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Impact of a Claims-based Frailty Indicator on the Prediction of Long-Term Mortality after Transcatheter Aortic Valve Replacement in Medicare Beneficiaries

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Abstract

Background: Prospectively collected frailty markers are associated with an incremental 1-year mortality risk after transcatheter aortic valve replacement (TAVR) compared to comorbidities alone. Whether information on frailty markers captured retrospectively in administrative billing data is similarly predictive of long-term mortality after TAVR is unknown. We sought to characterize the prognostic importance of frailty factors as identified in healthcare billing records in comparison to validated measures of frailty for the prediction of long-term mortality after TAVR.

Methods and Results: Adult patients undergoing TAVR between August 25, 2011 and September 29, 2015 were identified among Medicare fee-for-service beneficiaries. The Johns Hopkins Claims-based Frailty Indicator was used to identify frail patients. We used nested Cox regression models to identify claims-based predictors of mortality up to 4 years post-procedure. Four groups of variables including cardiac risk factors, non-cardiac risk factors, patient procedural risk factors, and non-traditional markers of frailty were introduced sequentially, and their integrated discrimination improvement (IDI) was assessed. A total of 52,338 TAVR patients from 558 clinical sites were identified, with a mean follow-up time period of 16 months. In total, 14,174 (27.1%) patients died within the study period. The mortality rate was 53.9% at 4-years post TAVR. A total of 34,863 (66.6%) patients were defined as frail. The discrimination of each of the 4 models was 0.60 (95% CI: 0.59–60), 0.65 (95% CI: 0.64–0.65), 0.68 (95% CI: 0.67–0.68) and 0.70 (95% CI: 0.69–0.70), respectively. The addition of non-traditional frailty markers as identified in claims improved mortality prediction above and beyond traditional risk factors (IDI: 0.019, $p < 0.001$).

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Conclusions: Risk prediction models that include frailty as identified in claims data can be used to predict long-term mortality risk after TAVR. Linkage to claims data may allow enhanced mortality risk prediction for studies that do not collect information on frailty.

INTRODUCTION

Severe calcific aortic valve stenosis is the most common cause of valve replacement in the elderly population in the United States (US).[1] While surgical aortic valve replacement (SAVR) remains the preferred treatment for severe symptomatic aortic stenosis in patients at low surgical risk, current guidelines recommend transcatheter aortic valve replacement (TAVR) as an alternative treatment in patients at increased surgical risk based on a number of clinical trials showing equivalence or superiority to surgery for patients with extreme, high, and intermediate surgical risk [2–8].

Risk stratification before TAVR is important when selecting those patients who will most likely benefit from the procedure. To date, clinical risk prediction models of 1-year mortality after TAVR have been developed using traditional risk scoring systems. These include the Society for Thoracic Surgery Predicted Risk of Mortality (STS-PROM) score [9, 10] and the logistic EuroSCORE [11], as well as other individual clinical risk predictors [12–16]. Prior studies have suggested that measurement of frailty can enhance the prediction of mortality after TAVR [17–30]. Additionally, a relatively small, prospective study recently showed that adding frailty measurements to conventional risk scores improved the assessment of 1-year mortality risk after TAVR [31].

However, the assessment of frailty in clinical practice can be challenging, and these factors are commonly not collected in the nationwide registries such as the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry. In the absence of prospectively collected data, the ability to identify these factors in billing records may allow for enhanced mortality prediction. To test this, we evaluated hospitalizations of patients undergoing TAVR in a Medicare inpatient database to determine whether the incorporation of claims-based measures of frailty might augment mortality prediction compared to using comorbidities alone.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

The Centers for Medicare and Medicaid Services (CMS) MedPAR files include administrative billing claims for all hospitalizations of Medicare fee-for-service beneficiaries, and have been used to study national patterns of procedure utilization in the US [32–34]. In the MedPAR database, hospitalizations of adult patients (≥18 years old) were included if they had at least one International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for either transfemoral (35.05) or transapical (35.06) TAVR performed between August 25, 2011 and September 29, 2015.

Cardiac and Non-cardiac Covariates and Procedural Risk Factors

A total of 34 cardiac and non-cardiac covariates and procedural risk factors were initially defined as possible risk factors for all-cause mortality after TAVR based on our clinical knowledge. Age, gender, race, chronic heart failure, smoking, peripheral vascular disease, diabetes mellitus and a couple of well-known cardiac diseases were defined as cardiac risk factors. Other comorbidities such chronic kidney, liver and obstructive pulmonary diseases, anemia, obesity, hypothyroidism, coagulopathy and the Charlson comorbidity index were defined as non-cardiac risk factors. Procedural risk factors included emergency or urgent admission, transapical access and pre-procedural shock.

Frailty Index

There are several ways to measure claims-based frailty [35–36]. In this study, the Johns Hopkins Claims-based Frailty Indicator, a previously developed and both internally and externally validated index, was used to identify frailty [37–40]. This index includes 21 criteria identifiable in claims data, such as demographic variables and markers of physical and cognitive dysfunction, to identify patients meeting Fried's Frailty Phenotype [41]. This has been extensively validated and shown to predict poor health outcomes including incidence of falls, worsening mobility, hospitalization, and death. Based on the Johns Hopkins Claims-based Frailty Indicator algorithm [37], a score cutoff of ≥ 0.12 was used to identify frail patients (Supplementary Table 1).

Some variables included in the John Hopkins Claims-based Frailty Indicator, such as age, sex, and Charlson comorbidity index, overlap with variables commonly used for risk adjustment in TAVR patients. In order to examine the prognostic importance of frailty variables often omitted from risk adjustment, we classified a subgroup of variables in the Frailty Indicator as non-traditional frailty markers. These included impaired mobility, depression, Parkinson's disease, any type of arthritis, cognitive impairment, paranoia, chronic skin ulcer, pneumonia, skin and soft tissue infections, mycoses, gout or other crystal-induced arthropathies, falls, musculosketal problems and urinary tract infection.

All covariates were ascertained using secondary diagnosis codes that were coded as "present on admission" during the index hospitalization, as well as from principal and secondary diagnosis codes from all hospitalizations in the year prior to the date of admission of the index hospitalization (Supplementary Table 2).

Outcomes—The primary outcome for this study was all-cause long-term mortality, determined through linkage of the MedPAR files to the CMS denominator file which includes information on a patient's vital status. Time to death was calculated as the time between the date of procedure and date of death. Patients were censored if they were no longer enrolled in Medicare according to the denominator file as of December 31, 2015, which marked the end of the follow-up period. The study was approved by the institutional review board of Beth Israel Deaconess Medical Center with a waiver of informed consent for retrospective data analysis.

Statistical Analysis—Continuous variables are presented as means and standard deviations, and categorical variables are presented as counts and percentages. Covariates were compared between surviving and non-surviving patients using chi-square statistics and t-tests. Kaplan-Meier plots were created to plot time to death with a 30-day landmark analysis, stratified by the number of non-traditional frailty markers included. The log-rank test was used to compare the survival distributions of each frailty scale.

Covariates with a p-value of <0.1 in univariate Cox regression analysis were ultimately included in the model. Subsequently, nested multivariable Cox regression incorporating random hospital effects was performed using four sequential models to determine the incremental improvement in prediction of long-term mortality with the addition of four sets of covariates. The sequential models included variables associated with 1) cardiac risk factors, 2) non-cardiac risk factors, 3) procedural risk factors and 4) non-traditional frailty markers. Harrell's c-statistic was used to assess model discrimination, and the improvement in discrimination with the addition of variables was assessed by the change in the c-statistic and the DeLong test [42]. An integrated discrimination improvement (IDI) test was used to assess discrimination improvement [43]. All statistical analyses were performed in STATA software, version 15.0 (Stata Corporation, College Station, TX) using a two-tailed p-value for significance of <0.05.

RESULTS

A total of 52,338 hospitalizations from 558 clinical sites involved receipt of TAVR over the study period. The baseline characteristics of patients are shown in Table 1. A total of 27,147 (51.9%) were men and the mean age was 82.4 ±8.0 years. There were 34,863 (66.6%) patients that were identified as frail. Musculoskeletal problems (15.5%) and arthritis (13.9%) were the most prevalent non-traditional frailty markers.

Mortality

In total, 14,174 (27.1%) patients died within the study period, with a mean follow-up time of 16 months. The all-cause mortality rate was 3.6% in-hospital, 5.1% at 30-days, 19.0% at 1-year, 30.1% at 2-years, 42.3% at 3-years, and 53.9% at 4-years post-TAVR. Kaplan–Meier curves showing overall mortality up to 4 years after TAVR stratified by the number of non-traditional frailty markers are shown in Figure 1. Compared to those without any non-traditional frailty markers, the hazard ratio (HR) was 1.166 (95% confidence interval [CI]: 1.122–1.211) for patients with one frailty marker, 1.417 (95% CI: 1.350–1.488) for those with two frailty markers, and 1.490 (95% CI: 1.383–1.610) for those with ≥3 frailty markers (p<0.001 for all). The predicted 4-year mortality was 57% for frail patients and 48% for non-frail patients (HR = 1.342, 95% CI: 1.293–1.393, p<0.001). In the 30-day landmark analysis, compared to those without any non-traditional frailty markers, the HR was 1.010 (95% CI: 0.925–1.144) for patients with one frailty marker 1.185 (95% CI: 0.955–1.308) for those with two frailty markers, and 1.136 (95% CI: 0.935–1.380) for those with ≥3 frailty markers (p=0.135).

Discrimination Improvement and Model Covariates

In nested models, the discrimination of the first model including only cardiac risk factors was 0.60 (95% CI: 0.59–60). The addition of non-cardiac risk factors in the second model resulted in a c-statistic of 0.65 (95% CI: 0.64–0.65) (IDI=0.032, p<0.001 compared to the first model). With the incorporation of additional procedural characteristics in the third model, the c-statistic was 0.68 (95% CI: 0.67–0.68) (IDI=0.019, p<0.001 compared to the second model). Finally, the inclusion of non-traditional frailty markers resulted in a c-statistic of 0.70 (95% CI: 0.69–0.70) (IDI=0.019, p<0.001 compared to third model). Comparisons of the c-statistics using the DeLong test were statistically significant (p<0.001) for each model (Model 2 vs Model 1, Model 3 vs Model 2, Model 4 vs Model 3) (Table 2).

The hazard ratios for the final covariates, determined from nested cox regression analysis, are presented in Table 3. The covariates that were most strongly associated with increased long-term mortality were atrial fibrillation (HR: 1.394, 95% CI: 1.347–1.442, p<0.001), chronic heart failure (HR: 1.249, 95% CI: 1.195–1.304, p<0.001) , dialysis (HR: 2.033, 95% CI: 1.844–2.411, p<0.001), liver disease (HR: 2.046, 95% CI: 1.905–2.197, p<0.001), emergency admission (HR: 1.298, 95% CI: 1.225–1.374, p<0.001), pre-procedural-shock (HR: 2.369, 95% CI: 2.201–2.549, p<0.001), pneumonia (HR: 1.883, 95% 1.761–2.014), and chronic skin ulcer (HR: 1.670, 95% 1.540–1.811). As shown in Supplementary Table 3, the claims-based predictors of long-term mortality used in the current study are similar to those defined in clinical studies.

DISCUSSION

In the present study, we show that administrative codes can be used to identify cardiac and non-cardiac risk factors, procedural characteristics, and markers of frailty which likely rendered TAVR patients at high surgical risk. The majority of TAVR patients in the database were frail, and the incorporation of these factors into statistical models improved the prediction of long-term mortality in patients undergoing TAVR when combined with traditional risk factors. Furthermore, our results demonstrate that the rate of long-term mortality after TAVR gradually increases with an increasing number of recorded non-traditional frailty markers. These findings illustrate the impact of frailty on outcomes for patients undergoing TAVR.

Impact of Frailty on Long-Term Mortality

There is a paucity of clinical studies for patients with structural heart disease which include an assessment of risk factors for frailty. For instance, the STS/ACC TVT Registry, the largest registry collecting patient characteristics and outcomes related to TAVR procedures in the US, collects only a few frailty markers such albumin, hemoglobin, and the 5-meter speed test [44]. However, it has been demonstrated that incorporating frailty improves the prediction of mortality following TAVR. Adding a frailty index improved the c-statistic for discrimination of 1-year mortality of the STS-PROM score from 0.64 to 0.68 (p<0.001), and improved the discrimination of the logistic EuroSCORE from 0.67 to 0.72 (p<0.001) [31].

Afilalo *et al.* [19] reported that the average prevalence of frailty in the TAVR population, based on assessments using seven separate frailty scales, was 54% (37%−74%). Despite both its commonality and its importance, frailty scales are infrequently collected in routine clinical care [45]. In the absence of prospectively collected data on frailty, we show prognostic information can be identified in claims data. Further, we showed that including claims-based frailty alongside traditional risk factors in statistical modeling significantly improved the discrimination of long-term mortality. However, in our landmark analysis, adding non-traditional frailty markers did not predict differences in perioperative mortality. These results suggest that the incorporation of frailty is more important for the prediction of long-term mortality than perioperative mortality. Additionally, the improvement performance of adding frailty was similar in magnitude to adding procedural covariates which are well-known risk factors [10] in the TAVR population. We believe that by merging claims-based frailty data with ongoing structural heart registries, we might enhance the ability to define patient risk and understand long-term outcomes, improve hospital benchmarking, and increase the completeness of data collection.

Predictors of All-cause Mortality After TAVR

Predictive models for in-hospital and 30-day mortality have provided moderate discrimination in the TVT registry (c-statistic: 0.67 in the training dataset; 0.66 in the validation sample) [10] and the France-2 Registry (c-statistic: 0.67 in the training sample; 0.59 in the validation sample) [16]. The primary advantage of our analysis of MedPAR data is the inclusion of a large, generalized population with the ability to track mortality over the long term. Although we do not have all the necessary variables to calculate traditional surgical risk scores such as the STS-PROM or logistic EuroSCORE, the final model derived from MedPAR data had reasonable discrimination (c-statistic = 0.70), and the claims-based predictors of long-term mortality used in the current study are similar to those defined in clinical studies (Supplementary Table 3).

Limitations

There are several limitations to the present study. The indications and criteria for patient selection for TAVR are not available, and administrative coding may misclassify some comorbidities and complications compared with prospective collection using standard clinical trial definitions. Additionally, because the study population was limited to Medicare beneficiaries, we did not have information on all patients younger than 65 years of age who might have undergone TAVR in the US, and those patients < 65 who were included in the study may not be representative of younger patients overall.

CONCLUSIONS

Our findings show that risk prediction models that include frailty as identified in claims data can be used to more accurately predict long-term mortality risk after TAVR. Linkage to claims data may allow enhanced mortality risk prediction for studies that do not collect information on frailty.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is Known:

- Frailty and disability play a key role in the identification of older patients' potential for improvement after transcatheter aortic valve replacement.

What the Study Adds:

- Our findings show that the inclusion of frailty and disability markers as identified in Medicare beneficiaries significantly improved the prediction of long-term mortality.
- These claims-based risk factors may allow for enhanced mortality prediction in the absence of prospectively collected data.

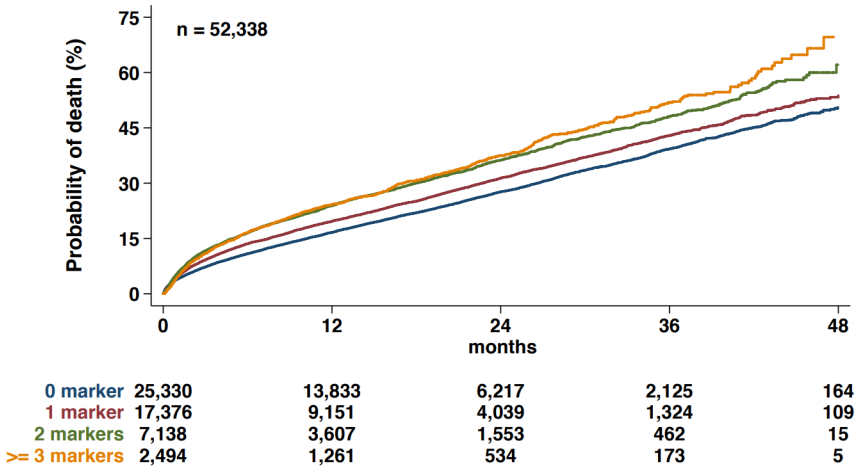

Figure 1.

Kaplan Meier curves for all-cause mortality according to presence of non-traditional frailty markers

Table 1.

Characteristics of the study population between surviving and dead patients

	Overall n=52,338	Alive n=38,164 (72.9%)	Dead n=14,174 (27.1%)	p-value
Cardiac History				
Age, years (mean±SD)	82.4±8.0	82.2±7.8	82.9±8.3	<0.001
Men, no. of pts (%)	27,147 (51.9)	19,444 (50.1)	7,703 (54.3)	<0.001
White race, no. of pts (%)	48,635 (92.9)	35,414 (92.8)	13,221 (93.3)	0.067
Chronic heart failure, no. of pts (%)	39,416 (75.3)	27,982 (73.3)	11,434 (80.7)	<0.001
Diabetes mellitus, no. of pts (%)	19,062 (36.4)	13,915 (36.5)	5,147 (36.3)	0.15
Smoker, no. of pts (%)	16,679 (31.9)	12,667 (33.2)	4,012 (28.3)	<0.001
Coronary artery disease without revascularization, no. of pts (%)	37,770 (72.2)	27,783 (72.8)	9,987 (70.5)	<0.001
Prior myocardial infarction, no. of pts (%)	8,419 (16.1)	6,057 (15.9)	2,362 (16.7)	0.028
Prior percutaneous coronary intervention, no. of pts (%)	11,465 (21.9)	8,693 (22.8)	2,772 (19.6)	<0.001
Prior valvular surgery, no. of pts (%)	855 (1.6)	649 (1.7)	206 (1.5)	0.047
Prior aortic surgery, no. of pts (%)	211 (0.4)	140 (0.4)	71 (0.5)	0.031
Prior coronary artery bypass graft surgery, no. of pts (%)	12,073 (23.1)	9,133 (23.9)	2,940 (20.7)	<0.001
Peripheral vascular disease, no. of pts (%)	5,382 (10.3)	3,853 (10.1)	1,529 (10.8)	0.021
Atrial fibrillation, no. of pts (%)	24,567 (46.9)	16,671 (43.7)	7,896 (55.7)	<0.001
Center bundle branch block, no. of pts (%)	5,502 (10.5)	4,323 (11.3)	1,179 (8.3)	<0.001
Right bundle branch block, no. of pts (%)	2,000 (3.8)	1,555 (4.1)	445 (3.1)	<0.001
Cerebrovascular disease, no. of pts (%)	7,230 (13.8)	5,108 (13.4)	2,122 (15.0)	<0.001
Tricuspid valve disorders, no. of pts (%)	4,557 (8.7)	3,177 (8.3%)	1,380 (9.7%)	<0.001
Endocarditis, no. of pts (%)	45 (0.1)	23 (0.1)	22 (0.2)	0.001
Aortic aneurysm, no. of pts (%)	1,876 (3.6)	1,283 (3.4)	593 (4.2)	0.001
Non-Cardiac History				
Chronic kidney disease without dialysis, no. of pts (%)	21,071 (40.3)	14,113 (37.0)	6,958 (49.1)	<0.001
Renal dialysis, no. of pts (%)	1,269 (2.4)	714 (1.9)	555 (3.9)	<0.001
Liver disease, no. of pts (%)	1,915 (3.7)	1,042 (2.7)	873 (6.2)	<0.001
Chronic obstructive pulmonary disease, no. of pts (%)	17,566 (33.6)	12,226 (32.0)	5,340 (37.7)	<0.001
Home O_2, no. of pts (%)	3,551 (6.8)	2,207 (5.8)	1,344 (9.5)	<0.001
Hypothyroidism, no. of pts (%)	11,456 (21.9)	8,311 (21.8)	3,145 (22.2)	0.31
Coagulopathy, no. of pts (%)	10,285 (19.7)	6,973 (18.3)	3,312 (23.4)	<0.001
Obesity, no. of pts (%)	7,852 (15.0)	6,197 (16.2)	1,655 (11.7)	<0.001
Anemia, no. of pts (%)	26,328 (50.3)	18,282 (47.9)	8,046 (56.8)	<0.001
Charlson Comorbidity Index, (mean±SD)	3.30±1.87	3.14±1.83	3.74±1.92	<0.001
Procedural Characteristics				
Emergency admission, no. of pts (%)	3,819 (7.3)	2,396 (6.3)	1,423 (10.0)	<0.001

	Overall n=52,338	Alive n=38,164 (72.9%)	Dead n=14,174 (27.1%)	p-value
Urgent admission, no. of pts (%)	7,377 (14.1)	4,927 (12.9)	2,450 (17.3)	<0.001
Transapical, no. of pts (%)	8,071 (15.4)	5,218 (13.7)	2,853 (20.1)	<0.001
Pre-procedural shock, no. of pts (%)	1,423 (2.7)	535 (1.4)	888 (6.3)	<0.001
Non-Traditional Frailty Markers				
Impaired mobility, no. of pts (%)	314 (0.6)	212 (0.6)	102 (0.7)	0.031
Depression, no. of pts (%)	4,243 (8.1)	3,099 (8.1)	1,144 (8.1)	0.85
Parkinson's Disease, no. of pts (%)	717 (1.4)	517 (1.4)	200 (1.4)	0.62
Arthritis (Any Type), no. of pts (%)	7,290 (13.9)	5,537 (14.5)	1,753 (12.4)	<0.001
Cognitive Impairment, no. of pts (%)	4,924 (9.4)	3,381 (8.9)	1,543 (10.9)	<0.001
Paranoia, no. of pts (%)	493 (0.9)	326 (0.9)	167 (1.2)	<0.001
Chronic Skin Ulcer, no. of pts (%)	1,283 (2.5)	629 (1.6)	654 (4.6)	<0.001
Pneumonia, no. of pts (%)	1,782 (3.5)	777 (2.0)	1,005 (7.3)	<0.001
Falls, no. of pts (%)	60 (0.1)	36 (0.1)	24 (0.1)	0.20
Skin and Soft Tissue Infections, no. of pts (%)	515 (1.0)	304 (0.8)	211 (1.5)	<0.001
Mycoses, no. of pts (%)	748 (1.4)	379 (1.0)	369 (2.6)	<0.001
Gout or Other Crystal-Induced Arthropathies, no. of pts (%)	3,309 (6.3)	2,387 (6.3)	922 (6.5)	0.30
Musculosketal Problems, no. of pts (%)	8,101 (15.5)	6,244 (16.4)	1,857 (13.1)	<0.001
Urinary Tract Infection, no. of pts (%)	4,888 (9.3)	3,032 (7.9)	1,856 (13.1)	<0.001

SD = standard deviation

Table 2.

Results of multivariable nested Cox regression

	Hazard Ratio	95% CIs	p-value
Cardiac History			
Age (by year)	1.015	1.013–1.018	<0.001
Male	1.223	1.179–1.269	<0.001
Chronic heart failure	1.249	1.195–1.304	<0.001
Diabetes mellitus	1.047	1.009–1.086	0.013
Smoker	0.886	0.852–0.921	<0.001
Coronary artery disease without revascularization	0.924	0.887–0.962	<0.001
Prior percutaneous coronary intervention	0.930	0.889–0.972	0.001
Prior coronary artery bypass graft surgery	0.883	0.845–0.923	<0.001
Atrial fibrillation	1.394	1.347–1.442	<0.001
Center bundle branch block	0.893	0.841–0.948	<0.001
Right bundle branch block	0.840	0.763–0.924	0.004
Aortic aneurysm	1.141	1.046–1.244	0.003
Non-Cardiac History			
Chronic kidney disease without dialysis	1.378	1.330–1.427	<0.001
Renal dialysis	2.033	1.844–2.411	<0.001
Liver disease	2.046	1.905–2.197	<0.001
Chronic obstructive pulmonary disease	1.198	1.155–1.243	<0.001
Home O_2	1.556	1.466–1.652	<0.001
Coagulopathy	1.100	1.057–1.145	<0.001
Obesity	0.789	0.748–0.833	<0.001
Anemia	1.132	1.093–1.172	<0.001
Charlson Comorbidity Index	1.136	1.125–1.146	<0.001
Procedural Characteristics			
Emergency admission	1.298	1.225–1.374	<0.001
Urgent admission	1.166	1.114–1.220	<0.001
Transapical	1.123	1.076–1.172	0.020
Pre-procedural shock	2.369	2.201–2.549	<0.001
non-Traditional Frailty Markers			
Impaired mobility	1.240	1.015–1.516	0.035
Depression	1.067	1.003–1.135	0.038
Cognitive Impairment	1.229	1.165–1.297	0.001
Paranoia	1.252	1.075–1.459	0.004
Chronic Skin Ulcer	1.670	1.540–1.811	<0.001
Pneumonia	1.883	1.761–2.014	<0.001
Skin and Soft Tissue Infections	1.269	1.106–1.457	<0.001

	Hazard Ratio	95% CIs	p-value
Mycoses	1.446	1.301–1.607	<0.001
Urinary Tract Infection	1.279	1.215–1.345	<0.001

CI = confidence interval

Table 3.

Comparison of the c-statistics in each model

	C-statistic (95% CI)	IDI	IDI(p-value)	DeLong(p-value)
Model 1 (Cardiac risk factors)	0.60 (0.59–0.60)	–	–	–
Model 2 (Model 1 + non-cardiac risk factors)	0.65 (0.64–0.65)	0.032 *	<0.001 *	<0.001 *
Model 3 (Model 2 + procedural characteristics)	0.68 (0.67–0.68)	0.019 †	<0.001 †	<0.001 †
Model 4 (Model 3 + non-traditional frailty markers)	0.70 (0.69–0.70)	0.019‡	<0.001 ‡	<0.001 ‡

* Model 2 vs Model 1,

† Model 3 vs Model 2,

‡ Model 4 vs Model 3.

IDI = integrated discrimination improvement; CI = confidence interval