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ORIGINAL ARTICLE
Cardiovascular Intervention

Impact of Cognitive Impairment on Long-Term Outcomes After Transcatheter Aortic Valve Implantation

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Background: Cognitive impairment assessed using the Mini-Mental Status Examination (MMSE) is associated with short-term mortality after transcatheter aortic valve implantation (TAVI). We assessed the long-term prognostic impact of cognitive impairment in patients with severe aortic stenosis post-TAVI.

Methods and Results: We enrolled 1,057 consecutive patients who underwent TAVI at the Kokura Memorial Hospital and prospectively assessed them using the MMSE. Results showed that 319 (30%) patients had cognitive impairment. Compared with normal cognition, cognitive impairment was associated with an increased risk for 5-year all-cause mortality (55% vs. 39%; P<0.001), cardiovascular mortality (23% vs. 14%; P=0.007), and non-cardiovascular mortality (42% vs. 29%; P<0.001). Multivariable analysis showed that cognitive impairment was independently associated with all-cause mortality (adjusted hazard ratio [aHR] 1.37; 95% confidence interval [CI] 1.10–1.70; P=0.005), and this result was consistent regardless of stratification based on age, sex, body mass index, left ventricular ejection fraction and clinical frailty scale without significant interaction. Patients with MMSE scores <16 had a significantly higher mortality rate compared with patients with MMSE scores >25, 21–25, and 16–20, respectively.

Conclusions: Cognitive impairment assessed using MMSE scores is independently associated with an increased risk for 5-year all-cause mortality in patients undergoing TAVI.

Key Words: Cognitive impairment; Structural heart disease; Transcatheter aortic valve implantation (TAVI)

Transcatheter aortic valve implantation (TAVI) has been established as a therapeutic alternative to surgical aortic valve replacement for inoperable or high-risk patients with severe aortic stenosis. However, recently, the indications for TAVI have been expanded to include younger and/or lower-risk patients. Therefore, it is necessary to identify predictors that stratify long-term prognosis post-TAVI. Frailty, which is not included in the classical surgical risk model, is a geriatric syndrome of impaired physiologic reserve and decreased resistance to stressors,[1,2] and is associated with poor prognosis in patients with cardiovascular disease (CVD).[3–5] Cognitive impairment, which is a common component of frailty, is characterized by diminished memory and reduced ability to complete typical daily activities. Cognitive impairment predicts CVD events independently,[6] and is associated with a poor prognosis in patients with CVD.[7,8] However, patients with cognitive impairment are not frequently enrolled into randomized cardiovascular clinical trials. Thus, evidence of the benefits of cardiovascular medications and procedural interventions is weak, which can be especially problematic in older patients with cognitive impairment for whom the benefits of invasive cardiac treatment must be considered along with the associated higher potential risks. A pivotal study from the Optimized Catheter Valvular Intervention (OCEAN)-TAVI multicenter registry reported that cognitive impairment is independently associated with 1-year prognosis after TAVI.[9] However, data on the long-term prognosis are lacking. Therefore, in the present study, we aimed to investigate the impact of cognitive impairment on

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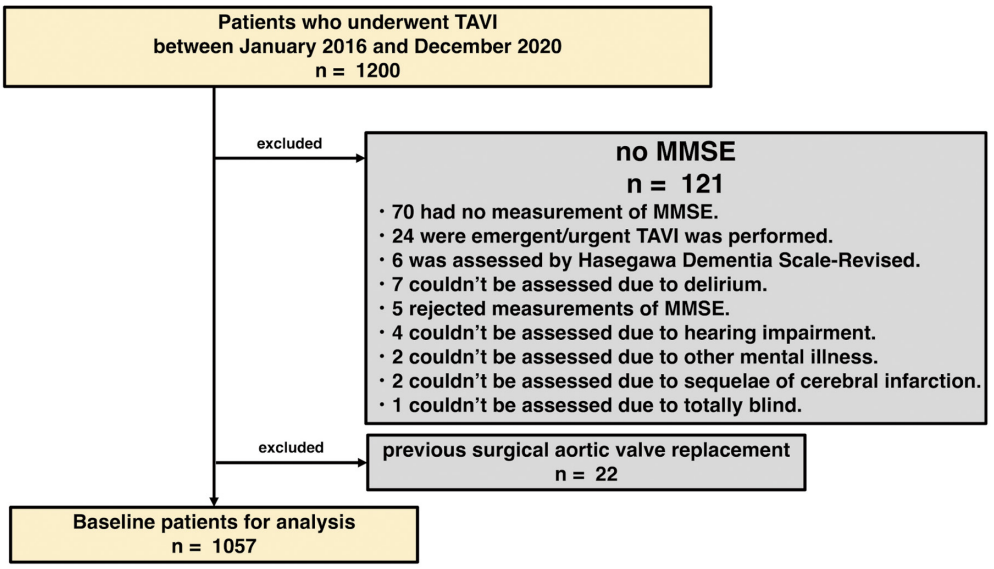


Figure 1. Study patient flowchart. MMSE, Mini-Mental State Examination; TAVI, transcatheter aortic valve implantation.

the long-term prognosis of patients undergoing TAVI.

Methods

From January 2013 to December 2020, we prospectively included 1200 consecutive patients with symptomatic severe aortic stenosis undergoing TAVI at the Kokura Memorial Hospital in Kokura Memorial Hospital's database. After excluding 143 patients with no Mini-Mental Status Examination (MMSE) measurements or those with previous aortic bioprostheses, a total of 1,057 patients was included in the final analysis (**Figure 1**). We assessed the patients by using the MMSE before the TAVI procedure, and then compared the baseline and procedural characteristics and clinical outcomes after TAVI between patients with normal cognition and those with cognitive impairment. Experienced interviewers evaluated the patients' MMSE scores. According to the National Institute for Health and Care Excellence clinical guidelines, normal cognition was defined as MMSE score 25–30, with 30 being the maximum score, while cognitive impairment was defined as MMSE score <25.[10] To investigate sensitivity, an additional analysis was performed using the modified criteria with a different cutoff value of MMSE <23.[11] Members of a dedicated heart team discussed the indications for TAVI on the basis of not only surgical risk scores but also multiple factors, such as age, frailty, and preoperative state for non-cardiac surgery.[12] MMSE scores were not used as a criterion to determine the indication for TAVI.

The present study conformed to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of Kokura Memorial Hospital. Written informed consent was obtained from all patients before TAVI.

We determined the sizes of transcatheter heart valves (THVs) mainly on the basis of preprocedural multidetector computed tomography or echocardiography. For the approach route, we selected the femoral artery first; if femoral access was inappropriate, we considered the iliac artery, apical, subclavian, or direct aortic route. We assessed procedural outcomes and post-procedural THV function on the basis of the Valve Academic Research Consortium-3 criteria.[13]

All computed tomography examinations were based on current guidelines.[14] We used 3mensio Valves software (version 7.0 or 8.0; Pie Medical Imaging, Maastricht, The Netherlands) to reconstruct and assess images. The aortic annulus and the left ventricular outflow tract area were measured in mid-systole, while residual structures, including the sinus of Valsalva and the sinotubular junction, were evaluated at the end of diastole. We also measured coronary artery heights from the annular plane to the inferior border of each coronary ostium in a stretched multiplanar image.

The primary outcome measure of this study was all-cause mortality after TAVI. The cause of death was categorized into cardiovascular and non-cardiovascular deaths. We also applied the definition of cardiovascular mortality to the Valve Academic Research Consortium-3 criteria,[13] and included deaths attributed to cardiac causes and non-coronary vascular conditions, such as stroke associated with neurological events, procedure-related aortic dissection, rupture, or other vascular diseases. In addition, we classified all procedure- and valve-associated deaths and sudden, unwitnessed, and unknown deaths into cardiovascular mortality. 'Pulmonary disease' in cause of death was defined as any pulmonary disease except respiratory infection and lung cancer. 'Active cancer' was defined as cancer under treatment. We obtained information about the occurrence of adverse events after discharge from follow-up outpatient visits or telephone interviews conducted on day 30, in month 6, and annually thereafter.

Categorical variables were described as numbers (percentages) and compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables were described as mean±SD or median (interquartile range [IQR]) and were compared using one-way analysis of

Table 1. Baseline Characteristics According to Cognitive Impairment

	Total (N=1,057)	Cognitive impairment		P value
		Yes (n=319)	No (n=738)	
Demographics				
Age (years)	85 [82–88]	86 [83–90]	85 [81–88]	<0.001
Female	723 (68.4)	230 (72.1)	493 (66.8)	0.087
BMI (kg/m^2)	22.0 [19.8–24.5]	21.2 [19.1–24.0]	22.4 [20.0–24.8]	<0.001
NYHA functional class III/IV	438 (41.4)	171 (53.6)	267 (36.2)	<0.001
STS score (%)	5.84 [3.94–8.61]	6.55 [4.54–9.52]	5.40 [3.69–8.26]	<0.001
Comorbidities				
Diabetes	238 (22.5)	53 (16.6)	185 (25.1)	0.002
Atrial fibrillation	230 (21.8)	79 (24.8)	151 (20.5)	0.123
Previous pacemaker	68 (6.4)	19 (6.0)	49 (6.6)	0.676
Previous MI	46 (4.4)	15 (4.7)	31 (4.2)	0.712
Previous PCI	233 (22.0)	70 (21.9)	163 (22.1)	0.956
Previous valve surgery	10 (1.0)	2 (0.6)	8 (1.1)	0.464
Peripheral artery disease	93 (8.8)	32 (10.0)	61 (8.3)	0.358
COPD	102 (9.7)	31 (9.7)	71 (9.6)	0.961
Cirrhosis	15 (1.4)	4 (1.3)	11 (1.5)	0.763
Previous stroke	115 (10.9)	48 (15.1)	67 (9.1)	0.005
Active cancer	54 (5.1)	11 (3.5)	43 (5.8)	0.095
MMSE score	27 [24–29]	21 [17–23]	28 [27–29]	<0.001
CFS				
Low (1–3)	549 (51.9)	110 (34.5)	439 (59.5)	<0.001
Intermediate (4–6)	451 (42.7)	172 (53.9)	279 (37.8)	
High (7–9)	57 (5.4)	37 (11.6)	20 (2.7)	
Blood tests				
Hemoglobin (g/dL)	11.3 [10.1–12.4]	10.9 [9.6–12.0]	11.4 [10.3–12.5]	<0.001
eGFR (mL/min/1.73 m^2)	50.6 [38.4–64.1]	47.7 [36.4–61.0]	51.6 [39.0–65.2]	0.005
Albumin (g/dL)	3.8 [3.4–4.1]	3.6 [3.3–3.9]	3.8 [3.5–4.1]	<0.001
BNP (pg/mL)	166.8 [72.8–370.7]	234.4 [104.5–466.1]	127.2 [63.6–302.9]	<0.001
Echocardiography data				
Mean aortic gradient (mmHg)	45.4 [35.5–59.2]	47.4 [35.0–61.9]	44.8 [35.6–58.3]	0.137
LVEF (%)	62.5 [56.2–65.5]	62.3 [54.8–65.4]	62.7 [56.6–65.9]	0.085
Pre-TAVI CT data				
Annulus area (mm^2)	398 [354.8–458.0]	396.5 [354.3–451.0]	401.2 [355.0–463.0]	0.328
Annulus perimeter (mm)	71.6 [67.8–76.6]	71.2 [67.9–76.0]	72.0 [67.8–77.1]	0.368
LVOT area (mm^2)	387.2 [328.1–472.4]	381.3 [322.8–458.0]	388.6 [329.8–477.6]	0.237
STJ height (mm)	18.7 [16.9–20.6]	18.4 [16.8–20.4]	18.7 [16.9–20.7]	0.228
STJ diameter (mm)	25.3 [23.4–27.7]	25.3 [23.4–27.7]	25.3 [23.4–27.7]	0.986
Mean SOV diameter (mm)	29.5 [27.7–31.7]	29.6 [27.9–31.8]	29.4 [27.7–31.7]	0.521
Ascending aorta diameter at 40 mm (mm)	32.4 [30.4–34.5]	32.7 [30.9–35.0]	33.2 [30.4–34.3]	0.044
Pre-TAVI antithrombotic drugs				
Antiplatelet	409 (38.7)	121 (37.9)	288 (39.0)	0.737
Anticoagulation	232 (22.0)	78 (24.5)	154 (20.9)	0.200

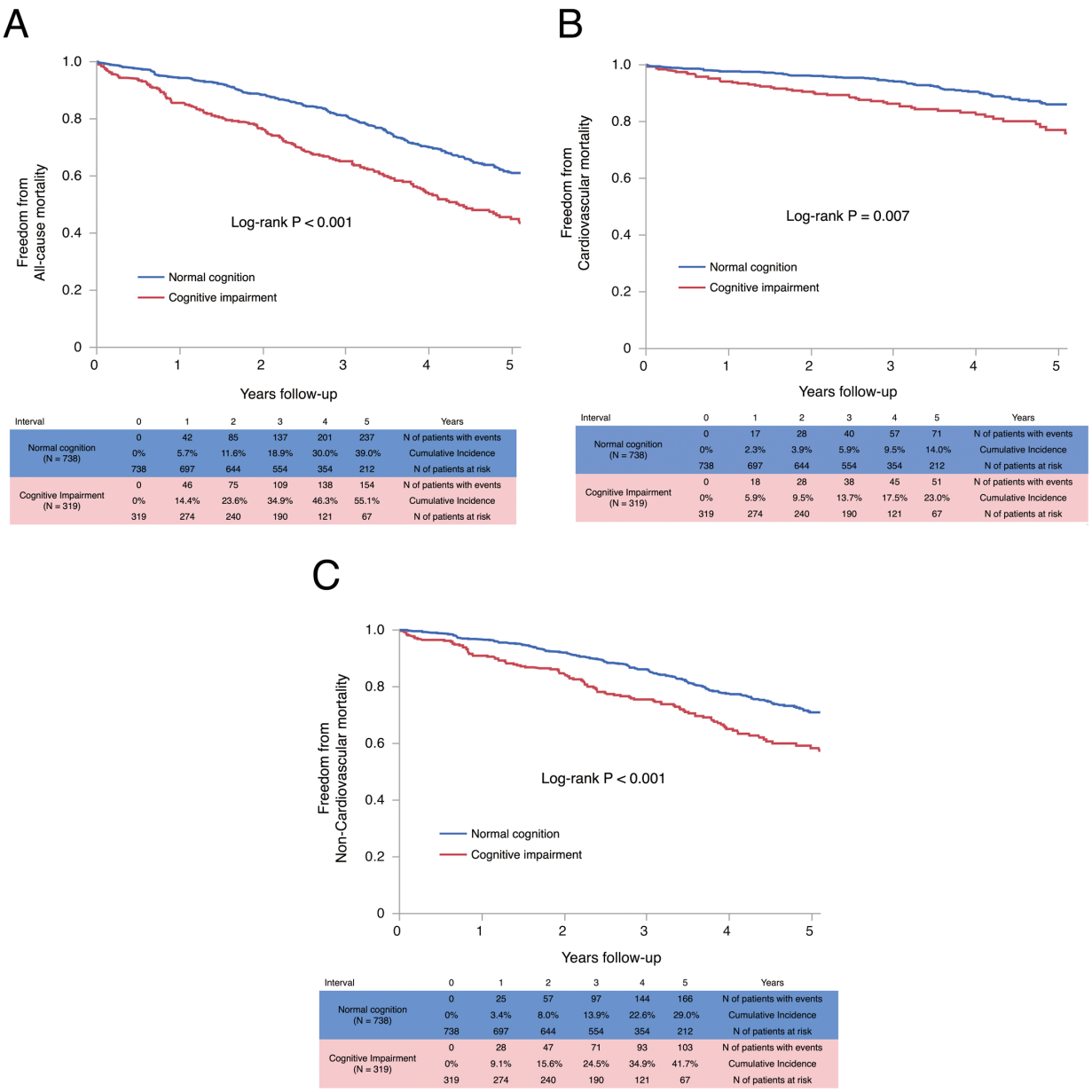
Data are presented as n (%), or median [interquartile range]. BMI, body mass index; BNP, B-type natriuretic peptide; CFS, Clinical Frailty Scale; COPD, chronic obstructive pulmonary disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MI, myocardial infarction; MMSE, Mini-Mental State Examination; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SOV, sinus of Valsalva; STJ, sinotubular junction; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

variance or the Kruskal-Wallis test, depending on their distributions. The cumulative event rates were analyzed using the Kaplan-Meier estimation and differences assessed using the log-rank test according to the categorical MMSE score. To test the predictive ability of cognitive impairment, multivariable Cox proportional hazard models were constructed comprising variables associated with poor prognosis based on clinical plausibility or P values <0.05 in univariate analysis; the Breslow approximation was used to handle ties. For post hoc analyses, we divided patients based on the following factors to assess their effect on cognitive impairment: (1) age (median 85 years); (2) sex; (3) body mass index (BMI; median 22.0 kg/m^2); (4) Society of Thoracic Surgeons (STS) score (high risk ≥8%, or not); (5) left ventricular ejection fraction (LVEF; preserved ≥50%, or not);[15] and (6) Clinical Frailty Scale (CFS; low group

Table 2. Peri- and Post-Procedural Patient Characteristics and 30-Day In-Hospital Outcomes According to Cognitive Impairment

	Total (N=1,057)	Cognitive impairment		P value
		Yes (n=319)	No (n=738)	
Procedural characteristics				
SAPIEN 3	625 (59.1)	189 (59.3)	436 (59.1)	0.230
SAPIEN XT	171 (16.2)	62 (19.4)	109 (14.8)	
Evolut R/PRO	244 (23.1)	62 (19.4)	197 (24.7)	
Corevalve	17 (1.6)	6 (1.9)	11 (1.5)	
Valve size (mm)				
20	15 (1.4)	8 (2.5)	7 (1.0)	0.032
23	421 (39.8)	143 (44.8)	278 (37.7)	
26	461 (43.6)	129 (40.4)	332 (45.0)	
29	159 (15.0)	39 (12.2)	120 (16.3)	
34	1 (0.1)	0 (0.0)	1 (0.1)	
Transfemoral approach	938 (88.7)	277 (86.8)	661 (89.6)	0.203
Local anesthesia	714 (67.6)	203 (63.6)	511 (69.2)	0.076
Emergent and urgent TAVI	31 (2.9)	17 (5.3)	14 (1.9)	0.004
Post-procedural variable				
Disabling stroke	13 (1.2)	6 (1.9)	7 (1.0)	0.224
Life-threating/disabling bleeding	37 (3.5)	19 (6.0)	18 (2.4)	0.006
Major bleeding	85 (8.0)	36 (11.3)	49 (6.6)	0.013
Coronary obstruction	7 (0.7)	1 (0.3)	6 (0.8)	0.325
Major vascular complications	44 (4.2)	23 (7.2)	21 (2.9)	0.002
Conversion to open surgery	34 (3.2)	11 (3.5)	23 (3.1)	0.780
Acute kidney injury	48 (4.5)	19 (6.0)	29 (3.9)	0.156
New pacemaker implantation	83 (7.9)	26 (8.2)	57 (7.7)	0.813
Cardiac tamponade	10 (1.0)	5 (1.6)	6 (0.7)	0.189
Post-procedural echocardiography data				
EOA (cm^2)	1.70 [1.47–2.00]	1.61 [1.40–1.87]	1.74 [1.49–2.04]	<0.001
Index EOA (cm^2/m^2)	1.20 [1.03–1.39]	1.19 [1.02–1.38]	1.21 [1.03–1.39]	0.394
Mean pressure gradient (mmHg)	10.3 [8.0–13.2]	10.8 [8.2–13.6]	10.5 [8.0–13.6]	0.653
PVL >moderate	2 (0.2)	2 (0.6)	0 (0.0)	0.028
LVEF (%)	62.1 [56.5–65.8]	61.7 [55.6–66.0]	62.5 [56.7–65.7]	0.601
PPM	63 (6.0)	22 (6.9)	41 (5.6)	0.407
Moderate PPM	57 (5.4)	19 (6.0)	38 (5.2)	0.601
Severe PPM	6 (0.6)	3 (0.9)	3 (0.4)	0.310
Post-TAVI antithrombotic drugs				
Antiplatelet	755 (71.4)	222 (69.6)	533 (72.2)	0.387
Anticoagulation	416 (39.4)	132 (41.4)	284 (38.5)	0.377
Outcomes at 30 days				
All-cause mortality	10 (1.0)	6 (1.9)	4 (0.5)	0.050
Cardiovascular mortality	6 (0.6)	2 (0.6)	4 (0.5)	0.867
Non-cardiovascular	4 (0.4)	4 (1.3)	0	0.002
Infection	0	0	0	–
Cancer	0	0	0	–
Pulmonary	0	0	0	–
In-hospital outcomes				
Days in hospital	12 [9–21]	15 [10–26]	12 [9–18]	<0.001
Days in intensive care unit	1 [1–2]	1 [1–2]	1 [1–2]	0.007
All-cause mortality	13 (1.2)	6 (1.9)	7 (1.0)	0.224
Cardiovascular mortality	8 (0.8)	2 (0.6)	6 (0.8)	0.744
Non-cardiovascular	5 (0.4)	4 (1.3)	1 (0.2)	0.021
Infection	2 (0.2)	2 (0.2)	0	0.028
Cancer	0	0	0	–
Pulmonary	1 (0.1)	0	1 (0.1)	0.397
Cause of death at 5 years				
Cardiovascular	122 (11.5)	51 (16.0)	71 (9.6)	0.004
Non-cardiovascular	269 (25.5)	103 (32.3)	166 (22.5)	<0.001
Infection	78 (7.4)	35 (11.0)	43 (5.8)	0.005
Cancer	33 (3.1)	8 (2.5)	25 (3.4)	0.441
Pulmonary	14 (1.3)	1 (0.3)	13 (1.3)	0.059

Data are presented as n (%), or median [interquartile range]. EOA, effective orifice area; PPM, prosthesis-patient mismatch; PVL, paravalvular leakage; TAVI, transcatheter aortic valve implantation.



Interval	0	1	2	3	4	5	Years
Normal cognition (N = 738)	0	42	85	137	201	237	N of patients with events
	0%	5.7%	11.6%	18.9%	30.0%	39.0%	Cumulative Incidence
	738	697	644	554	354	212	N of patients at risk
Cognitive Impairment (N = 319)	0	46	75	109	138	154	N of patients with events
	0%	14.4%	23.6%	34.9%	46.3%	55.1%	Cumulative Incidence
	319	274	240	190	121	67	N of patients at risk

Interval	0	1	2	3	4	5	Years
Normal cognition (N = 738)	0	17	28	40	57	71	N of patients with events
	0%	2.3%	3.9%	5.9%	9.5%	14.0%	Cumulative Incidence
	738	697	644	554	354	212	N of patients at risk
Cognitive Impairment (N = 319)	0	18	28	38	45	51	N of patients with events
	0%	5.9%	9.5%	13.7%	17.5%	23.0%	Cumulative Incidence
	319	274	240	190	121	67	N of patients at risk

Interval	0	1	2	3	4	5	Years
Normal cognition (N = 738)	0	25	57	97	144	166	N of patients with events
	0%	3.4%	8.0%	13.9%	22.6%	29.0%	Cumulative Incidence
	738	697	644	554	354	212	N of patients at risk
Cognitive Impairment (N = 319)	0	28	47	71	93	103	N of patients with events
	0%	9.1%	15.6%	24.5%	34.9%	41.7%	Cumulative Incidence
	319	274	240	190	121	67	N of patients at risk

Figure 2. Kaplan-Meier curves for (**A**) all-cause mortality, (**B**) cardiovascular mortality, and (**C**) non-cardiovascular mortality according to cognitive function. MMSE, Mini-Mental State Examination.

1–3, intermediate group 4–6, or high group 7–9).

All statistical analyses were performed using JMP Pro 16.1.0 (SAS Institute Inc., Cary, NC, USA) and R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Two-tailed P<0.05 was considered statistically significant for all tests.

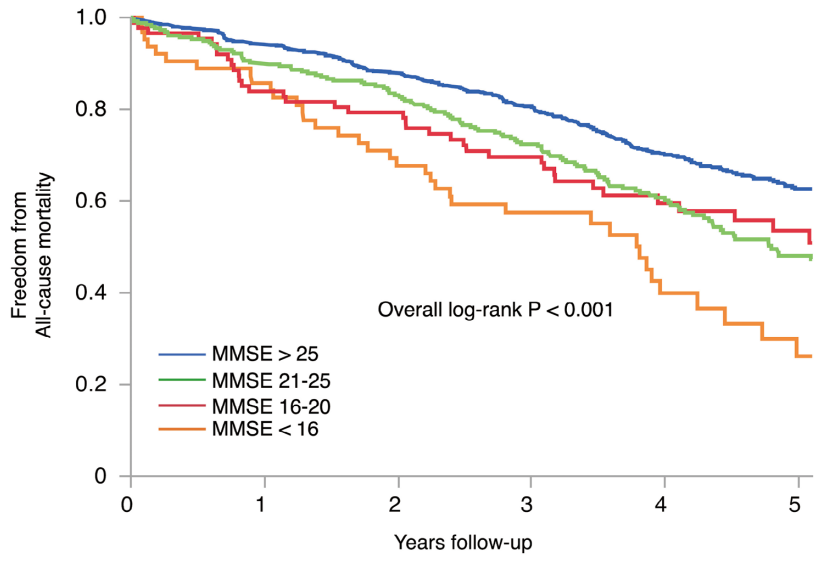
Results

Of the 1,057 patients included in the analysis, 319 (30.2%) had cognitive impairment, with MMSE score <25. Baseline clinical characteristics according to cognitive impairment are summarized in **Table 1**. The median age was 85 (IQR 82–88) years, 334 (31.6%) patients were male, and the median STS score was 5.84% (IQR 3.94–8.61). Compared with patients with normal cognition (MMSE score ≥25), patients with cognitive impairment were older and frequently had a low BMI, high STS score, and were categorized as New York Heart Association (NYHA) class III/IV. In addition, patients with cognitive impairment had significantly lower serum albumin, hemoglobin levels, and estimated glomerular filtration rate compared with patients without cognitive impairment. The CFS was used to assess the frailty of patients by dividing them into the following three groups: low CFS (CFS levels 1–3); intermediate CFS (CFS levels 4–6); and high CFS (CFS levels 7–9). The levels

Table 3. Univariate and Multivariable Cox Proportional Hazard Models for All-Cause Mortality at 5 Years According to Cognitive Impairment and MMSE Scores

Predictor	Univariate analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Cognitive impairment	1.79	1.45–2.21	<0.001	1.34	1.08–1.67	0.008
MMSE scores						
<16		Ref.			Ref.	
16–20	0.57	0.36–0.91	0.018	0.55	0.34–0.88	0.012
21–25	0.58	0.40–0.85	0.004	0.64	0.43–0.95	0.028
>25	0.38	0.27–0.54	<0.001	0.51	0.35–0.75	<0.001

Adjusted for the following variables: age; sex; BMI; STS score; NYHA class III/IV; BNP; albumin; hemoglobin; eGFR; atrial fibrillation; peripheral artery disease; previous valve surgery; previous MI; mean aortic gradient; COPD; previous stroke; active cancer; LVEF; local anesthesia; transfemoral approach; emergent and urgent transcatheter aortic valve implantation; CFS. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.



Interval	0	1	2	3	4	5	Years
MMSE > 25 (N = 652)	0	39	79	125	178	204	N of patients with events
	0%	6.0%	12.2%	19.5%	29.9%	37.4%	Cumulative Incidence
	652	614	565	486	311	188	N of patients at risk
MMSE 21-25 (N = 255)	0	26	43	69	95	114	N of patients with events
	0%	10.2%	16.9%	27.6%	39.8%	51.9%	Cumulative Incidence
	255	230	210	173	115	64	N of patients at risk
MMSE 16-20 (N = 87)	0	14	18	26	33	36	N of patients with events
	0%	16.1%	20.7%	30.4%	40.5%	46.4%	Cumulative Incidence
	87	74	70	56	36	21	N of patients at risk
MMSE < 16 (N = 63)	0	9	20	26	33	37	N of patients with events
	0%	14.3%	32.3%	42.5%	60.1%	73.8%	Cumulative Incidence
	63	55	42	31	15	8	N of patients at risk

Figure 3. Cumulative all-cause mortality according to the Mini-Mental State Examination (MMSE) scores, estimated using the Kaplan-Meier curve. MMSE scores: <16, 16–20, 21–25, or >25.

of B-type natriuretic peptide and creatine and the number of patients with diabetes, previous stroke and higher CFS differed between patients with and without cognitive impairment. Regarding echocardiography data, no significant differences were observed between patients with and without cognitive impairment. For the computed tomography data before TAVI, the diameter of the ascending aorta was significantly larger in patients without cognitive impairment.

The median MMSE scores were 21 (IQR 17–23) for patients with cognitive impairment and 28 (IQR 27–29) for those with normal cognition (P<0.001).

The procedural characteristics and in-hospital outcomes are listed in **Table 2**. Compared with patients with normal cognition, patients with cognitive impairment more frequently underwent emergent or urgent procedures

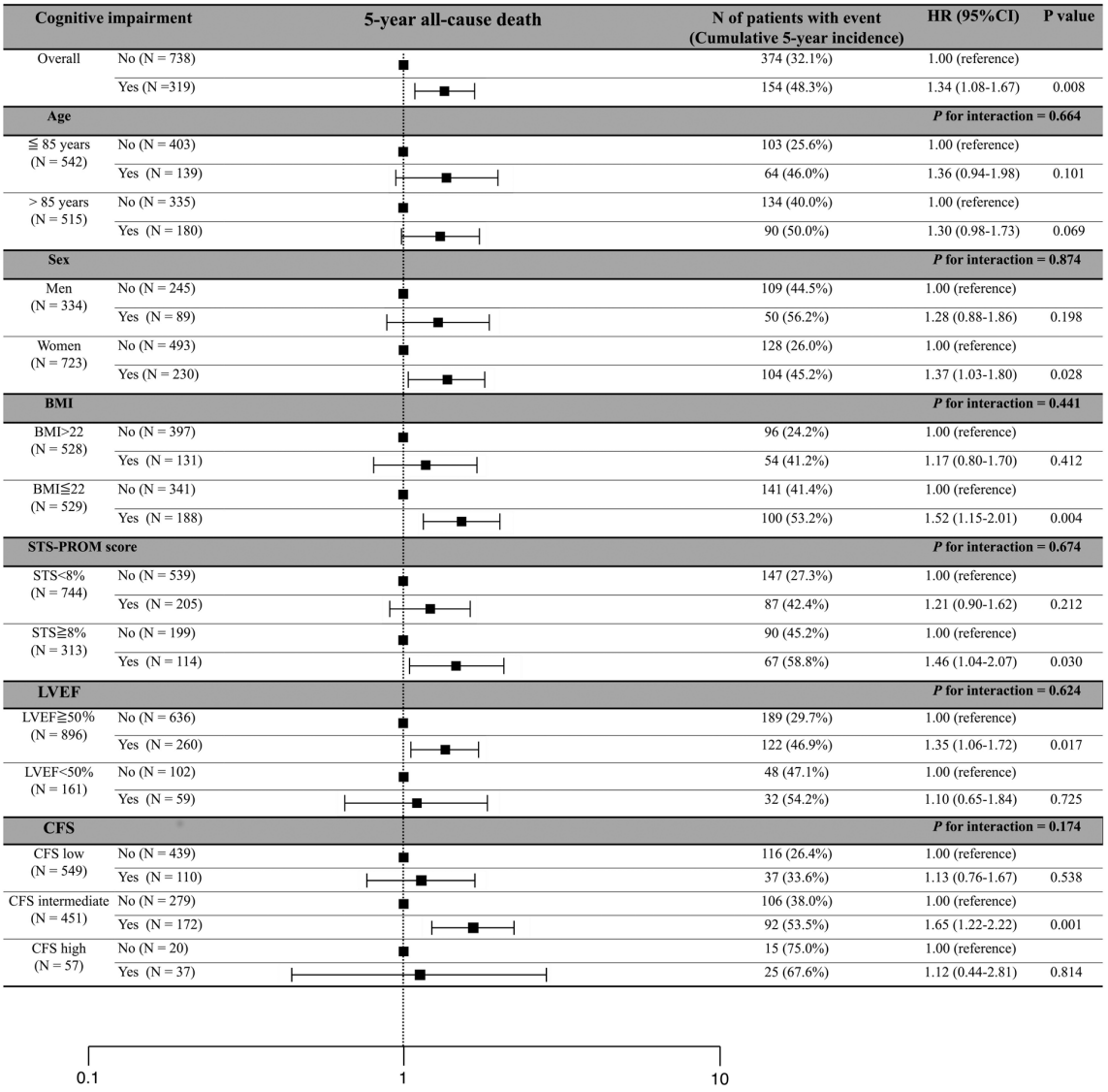


Figure 4. Forest plots for the adjusted hazard ratios (HRs) of 5-year all-cause mortality according to cognitive function. BMI, body mass index; CFS, Clinical Frailty Scale; CI, confidence interval; LVEF, left ventricular ejection fraction; MMSE, Mini-Mental State Examination; PROM, predicted risk of mortality; STS, Society of Thoracic Surgeons.

(P=0.004). TAVI was performed using balloon-expandable THVs in 796 (75.3%) patients and self-expandable THVs in 261 (24.7%) patients; significant group differences were detected in the prosthesis type size. In addition, we observed in-hospital death in 13 (1%) patients, including cardiovascular mortality in 8 patients and non-cardiovascular mortality in 5 patients. Cognitive impairment was associated with a higher life-threatening/disabling bleeding rate (P=0.006), a higher major vascular complication rate (P=0.002), and a longer intensive care unit (P=0.007) and hospital (P<0.001) stay post-TAVI. The cause of 5-year mortality was CVD (n=122; 12%), infection (n=78; 7%), cancer (n=33; 3%), and pulmonary disease (n=14; 1%). Cognitive impairment was statistically associated with death due to CVD (16% vs. 10%; P=0.004) and infection (11% vs. 6%; P=0.005).

All 1,057 patients underwent post-procedural echocardiography follow up. All patients showed acceptable THV function (median indexed effective orifice area [EOA] of 1.20 [IQR 1.03–1.39] cm^2/m^2 and a mean pressure gradient of 10.3 [IQR 8.0–13.2] mmHg). We found severe prosthesis-patient mismatches in 3 (0.9%) patients with cognitive impairment and 3 (0.4%) patients without cognitive impairment. In addition, we observed moderate-to-severe paravalvular leakage (PVL) in only 2 (0.6%) patients with cognitive impairment. The incidence of prosthesis-patient mismatch was comparable between patients with and without cognitive impairment. Compared with patients with normal cognition, patients with cognitive impairment had a smaller EOA and a lower mean pressure gradient (P<0.001).

At a mean follow-up period of 1388±683 days, a total of

391 (37%) patients with all-cause mortality were identified; of these, 122 (31%) patients died due to CVD, while the remaining 269 (69%) patients died due to non-cardiovascular reasons. The 5-year cumulative all-cause mortality rate was 55% in patients with cognitive impairment and 39% in patients with normal cognition (log-rank P<0.001; **Figure 2A**). In multivariable analysis, cognitive impairment was independently associated with all-cause mortality (adjusted hazard ratio [aHR] 1.37; 95% confidence interval [CI] 1.10–1.70; P=0.005; **Table 3**). The 5-year cumulative cardiovascular mortality rate was 23% in patients with cognitive impairment and 14% in patients with normal cognition (log-rank P=0.007; **Figure 2B**). The 5-year cumulative non-cardiovascular mortality rate was 42% in patients with cognitive impairment and 29% in patients with normal cognition (log-rank P<0.001; **Figure 2C**). Patients with MMSE score <16 had a significantly higher mortality rate (74%) compared with other patients (MMSE score >25: mortality rate 37%; aHR 0.51; 95% CI 0.35–0.75; P<0.001; MMSE score 21–25: mortality rate 52%; aHR 0.64; 95% CI 0.43–0.95; P=0.028; MMSE score 16–20: mortality rate 46%; aHR 0.55; 95% CI 0.34–0.88; P=0.012; reference: MMSE score <16; **Figure 3**, **Table 3**).

We also performed sensitivity analyses using different cutoffs for MMSE. The 5-year cumulative all-cause mortality rate was 62% in patients with cognitive impairment and 40% in patients with normal cognition (log-rank P<0.001; **Supplementary Figure A**). In multivariable analysis, cognitive impairment was independently associated with all-cause mortality (aHR 1.52; 95% CI 1.19–1.94; P<0.001; **Supplementary Table**). The 5-year cumulative cardiovascular mortality rate was 23% in patients with cognitive impairment and 15% in patients with normal cognition (log-rank P=0.002; **Supplementary Figure B**). The 5-year cumulative non-cardiovascular mortality rate was 50% in patients with cognitive impairment and 29% in patients with normal cognition (log-rank P<0.001; **Supplementary Figure C**).

To identify factors that modify the impact of cognitive impairment on these clinical outcomes, we performed subgroup analyses, as shown in **Figure 4**. The multivariable analyses showed that cognitive impairment was associated with an increased risk for all-cause mortality regardless of stratification based on age, sex, BMI, STS score, LVEF, and CFS without significant interaction.

Discussion

In the present study, we evaluated the long-term prognostic impact of cognitive impairment on patients undergoing TAVI. The main study findings are as follows: (1) in an all-comer, single-center TAVI registry of patients with a median age of 85 years, 30.2% of the patients had cognitive impairment based on their MMSE scores; (2) cognitive impairment was independently associated with 5-year all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality; (3) cognitive impairment was associated with an increased risk of 5-year all-cause mortality regardless of stratification based on age, sex, BMI, STS score, LVEF and CFS; and (4) patients with MMSE scores <16 had significantly higher 5-year all-cause mortality.

Frailty is a geriatric syndrome of impaired resiliency to stressors that is strongly associated with adverse health outcomes in older adults.[1,2] Cognitive function is a common component of frailty, so it is essential to assess cognitive dysfunction, in addition to the surgical risk score and cognitive impairment, when making treatment choices for patients with severe aortic stenosis. Although recent guidelines for valvular heart disease recommend assessing a patient's frailty status,[16] there are no recommendations for the measurement of cognitive function. A few studies have reported the prognostic impact of cognitive impairment after TAVI.[9,17] However, most of these data are limited to 1-year prognosis or have different definitions for longer-term prognosis. Therefore, longer-term data with established definitions are required, considering that TAVI indications are being expanded to include patients who are at a lower surgical risk. In this study, we evaluated the 5-year prognostic value of cognitive impairment.

A prior pivotal study from the OCEAN-TAVI multicenter registry reported that the 1-year cardiovascular mortality rate is 3% in patients with cognitive impairment and 3% in patients with normal cognition, which are not significantly different values.[9] However, in the present study, the 1-year cardiovascular mortality rate was 6% and 2% for patients with cognitive impairment and those with normal cognition, respectively, and was significantly higher in the former group. The reason for this was that baseline causes of cardiovascular mortality, such as previous stroke, were significantly more common in patients with cognitive impairment. Some patients with cognitive impairment have vascular cognitive impairment due to reduced blood supply and multiple vascular risks,[18] which may lead to increased cardiovascular mortality.

In the present study, mortality due to infection was significantly higher in patients with cognitive impairment, which probably led to the significantly higher 5-year non-cardiovascular mortality rate in this group. These data suggest that clinicians should consider and manage prevention, early detection, and treatment of infection after TAVI. The absence of reported infection or symptoms, along with reduced immunity, may delay optimal therapeutic intervention, especially in patients with cognitive impairment.

Patients with MMSE scores <16 had a significantly high 5-year all-cause mortality rate (74%) compared with other patients. Although recent advancements in devices and procedures have substantially increased survival rates after TAVI, patients may not fully benefit from TAVI despite a technically successful procedure.[19] Therefore, palliative care is increasingly being considered for those patients instead of proceeding with a futile invasive procedure. We need to acknowledge that cognitive impairment is associated with not only early but also late mortality after TAVI. In addition, TAVI for patients with severe cognitive impairment may be less cost-effective due to longer hospital stays and higher mortality rates, which cannot be described in detail in this paper.

Study Limitations

The present study has several limitations. First, this was a single-center observational study including a retrospective analysis with all its inherent limitations. Second, we did not compare the prognostic value of the MMSE with other cognitive function assessment tools. Third, we did not assess postoperative cognitive function. Further studies are needed to investigate whether we can modify cognitive function through symptom relief after TAVI and improve clinical outcomes in patients with severe aortic stenosis. Last, we assessed multiple statistical testing without adjusting for multiplicity.

Conclusions

Cognitive impairment assessed using MMSE scores is independently associated with an increased risk for 5-year all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality in patients undergoing TAVI.

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Disclosures

K.I. is the proctor of intracardiac echocardiography-guided TAVI for Johnson and Johnson. S.S. is the proctor of transfemoral-TAVI for Edwards Lifesciences, Medtronic, and Abbott Medical. The other authors have no conflicts of interest to declare.

IRB Information

The present study was conducted by the registry whose reference number is #15091601.

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

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