present in 31% ($n = 67$) and 43% ($n = 92$) of the patients, respectively.

3.2. Short and long term outcomes

Except for delirium and 1-year mortality, there were no differences in rates of other major adverse clinical events according to frailty baseline status, including 30-day mortality, major vascular complications (including stroke, major bleeding or other vascular complications) or infection.

3.2.1. Delirium

Post-operative delirium (POD) was diagnosed in 42 (20%) patients. Patients with POD were more often frail in comparison with those who were not frail [OR 3,3 (95% CI 1,55–7,10) $p = 0.002$]. Age [OR 1,06 (95% CI 0.99–1,14) $p = 0.077$], previous stroke [OR 4,2 (95% CI 1,68–10,34) $p = 0.002$], malnutrition [OR 2,9 (95% CI 1,06–7,81) $p = 0.04$], cognitive impairment [OR 2,7 (95% CI 1,27–5,58) $p = 0.009$] and IADL dependency [OR 2.4 (95% CI 1.15–4.94) $p = 0.02$] were also associated with the incidence of POD (Tables 3, 4a). Regarding procedural features, no significant difference was seen in the incidence of delirium in patients undergoing transfemoral access when compared with nontransfemoral access (10% vs 23%; $p = 0.32$) or general anesthesia when compared with local anesthesia (25,5% vs 20%; $p = 0.72$).

3.2.2. Mortality

31 patients died within 1-year of follow up, 9 died during the first 30 days after TAVI. None of the frailty components were associated with 30-day mortality. Frailty at baseline was associated with increased risk of 1-year mortality [HR 2.1 (95% CI 1.01–4.52) $p = 0.047$]. Other frailty components associated with all-cause mortality 1 year after TAVI: ADL, as continuous variable [HR 1.5 (95% CI 1.21–1.90) $p = 0.001$], IADL as continuous variable, [HR 1.2 (95% CI 1.07–1.33) $p = 0.002$], IADL as dichotomized variable [HR 2.3 (95% CI 1.06–4.90) $p = 0.04$], Gait speed per second as dichotomized variable [HR 3.3 (95% CI 1.25–8.51) $p = 0.02$], TUGT as continuous variable [HR 1.1 (95% CI 1.02–1.09) $p = 0.001$] (Tables 3, 4b).

4. Discussion

In the present study we found that frailty measured by the Erasmus Frailty Score is strongly and independently associated with postoperative delirium and 1-year mortality in older patients after TAVI. The association between frailty and other short-term outcomes was less consistent.

Assessing perioperative risks is crucial in deciding a treatment strategy for any intervention and risk stratification can be difficult in patients with similar patterns of risk factors. In these populations, the assessment of individual risks of morbidity and mortality can therefore be challenging. For this reason we have to use nontraditional discriminatory markers like frailty.

When patients transfer to a higher spectrum of perioperative risk, standard global risk scores will not be accurate and precise enough to predict operative complications [21]. In open heart surgery, risk scores like the logistic Euroscore or the Society of Thoracic Surgeons (STS) risk score are commonly used to predict surgical mortality. These traditional risk scores are not designed for patients undergoing TAVI [22,23] and studies have shown that prediction of outcome is not sufficient in high risk patients of 80 years and older with substantial comorbidities [2,24]. Moreover, these risk scores do not take into account the individual's biological age and frailty status. The assessment of frailty can have an additional prognostic role as geriatric biomarker in predicting short and long-term outcomes.

Frailty is a state of reduced physical, cognitive and social functioning, resulting in a reduction of reserve capacity for dealing with stressors [25]. Many definitions of frailty have been used in research and all represent a reflection from previously validated frailty assessment tools [26].

Customizing frailty scores in older and specific populations is important [27]. Frailty assessment will be more predictive if impairment in specific domains is indeed a reflection of one's individual frailty, instead of incorporating geriatric biomarkers that are influenced by the disease process itself, so that in fact they represent more the severity of the disease and not the person's frailty status.

Traditional risk scores consider baseline demographics and medical variables, but do not take into account biomarkers that can predict vitality. The assessment of frailty in older patients with comorbidities gives a clear definition of the individual vitality defining the somatic, cognitive and functional situation secondary to the damage due to chronic and intercurrent diseases and the individual capacity to react to external stressors. The Erasmus Frailty Score includes five geriatric domains,

Table 4a
Erasmus Frailty Score and association with delirium.

	OR[a] (95% CI)	*p* value	OR[b] (95% CI)	*p* value
Non-frail	1.0 (reference)		1.0 (reference)	
Frail (EFS ≥ 3)	3.4 (1.59–7.18)	0.002	3.3 (1.55–7.10)	0.002

EFS: Erasmus Frailty Score, OR: odds ratio, CI: confidence interval.
[a] Model adjusted for age, sex, previous stroke.
[b] Model adjusted for age, sex, previous stroke, dyslipidemia.

Table 4b
Erasmus Frailty Score and association with 1 year mortality.

	HR[a] (95% CI)	*p* value	HR[b] (95% CI)	*p* value	HR[c] (95% CI)	*p* value
Non-frail	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Frail (EFS > 3)	2.2 (1.04–4.70)	0.038	2.1 (1.01–4.51)	0.047	2.1 (0.89–4.87)	0.091

EFS: Erasmus Frailty Score, TUGT: Timed Up and Go Test, HR: Hazard Ratio, CI: confidence interval.
[a] Model adjusted for age, sex, diabetes mellitus.
[b] Model adjusted for age, sex, diabetes mellitus, dyslipidemia.
[c] Model adjusted for age, sex, diabetes mellitus, dyslipidemia, gait speed per second, TUGT.

which can predict vitality and reserve capacity to deal with negative health outcomes after an intervention more accurately than traditional risk scores.

The potential role of frailty in predicting complications in older persons after major procedures such as TAVI has been previously investigated. Baseline frailty status and geriatric components added to routinely used clinical models or global risk scores have been shown to predict 1-year mortality after TAVI [2,6,7,28,29].

The impact of frailty has also been studied for short-term perioperative complications, such as vascular complications, infection and 30-day mortality [1,6,7]. In these studies the occurrence of postoperative delirium (POD) has not been taken into account. However, POD has devastating effects in frail, older patients leading to a prolonged in-hospital stay and increasing mortality [5,30,31]. Since the incidence of delirium after TAVI is high (varying between 12 and 53%) depending on study design and diagnostic criteria [5,30,32], it is of paramount importance to know which factors can predict POD. Two previous studies investigated the role of frailty in predicting POD after TAVI and results are conflicting [9,32]. One study investigated predictors of POD and included markers of frailty, but did not find a relationship between markers of frailty and delirium. The study was performed in patients 80 years and older, and compared the incidence of delirium in patients treated with TAVI or SAVR in a population with relatively good cognitive and ADL function, what might influence the susceptibility of delirium for this population [32]. A recent study performed in The Netherlands, including a relatively small number of patients, found that the incidence of POD was higher in frail patients when compared with older non-frail patients undergoing TAVI [9].

To the best of our knowledge this is the first study, which investigates and shows the association of a self-developed frailty score and both short and long term complications after TAVI in older patients. Frailty, expressed in this score, could be helpful in optimizing risk stratification in this population of older patients.

The present study has some limitations. First, although we included just over 200 patients we are aware that we need large groups of patients before drawing conclusions on the possible application of the EFS in clinical practice. Second, this study was a single center study, imbedded in an academic center receiving a relatively selected population of patients with an intrinsic elevated perioperative risk and is, therefore, not representative for all patients with severe AoS. Third, the Erasmus Frailty Score has not been formally developed from coefficients from a predictive model, nor has there been a cohort for development and validation of this risk score. Although these are important limitations for developing a risk score, we do believe that the presented data is important and meaningful in the further development of this risk tool. The EFS has been based on variables obtained within the framework of a Comprehensive Geriatric Assessment and the composition of the EFS entails domains that have been studied previously in patients undergoing TAVI or with cardiovascular disease. Assuming each variable is essential for optimal functioning of patients, deficits in multiple variables is a quantitative measure of the patient's general condition. The EFS can be used to assess the frailty status of patients, and therefore be helpful identifying those patients with diminished physiological reserves and increased risk on negative health outcomes, but since the EFS has not been formally validated, the EFS should not be used in clinical practice as a risk score to aid decisions. Further research is needed to explore the value of this score. Strength of this study was the involvement of the geriatrician during the whole treatment course. According to the protocol, the geriatrician was directly and daily involved in the contacts with the patients, therefore, data on POD were obtained during the admission avoiding the possible misclassification on outcomes obtained retrospectively by reviewing charts.

In conclusion, in the present study we have found that frailty as defined by the Erasmus Frailty Score is associated with POD and 1-year mortality after TAVI in older patient. Frailty, expressed in this score can be of additional value to known risk factors and currently used global risk scores to optimize risk stratification in this population of older patients.

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None.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.093.

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