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ORIGINAL RESEARCH

Frailty and Recurrent Hospitalization After Transcatheter Aortic Valve Replacement

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BACKGROUND: For frail patients with limited life expectancy, time in hospital following transcatheter aortic valve replacement is an important measure of quality of life; however, data remain scarce. Thus, we aimed to investigate frailty and its relation to time in hospital during the first year after transcatheter aortic valve replacement.

METHODS AND RESULTS: From 2008 to 2020, all Danish patients who underwent transcatheter aortic valve replacement and were alive at discharge were included. Using the validated Hospital Frailty Risk Score, patients were categorized in the low, intermediate, and high frailty groups. Time in hospital and mortality up to 1 year are reported according to frailty groups. In total, 3437 (57.6%), 2277 (38.1%), and 257 (4.3%) were categorized in the low, intermediate, and high frailty groups, respectively. Median age was ≈81 years. Female sex and comorbidity burden were incrementally higher across frailty groups (low frailty: heart failure, 24.1%; stroke, 7.2%; and chronic kidney disease, 4.5%; versus high frailty: heart failure, 42.8%; stroke, 34.2%; and chronic kidney disease, 29.2%).

In the low frailty group, 50.5% survived 1 year without a hospital admission, 10.8% were hospitalized >15 days, and 5.8% of patients died. By contrast, 26.1% of patients in the high frailty group survived 1 year without a hospital admission, 26.4% were hospitalized >15 days, and 15.6% died within 1 year. Differences persisted in models adjusted for sex, age, frailty, and comorbidity burden (excluding overlapping comorbidities).

CONCLUSIONS: Among patients undergoing transcatheter aortic valve replacement, frailty is strongly associated with time in hospital and mortality. Prevention strategies for frail patients to reduce hospitalization burden could be beneficial.

Key Words: epidemiology ■ frailty ■ mortality ■ rehospitalization ■ transcatheter aortic valve replacement

Frailty, characterized as a decreased physiological reserve and diminished resistance to stressors, is common among elderly patients undergoing transcatheter aortic valve replacement (TAVR) in everyday clinical practice.[1,2] Although the definitions of identifying frail patients have varied across previous studies, it is becoming an increasingly recognized risk factor for poor outcomes after TAVR, including short- and long-term mortality and disabilities.[3–6] Consequently, with this limited life expectancy for frail patients, time in hospital

represents a central parameter of patient autonomy, quality of life, and quality of care. However, data on the relation between frailty and time in hospital remain scarce.

Furthermore, as readmissions and the associated duration of hospital stays are associated with substantial societal costs, a reduction may also be associated with great societal benefits. Moreover, rehospitalizations have gained increased attention and even been included in the primary end point of a major randomized

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CLINICAL PERSPECTIVE

What Is New?

- For highly frail patients, time in hospital is significant and mortality is high; almost half of patients spent >2 weeks in hospital or died within 1 year after transcatheter aortic valve replacement.

What Are the Clinical Implications?

- The Hospital Frailty Risk Score represents a tool for identification of highly frail patients.
- It can be used to guide resource management for pre–transcatheter aortic valve replacement and post–transcatheter aortic valve replacement optimization to improve outcomes.

Nonstandard Abbreviations and Acronyms

TAVR   transcatheter aortic valve replacement

controlled trial.[7,8] Despite frailty's importance in patient selection and recommendations from guidelines to assess it, no universally accepted frailty assessment tool exists.[9,10] Assessing frailty with clinical frailty tools can be time-consuming, may be subject to interobserver variability, and may not be standard procedure.[11]

Thus, to address these gaps in knowledge, we sought to investigate the relationship between frailty and time spent in hospital and readmission after TAVR using a validated frailty risk score leveraging administrative data.[12]

METHODS

Because of Danish laws, the underlying data, analytical methods, and study materials of the study cannot be shared. Moreover, no informed consent from patients is required.

Data Sources

This study leveraged data from Danish nationwide registries: through a unique personal identification provided to all permanent Danish residents, it is possible to cross-link information from the following registries at an individual level: the Danish Civil Registration System,[13] the Danish National Patient Registry,[14] and the Danish National Prescription Registry were used.[15] These registries have previously been described.[16] All registries have been extensively used for research purposes. The overall positive predictive value of cardiac diagnoses, procedures, and surgeries is high.[17,18]

Study Design, Population, and Outcome

This was a nationwide retrospective cohort study in which all patients undergoing first-time TAVR and surviving until discharge were identified from 2008 through 2020. As data on all hospital contacts were available through 2021, all patients included had a possibility of 1 year of full follow-up. Thus, patients were followed up until death, emigration, 1 year of follow-up, or December 31, 2021, whichever came first.

The outcome of interest was total number of days spent hospitalized: During follow-up, all overnight hospital admissions were identified. For each patient, the total number of unique hospitalizations and the time spent hospitalized (length of stay) were summed. The secondary outcome of interest was the proportion of patients dying within 1 year of follow-up.

Definition of Frailty, Comorbidities, and Comedication

To stratify patients in frailty groups at time of TAVR, we used The Hospital Frailty Risk Score.[12] It is a validated frailty risk assessment tool based on *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes originally developed, internally, and externally validated among older patients in the United Kingdom (Table S1 provides codes). From information on previous hospital admissions up to 10 years before date of TAVR, a score was calculated for each patient. Then, patients were categorized as low, intermediate, and high frailty risk if they scored 0 to 4, 5 to 15, and >15 points, respectively. Patients with a score ≥5 were considered frail. The Hospital Frailty Risk Score has been compared with 2 measures of frailty: the Fried Phenotype, in which a clinical frailty assessment is performed; and the Rockwood Frailty Index, consisting of a deficit accumulation that does not require a clinical evaluation. The comparison showed a fair overlap (κ scores 0.22 and 0.30, respectively).[12]

As done previously, other individual comorbidities were identified from inpatient and outpatient hospital contacts registered with a primary and optional secondary diagnosis codes in a period of up to 10 years before date of TAVR (Table S2 provides codes).[19] For diabetes, a filled prescription of a glucose-lowering drug was used as a proxy.[20] For comedication, all filled prescriptions at a Danish pharmacy in a period of up to 180 days before TAVR were identified (Table S2 provides codes). Likewise, ≥2 prescriptions filled for blood pressure–lowering drugs were used as a proxy for hypertension.[21]

Statistical Analysis

Baseline characteristics are presented with counts and percentages and medians and interquartile ranges (IQRs) for categorical and continuous variables,

respectively. To illustrate differences in time in hospital, patients were categorized into the following categories: "never hospitalized," "hospitalized 1 to 14 days," "hospitalized 15 to 28 days," and "hospitalized >28 days." A final category, "died," comprised the proportion of patients dying within 1 year of follow-up regardless of any prior admissions (ie, if a patient was hospitalized for 14 days and died subsequently, that patient was categorized as "died"). The same proportions were calculated according to frailty risk. Here, frailty groups were compared within each outcome category using the χ^2 test. The 1-year unadjusted risk of death was estimated with the reverse Kaplan-Meier estimator. For adjusted analysis, we associated frailty groups with the composite outcome of >14 days of hospitalization or death in the first year after TAVR in a multivariable logistic regression model. The low frailty group was the reference group, and the model was adjusted for sex, age, calendar year groups of TAVR procedure, and comorbidities not reflected in the Hospital Frailty Risk Score (heart failure, diabetes, peripheral artery disease, liver disease, and chronic obstructive pulmonary disease). The additional adjustment variables were chosen to limit residual confounding. The level of statistical significance was set at 5%. Data management, analyses, figures, and tables were all done using statistical software R version 4.0.3.[22]

Ethical Approval

The data responsible institution for this study was the Capital Region, and the study was performed under the approval number P-2019-191. In Denmark, retrospective cohort studies do not require approval from the Research Ethics Committee. To ensure data staypseudo anonymized, ranges and groups of observations with <5 patients were not reported.

RESULTS

Population Characteristics

From 2008 to 2020, 5971 patients underwent first-time TAVR and were discharged alive. The median age was 81 years, and 55.4% were men. Median length of stay for the TAVR procedure was 4 days (IQR, 2–7 days) and decreased to 2 days in 2020. The mean number of admissions in the year before TAVR was 1.9 (SD, 1.9), and the median was 1.0 (IQR, 1–3). The mean number of days spent hospitalized the year preceding TAVR was 9.2 days (SD, 13.6 days), and the median was 4 days (IQR, 1–12 days) (Table).

Of the 5971 patients, 3437 (57.6%), 2277 (38.1%), and 257 (4.3%) were categorized into low frailty group, intermediate frailty group, and high frailty group, respectively. The proportion of patients in the high frailty group increased during the study period from 7 of 375

(1.9%) high frailty patients in 2008 to 2010 to 140 of 3291 (4.3%) in 2017 to 2020 (Figure S1). Mean and median number of admissions in the year before TAVR increased from 1 and 1.6 in the low frailty group to 3 and 3.2 in the high frailty group. Moreover, the mean and median days in hospital in the year before TAVR increased from 3 and 6.9 in the low frailty group to 12 and 17.3 in the high frailty group. Cardiovascular and noncardiovascular comorbidity burden increased with higher frailty group (eg, history of stroke was present in 7.2% of the low frailty group versus 34.2% of the high frailty group, and history of chronic kidney disease was present in 4.5% versus 29.2%, respectively).

Time in Hospital and Mortality After TAVR

In the overall study population, 2646 of 5917 (44.3%) survived 1 full year without any readmissions, whereas the remaining 3271 of 5917 (55.7%) of patients were hospitalized at least once or died during follow-up. Of these patients, 1284 (21.5%) were hospitalized for >2 weeks or died within 1 year of TAVR (Figure 1).

Time in hospital increased with higher frailty: In the low frailty group, 50.5% survived 1 year without a hospital admission, and 10.8% were hospitalized for >2 weeks. By contrast, 26.1% of patients in the high frailty group survived 1 year without a hospital admission, and 26.4% were hospitalized for >2 weeks (Figure 2). Mortality was incrementally higher according to frailty group: The 1-year risk of death was 5.8% of patients in the low frailty group compared with 15.6% of patients in the high frailty group (Figure 3). Of the 473 patients who died within 1 year of TAVR, the median time in hospital was 17 days (IQR, 7–35 days). Time in hospital was lowest for low frailty patients who died within 1 year and highest for high frailty patients (low frailty: 14 days [IQR, 4–26 days] versus high frailty: 18 days [IQR, 9–42 days]).

From the multivariable logistic regression model of the composite outcome consisting of death or >14 days of hospitalization, increasing frailty group was associated with higher odds ratios of the outcome. The odds ratio was 1.65 (95% CI, 1.45–1.89) for the intermediate frailty group and 3.17 (95% CI, 2.41–4.17) for the high frailty group compared with the low frailty group.

DISCUSSION

In this nationwide study investigating frailty and time in hospital following TAVR, the main findings were as follows: (1) The proportion of high frailty patients was only 4.3%; however, the proportion increased throughout the study period. (2) Half of patients in the low frailty risk group versus one-quarter of patients in the high frailty risk group survived 1 year after TAVR and were never hospitalized. (3) In the low frailty risk

Table. Baseline Characteristics According to Frailty Risk Group

| Characteristic	Frailty risk group			Total
	Low	Intermediate	High	
Total No.	3437	2277	257	5971
Frailty score, median (IQR)	1.5 (0.0–2.6)	6.9 (5.3–9.5)	18.7 (16.6–22.9)	3.2 (1.1–6.6)
Men, n (%)	1904 (55.4)	1268 (55.7)	134 (52.1)	3306 (55.4)
Age, median (IQR), y	81 (77–85)	82 (77–85)	82 (76–85)	81 (77–85)
Length of stay, median (IQR), d	4 (2–7)	4 (3–7)	4 (2–8)	4 (2–7)
Admission in preceding year, n				
Median (IQR)	1 (1–2)	2 (1–3)	3 (1–4)	1 (1–3)
Mean (SD)	1.6 (1.5)	2.3 (2.1)	3.2 (3.1)	1.9 (1.9)
Time in hospital in preceding year, d				
Median (IQR)	3 (1–9)	7 (2–16)	12 (3–25)	4 (1–12)
Mean (SD)	6.9 (11.3)	11.8 (15.1)	17.3 (18.8)	9.2 (13.6)
Comorbidities, n (%)				
Stroke/systemic embolism	248 (7.2)	476 (20.9)	88 (34.2)	812 (13.6)
Myocardial infarction	359 (10.4)	298 (13.1)	47 (18.3)	704 (11.8)
Ischemic heart disease	1451 (42.2)	1203 (52.8)	142 (55.3)	2796 (46.8)
Heart failure	829 (24.1)	789 (34.7)	110 (42.8)	1728 (28.9)
Atrial fibrillation	1057 (30.8)	897 (39.4)	126 (49.0)	2080 (34.8)
Peripheral artery disease	306 (8.9)	332 (14.6)	58 (22.6)	696 (11.7)
Previous PCI	742 (21.6)	598 (26.3)	70 (27.2)	1410 (23.6)
Previous CABG	134 (3.9)	126 (5.5)	17 (6.6)	277 (4.6)
Diabetes	579 (16.8)	481 (21.1)	63 (24.5)	1123 (18.8)
COPD	355 (10.3)	403 (17.7)	64 (24.9)	822 (13.8)
Chronic kidney disease	156 (4.5)	368 (16.2)	75 (29.2)	599 (10.0)
Liver disease	50 (1.5)	61 (2.7)	9 (3.5)	120 (2.0)
Pharmacotherapy, n (%)				
Acetylsalicylic acid	1630 (47.4)	1039 (45.6)	93 (36.2)	2762 (46.3)
ADP receptor antagonist	749 (21.8)	636 (27.9)	76 (29.6)	1461 (24.5)
Oral anticoagulants	1033 (30.1)	822 (36.1)	106 (41.2)	1961 (32.8)
β Blockers	1646 (47.9)	1186 (52.1)	130 (50.6)	2962 (49.6)
Statins	2141 (62.3)	1437 (63.1)	154 (59.9)	3732 (62.5)
Calcium channel blockers	1124 (32.7)	757 (33.2)	67 (26.1)	1948 (32.6)
Renin-angiotensin system inhibitors	1854 (53.9)	1205 (52.9)	119 (46.3)	3178 (53.2)
Diuretics	1333 (38.8)	762 (33.5)	56 (21.8)	2151 (36.0)

CABG, indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; and PCI, percutaneous coronary intervention.

group, 16.6% of patients were admitted for >2 weeks or died within 1 year versus 42.0% in the high frailty risk group.

Frailty in TAVR

Previous studies have investigated the relation of frailty on outcomes after TAVR.[5,23–25] Abugroun et al reported higher in-hospital mortality and complications in a large sample of patients undergoing TAVR.[23] Moreover, Kundi et al found frailty to be a predictor of long-term mortality.[5] Finally, previous studies leveraging data from trials and trial registers found higher degrees of frailty to be associated with a poor prognosis.[24,25] Altogether with frailty being a marker of poor clinical outcomes and high mortality, the quality of life of patients is important, especially in those with a limited life expectancy. Here, time in hospital (inversely home time) is a good measure. Yet, the aforementioned studies leverage trial data with strict inclusion criteria (eg, few patients with impaired renal function despite patients with impaired
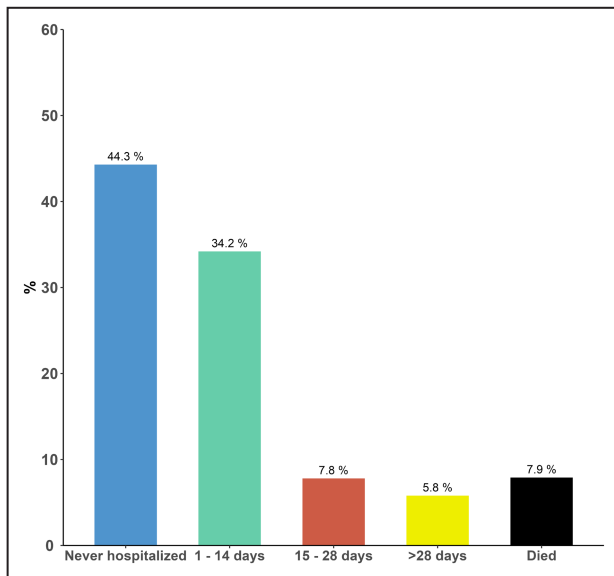
Figure 1. Overall time in hospital.
Proportion of patients who were never hospitalized, hospitalized for different time intervals, and died within 1 year of transcatheter aortic valve replacement. The figure shows that almost half of patients survived 1 year and were never hospitalized, whereas 21.5% of patients were hospitalized for >2 weeks or died within 1 year. The figure serves as a reference for the next figures, where the results are stratified on frailty group.

renal function constituting a large proportion of patients undergoing TAVR[24,25]) or focus on short-term clinical outcomes.[23]

We found an overall prevalence of 3.8% high frailty risk patients alive at discharge, and the absolute number of high frailty risk patients increased from 7 (1.9%) in 2008 to 2010 to 129 (4.3%) in 2017 to 2020. A study by Kundi et al investigating frailty and mortality included all patients undergoing TAVR in 2016 from the Centers of Medicare and Medicaid Services Medicare Provider and Review database.[1] Using the same methods to assess frailty risk, they reported a prevalence of 8.1% high frailty risk patients. However, they included all patients undergoing TAVR, whereas our study only included patients alive at discharge (12 high frailty patients did not survive until discharge). Furthermore, our study period spanned from 2008 to 2020, and previous studies have demonstrated that the comorbidity burden of patients is decreasing over time.[16,26] Last, our study included all patients undergoing TAVR, whereas Kundi et al included patients in the Centers of Medicare and Medicaid Services Medicare Provider and Review database, which may altogether partially explain the difference in prevalence. Despite these differences in prevalence of high frailty risk patients, frail patients continue to undergo TAVR and the use of TAVR is also increasing.[27] Thus, frailty among patients undergoing TAVR is still important to consider.

Mortality and Time in Hospital According to Frailty Risk

Kundi et al also reported 1-year mortality rates of 7.6% for low frailty risk patients and 30.1% for high frailty risk patients.[1] We found that 5.8% of low frailty patients died within 1 year and 15.6% of high frailty patients died within 1 year. In addition, previous studies have reported high overall rates of 1-year rehospitalization ranging from 12.0% to 53.2%.[28] Thus, with a high 1-year mortality rate and high overall rehospitalization rates, time in hospital is important for frail patients. Our study adds valuable information on this matter, as we focused on the time in hospital according to frailty risk; 50.5% of low frailty risk patients survived 1 year and were not hospitalized in the first year following TAVR, whereas 26.1% of high frailty risk patients survived 1 year without any hospitalizations. Notably, >15% of high frailty risk patients were in hospital for >28 days compared with 4.2% for low frailty risk patients. Not only is this easy-to-understand information for the physicians to convey and discuss with patients, but it also represents an area for future focus on strategies to reduce mortality and rehospitalizations (eg, optimizing pre-TAVR condition and appropriate selection of patients). However, it is unclear what measures should be implemented to meet these needs. Currently, clinical trials investigating the effect of prehabilitation on outcomes after TAVR are underway (TAVR-FRAILTY [Prehabilitation to Improve Functional and Clinical Outcomes in Patients With Aortic Stenosis], NCT02597985; and TAVR-Prehab [Prehabilitation for Patients Undergoing Trans-catheter Aortic Valve Replacement], NCT03107897).

Definition of Frailty

We used a frailty risk score based on electronic claims data, which reduces interobserver variability.[12] In addition to grading patients in a binary way into nonfrail (frailty score <5) and frail (frailty score ≥5) patients, it is possible to further categorize patients as low, intermediate, and high frailty.[12] As with other diseases, the degree of frailty may vary for patients. For our study, there was a marked difference in time in hospital between patients at intermediate frailty risk and high frailty risk, both of which are considered overall frail. For patients at intermediate frailty risk, 7.4% were hospitalized for >28 days and 10.3% died within 1 year compared with 13.2% and 15.6% for patients at high frailty risk. This suggests a more continuous spectrum of frailty rather than a binary nonfrail versus frail approach. It also offers a method to focus future strategies on smaller groups as only 257 patients were categorized as high frailty risk versus 2277 at intermediate frailty risk. Using a dichotomized system of frail versus nonfrail, the 257
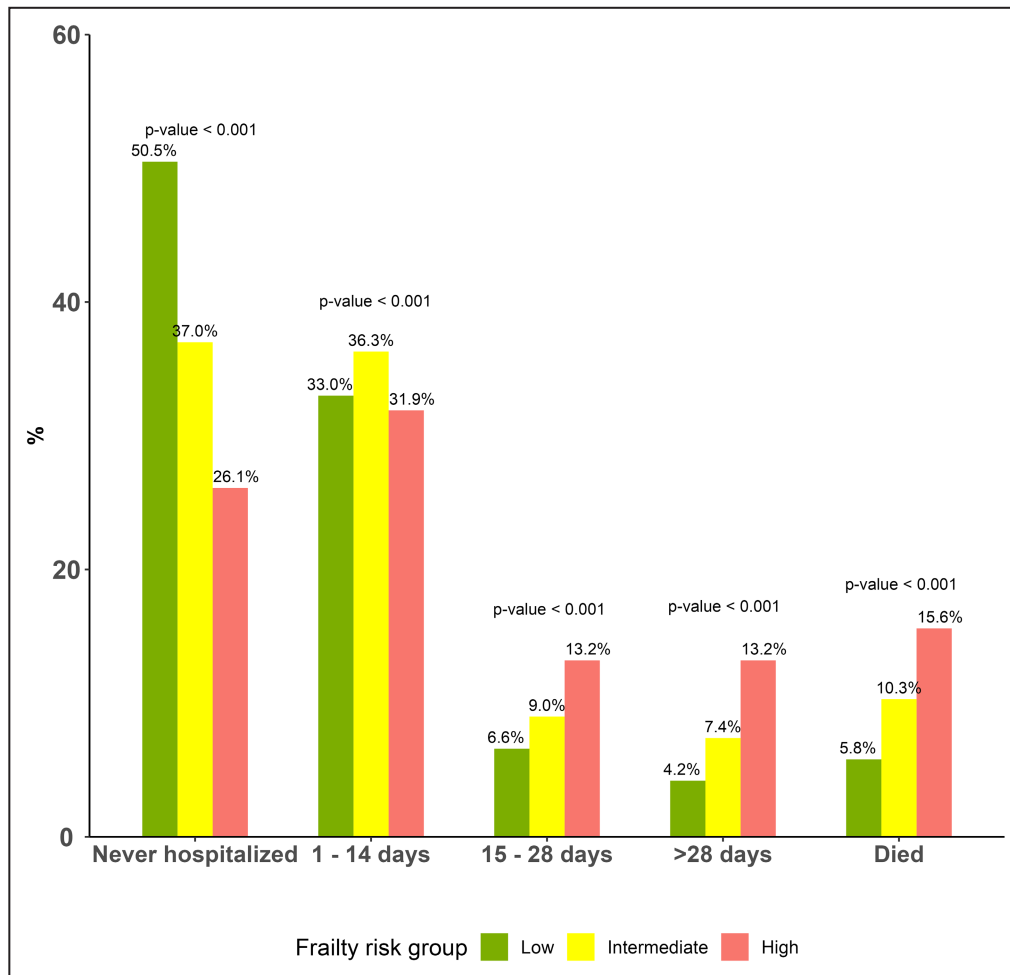
Figure 2. Time in hospital according to frailty.
Proportion of patients who were never hospitalized, hospitalized for different intervals, and died within 1 year of transcatheter aortic valve replacement stratified on frailty groups. The percentages above bars sum to 100% for each frailty group (ie, all green bars sum to 100%). For low frailty patients, 50% survived 1 year and were never hospitalized compared with 25% of high frailty patients. In the low frailty group, 10.9% were hospitalized for >2 weeks compared with 28.1% in the high frailty group. As such, time in hospital is incrementally higher across frailty groups. The *P* values from χ^2 test are presented above bars.

patients at high frailty risk would be difficult to differentiate from the combined 2534 frail patients.

Moreover, the Hospital Frailty Risk Score focuses not only on chronic diseases, as other comorbidity index scores largely do (eg, the Charlson Index and the Elixhauser Comorbidity Index).[29] It also incorporates nonmedical conditions, such as unspecified fall, superficial injury of the head, fractures, and infections, all of which award substantial points to the individual's frailty risk.[12] However, it does not capture other areas, such as walking assistance devices.

Strengths and Limitations

A major strength of this study was the method of frailty assessment with the Hospital Frailty Risk Score in combination with robust underlying data. The Hospital Frailty Risk Score is easy to implement as the data are collected routinely and many countries use the *ICD-10* system; however, the performance of the model relies on the quality of the claims data used. The Danish National Patient Registry is complete and suitable for large-scale epidemiological research.[30] Moreover, with the unique personal identification number used to cross-link information from the other registries used, it is possible to observe patients from birth until emigration or death, limiting a potential underestimation of frailty because of a lack of data registration.

This study had limitations: the Hospital Frailty Risk Score assigns the different diagnoses a prespecified score. However, as stated in the original article, the severity of the diseases may vary (eg, the severity of
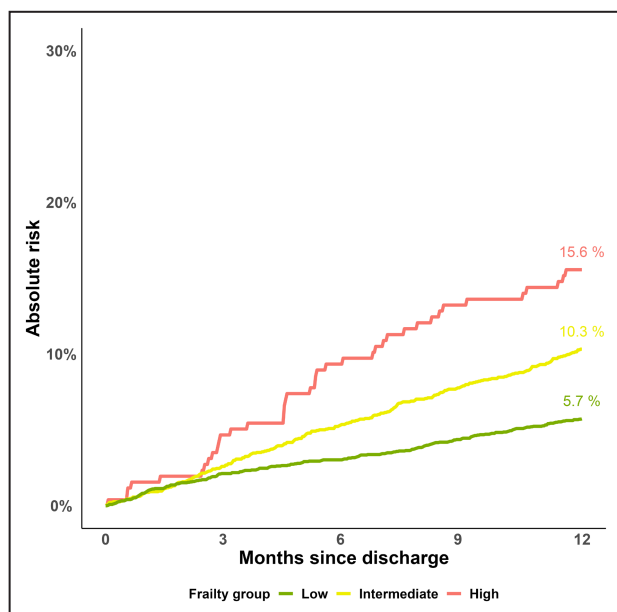
Figure 3. Risk of death.
The 1-year risk of death according to frailty. The *x* axis represents months since transcatheter aortic valve replacement discharge. The *y* axis depicts the absolute risk of death. In the low frailty group, 5.9% died within 1 year compared with 16.1% in the high frailty group. As such, mortality is incrementally higher across frailty groups.

ICD-10 code N18: chronic renal failure). Furthermore, the Hospital Frailty Risk Score was not developed specifically for patients undergoing TAVR. Data on time spent in skilled nursing facilities were not available in the registers, which could have contributed to reflect home time rather than time in hospital.[31] However, the incidence of nursing home admission is low and comparable to that of the general population in Denmark.[32]

CONCLUSIONS

Time in hospital for frail patients is significant, and rehospitalizations are common in the first year after TAVR. Frailty assessed with the Hospital Frailty Risk Score was associated with time in hospital and mortality and should be used for patient selection to take days outside the hospital into account when 1-year life expectancy is estimated before referral for a TAVR. Prevention strategies for frail patients to reduce hospitalization burden are warranted.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2
Figure S1

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Supplemental Material

Table S1. The Hospital Frailty Risk Score.

Codes used and points awarded. Patients were categorized as low (0–4 points), intermediate (5–15 points), and high (>15 points) frailty risk

Diagnosis description	Diagnosis code	Points awarded
Dementia in Alzheimer disease	F00	7.1
Hemiplegia	G81	4.4
Alzheimer's disease	G30	4.0
Sequelae of cerebrovascular disease	I69	3.7
Other symptoms and signs involving the nervous and musculoskeletal systems (R29.6 Tendency to fall)	R29	3.6
Other disorders of urinary system (includes urinary tract infection and urinary incontinence)	N39	3.2
Delirium, not induced by alcohol and other psychoactive substances	F05	3.2
Unspecified fall	W19	3.2
Superficial injury of head	S00	3.2
Unspecified hematuria	R31	3.0
Other bacterial agents as the cause of diseases classified to other chapters (secondary code)	B96	2.9
Other symptoms and signs involving cognitive functions and awareness	R41	2.7
Abnormalities of gait and mobility	R26	2.6
Other cerebrovascular diseases	I67	2.6
Convulsions, not elsewhere classified	R56	2.6
Somnolence, stupor and coma	R40	2.5
Complications of genitourinary prosthetic devices, implants, and grafts	T83	2.4
Intracranial injury	S06	2.4
Fracture of shoulder and upper arm	S42	2.3
Other disorders of fluid, electrolyte, and acid-base balance	E87	2.3

Other joint disorders, not elsewhere classified	M25	2.3
Volume depletion	E86	2.3
Senility	R54	2.2
Care involving use of rehabilitation procedures	Z50	2.1
Unspecified dementia	F03	2.1
Other fall on same level	W18	2.1
Problems related to medical facilities and other health care	Z75	2.0
Vascular dementia	F01	2.0
Superficial injury of lower leg	S80	2.0
Cellulitis	L03	2.0
Blindness and low vision	H54	1.9
Deficiency of other B group vitamins	E53	1.9
Problems related to social environment	Z60	1.8
Parkinson's disease	G20	1.8
Syncope and collapse	R55	1.8
Fracture of rib(s), sternum and thoracic spine	S22	1.8
Other functional intestinal disorders	K59	1.8
Acute renal failure	N17	1.8
Decubitus ulcer	L89	1.7
Carrier of infectious disease	Z22	1.7
Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95	1.7
Ulcer of lower limb, not elsewhere classified	L97	1.6
Other symptoms and signs involving general sensations and perceptions	R44	1.6
Duodenal ulcer	K26	1.6
Hypotension	I95	1.6
Unspecified renal failure	N19	1.6
Other septicemia	A41	1.6

Personal history of other diseases and conditions	Z87	1.5
Respiratory failure, not elsewhere classified	J96	1.5
Exposure to unspecified factor	X59	1.5
Other arthrosis	M19	1.5
Epilepsy	G40	1.5
Osteoporosis without pathological fracture	M81	1.4
Fracture of femur	S72	1.4
Fracture of lumbar spine and pelvis	S32	1.4
Other disorders of pancreatic internal secretion	E16	1.4
Abnormal results of function studies	R94	1.4
Chronic renal failure	N18	1.4
Retention of urine	R33	1.3
Unknown and unspecified causes of morbidity	R69	1.3
Other disorders of kidney and ureter, not elsewhere classified	N28	1.3
Unspecified urinary incontinence	R32	1.2
Other degenerative diseases of nervous system, not elsewhere classified	G31	1.2
Nosocomial condition	Y95	1.2
Other and unspecified injuries of head	S09	1.2
Symptoms and signs involving emotional state	R45	1.2
Transient cerebral ischemic attacks and related syndromes	G45	1.2
Problems related to care-provider dependency	Z74	1.1
Other soft tissue disorders, not elsewhere classified	M79	1.1
Fall involving bed	W06	1.1
Open wound of head	S01	1.1
Other bacterial intestinal infections	A04	1.1
Diarrhea and gastroenteritis of presumed infectious origin	A09	1.1

Pneumonia, organism unspecified	J18	1.1
Pneumonitis due to solids and liquids	J69	1.0
Speech disturbances, not elsewhere classified	R47	1.0
Vitamin D deficiency	E55	1.0
Artificial opening status	Z93	1.0
Gangrene, not elsewhere classified	R02	1.0
Symptoms and signs concerning food and fluid intake	R63	0.9
Other hearing loss	H91	0.9
Fall on and from stairs and steps	W10	0.9
Fall on same level from slipping, tripping, and stumbling	W01	0.9
Thyrotoxicosis [hyperthyroidism]	E05	0.9
Scoliosis	M41	0.9
Dysphagia	R13	0.8
Dependence on enabling machines and devices	Z99	0.8
Agent resistant to penicillin and related antibiotics	U80	0.8
Osteoporosis with pathological fracture	M80	0.8
Other diseases of digestive system	K92	0.8
Cerebral Infarction	I63	0.8
Calculus of kidney and ureter	N20	0.7
Mental and behavioral disorders due to use of alcohol	F10	0.7
Other medical procedures as the cause of abnormal reaction of the patient	Y84	0.7
Abnormalities of heartbeat	R00	0.7
Unspecified acute lower respiratory infection	J22	0.7
Problems related to life-management difficulty	Z73	0.6
Other abnormal findings of blood chemistry	R79	0.6
Personal history of risk-factors, not elsewhere classified	Z91	0.5
Open wound of forearm	S51	0.5
Depressive episode	F32	0.5

Spinal stenosis	M48	0.5
Disorders of mineral metabolism	E83	0.4
Polyarthrosis	M15	0.4
Other anemias	D64	0.4
Other local infections of skin and subcutaneous tissue	L08	0.4
Nausea and vomiting	R11	0.3
Other noninfective gastroenteritis and colitis	K52	0.3
Fever of unknown origin	R50	0.1

Table S2. List of ICD10-, ATC-, NCSP-, and NPU-codes.

| Population		
Transcatheter Aortic Valve Replacement	Defined from surgical procedures	**NCSP:** KFMD11, KFMD12, KFMD14
Exposure		
Frailty groups: Low (reference), intermediate, and high	Defined with the Hospital Frailty Risk Score	
Comorbidities		
Percutaneous coronary intervention	Defined from surgical procedures	**NCSP:** KFNG00, KFNG02, KFNG05, KFNG10, KFNG12, KFNG96
Coronary artery bypass grafting	Defined from surgical procedures	**NCSP:** KNFA, KFNB, KFNC, KFND, KFNE
Stroke/systemic embolism	Defined from diagnoses codes	**ICD10:** I63, I64, I74, G458, G459
Myocardial infarction	Defined from diagnoses codes	**ICD10:** I21-I22
Ischemic heart disease	Defined from diagnoses codes	**ICD10:** I20-I25
Heart failure	Defined from diagnoses codes	**ICD10:** I110, I130, I132, I420, I426, I427, I428, I429, I50
Atrial fibrillation	Defined from diagnoses codes	**ICD10**: I48
Peripheral artery disease	Defined from diagnoses codes or surgical procedures	**ICD10**: I70, I74, I739 **NCSP:** KPDE, KPDF, KPDG, KPDH, KPDN, KPDP, KPDQ, KPDR, KPDU, KPEE, KPEF, KPEG, KPEH, KPEN, KPEP, KPEQ, KPER, KPEU
Hypertension	Defined from diagnoses codes or treatment with 2 or more antihypertensive drugs: adrenergic α-antagonists, non-loop diuretics, vasodilators, β-blockers, calcium channel	**ICD10**: I10-15 **ATC**: C02A, C02B, C02C, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C02DA, C09BA, C09DA, C02DB, C02DD, C02DG, C07A,

	blockers, renin-angiotensin system inhibitors.	C07B, C07C, C07D, C07F, C08, C09BB, C09DB, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52, C03C, C03EB
Diabetes mellitus	Defined from glucose-lowering medication	**ATC**: A10
Chronic kidney disease	Defined from diagnoses codes	**ICD10:** E102, E112, E122 E132, E142, I120, N02-N08, N11, N12, N14, N18, N19, N26, Q61, N158, N159, N160, N162, N163, N164, N168, N391, Q612, Q613, Q615, Q619, Z940, Z992
Chronic obstructive pulmonary disease	Defined from diagnoses codes	**ICD10**: J44
Pharmacotherapy		
Adenosine-phosphate receptor antagonists	Defined from ATC codes	**ATC**: B01AC04, B01AC22, B01AC24
Aspirin	Defined from ATC codes	**ATC**: B01AC06 N02BA01
Non-steroidal-anti-inflammatory-drugs	Defined from ATC codes	**ATC**: M01A, except M01AX05
Beta-blockers	Defined from ATC codes	**ATC**: C07A, C07B, C07C, C07D, C07F
Calcium channel blockers	Defined from ATC codes	**ATC**: C07F, C08, C09BB, C09DB
Renin-angiotensin system inhibitors	Defined from ATC codes	**ATC**: C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
Loop diuretics	Defined from ATC codes	**ATC**: C03C C03EB

Figure S1. Trends in frailty over time.
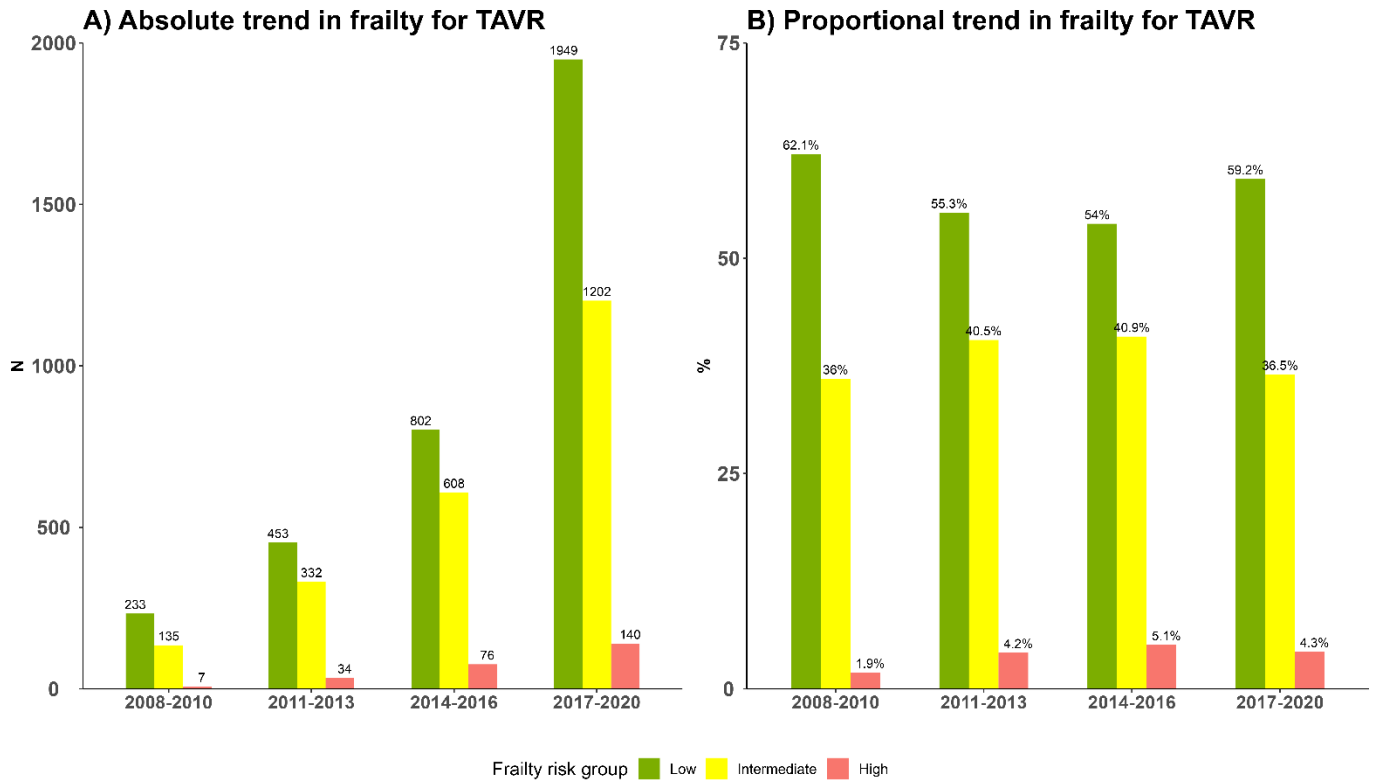
Panel A shows the absolute trend in frailty for TAVR over time with the x-axis illustrating year groups and the y-axis number of patients (also illustrated in the numbers above bars). Panel B shows the proportional trend in frailty for TAVR over time. The x-axis represents calendar year groups. The y-axis shows the proportion of patients in each frailty group for a given calendar year group. As such, the numbers above bars sum to 100%.

TAVR: Transcatheter aortic valve replacement.