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Original article

Cognitive assessment using the revised Hasegawa's dementia scale to determine the mid-term outcomes following transcatheter aortic valve replacement

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ABSTRACT

Background: Several predictors are available to guide patient selection for transcatheter aortic valve replacement (TAVR) to achieve better outcomes, and cognitive function is one of these predictors. This study investigated whether the revised Hasegawa's dementia scale (HDS-R) could independently predict mid-term outcomes following TAVR.
Methods: The study population comprised 455 patients with severe aortic stenosis who underwent TAVR at the Sakakibara Heart Institute between 2010 and 2018. The primary endpoint was all-cause mortality following TAVR. Patients were dichotomized into two groups according to the receiver operating characteristic analysis (HDS-R $\leq$23 and $>$23).
Results: Patients with HDS-R $\leq$23 were older, were more frail, were more likely to have peripheral artery disease, had lower serum albumin levels, had lower ejection fractions, and had smaller aortic valve areas than those with HDS-R $>$23. By definition, 81 of the 455 patients (17.8%) were considered to have dementia (HDS-R $\leq$20) before TAVR. The discriminatory performance for predicting all-cause mortality at 3 years was greater for dichotomization with 23/24 than that with 20/21 [area under the curve (AUC): 0.63, 95% confidence interval (CI): 0.50–0.76, $p = 0.047$ vs. AUC: 0.52, 95% CI: 0.39–0.65, $p = 0.713$]. From the Kaplan–Meier analysis, patients with HDS-R $\leq$23 had higher mortality rates than those with HDS-R $>$23 (86.8 $\pm$ 3.3% and 75.4 $\pm$ 4.7% at 3 years, respectively; log-rank $p = 0.001$). The multivariate Cox regression analysis found that the HDS-R was independently associated with all-cause mortality (hazard ratio 2.11, 95% CI 1.21–3.69, $p = 0.008$).
Conclusions: Patients with HDS-R $\leq$23 were sicker and more frail and had greater cognitive impairment. Additionally, HDS-R could independently predict mid-term outcomes following TAVR.

Introduction

Over the past few decades, transcatheter aortic valve replacement (TAVR) has emerged as a less invasive alternative to surgical aortic valve replacement [1–3]. Although there was a tremendous survival advantage and symptom benefit for many patients undergoing TAVR, compared with medical therapy, some patients died soon after the procedures [4,5]. Recently, variable frailty markers have been developed to guide better patient selection and are considered to be essential components of patient care in TAVR [6–9].

The revised Hasegawa's dementia scale (HDS-R), which is composed of nine simple questions, was initially developed in

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1974 by Hasegawa et al. and has been widely accepted in Asian populations for clinical use and for use in epidemiological surveys for the evaluation of cognitive impairment [10]. Cognitive impairment has been recognized as one of the more important components of frailty in elderly patients, and its association with the TAVR population has been recently reported [11–13]. However, there is a lack of information regarding the association between HDS-R and outcomes following TAVR. The purpose of this study was to investigate the characteristics in patients with lower HDS-R scores, and whether the HDS-R scores could independently predict mid-term outcomes following TAVR.

Materials and methods

Study population

The study population comprised 455 patients with severe aortic stenosis who underwent TAVR at the Sakakibara Heart Institute between October 2013 and May 2018. The treatment was initially determined according to the following criteria: (1) presence of symptoms; (2) degenerative aortic stenosis; (3) mean gradient >40 mmHg or a jet velocity >4.0 m/s; or (4) aortic valve area <1 cm^2 (0.6 cm^2/m^2). All cases were reviewed by a multidisciplinary team consisting of cardiac surgeons, interventional cardiologists, and imaging specialists and were deemed to be high-risk or inoperable. Patients who were on dialysis, who had active endocarditis, who had other active infections, or who had an estimated life expectancy <12 months due to noncardiac conditions were excluded from this study. The Society of Thoracic Surgeons (STS) risk score for predicted risk of mortality was calculated. Our institutional review board approved the study. The study was performed in accordance with the ethical principles set forth in the Declaration of Helsinki and was approved by the Human Investigation Committee of Sakakibara Heart Institute. All information was retrospectively obtained from patients' medical records or from telephone interviews. Therefore, follow-ups and accountabilities of all patients were ensured. Informed consent was obtained from each patient.

Revised Hasegawa's dementia score

The Revised Hasegawa's dementia scale (HDS-R) is a useful screening test for age-associated dementia that was established in 1991 and consists of nine simple questions with a total maximum score of 30. The questions of the HDS-R include age (1 point), orientation to time (4 points) and place (2 points), the repetition of 3 words (3 points), serial subtractions of 7 (2 points), the counting of digits backwards (2 points), the recall of 3 words (6 points), confrontational naming and the immediate recall of 5 objects (5 points), and a category fluency test (5 points) (Supplement 1). Dementia was defined as an HDS-R ≤20 due to a previous report showing a sensitivity of 90% and a specificity of 82% in the diagnosis of dementia in a Japanese population [10].

Endpoint and other criteria

The primary endpoint was all-cause mortality following TAVR. Echocardiographic findings were analyzed by full-time academic echocardiographers using the American College of Cardiology/American Heart Association guidelines [14]. Procedural complications were defined according to the Valve Academic Research Consortium-2 Criteria [15]. Device success was defined as the absence of procedural mortality, the correct positioning of a single prosthetic valve, and the performance of the prosthetic valve as initially intended. The complications at 30 days included all-cause mortality, all stroke, life-threatening bleeding, acute kidney injury (Acute Kidney Injury Network stage 2 or 3), a coronary obstruction requiring intervention, major vascular complications, and valve-related dysfunction requiring a repeat procedure. TAVR was performed as previously described [1].

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation or the median with the interquartile range, and categorical variables were expressed as numbers and percentages. The normality of distribution of the continuous variables was tested using the Shapiro–Wilk test. A 2-sided *p*-value <0.05 was considered to be statistically significant.

Although patients with HDS-R ≤20 were considered to have dementia by definition, the HDS-R scores were dichotomized into two groups (HDS-R ≤23 and >23) according to the best cut-off point in the receiver operating characteristic (ROC) analysis for all-cause mortality at 3 years in the present study [5,10]. Kaplan–Meier analysis was used to estimate the cumulative mortality in each group. To determine the influence on the relationship between the outcomes, variables (shown in Table 1) with *p*-values <0.15 in the univariate analysis were entered into multivariate Cox regression analysis. To avoid collinearity in the present study, the STS scores were excluded from multivariate analysis, because some of their components were inserted into the model. Next, in sensitivity analysis, multivariate analysis was conducted with STS score to determine the influence on the relationship between the outcomes. ROC analysis was performed using all-cause mortality at 3 years (n = 157), and the area under the curve was compared. All analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA).

Results

Characteristics and overall outcomes after TAVR

The patient demographic and clinical characteristics at baseline are shown in Table 1. Patients with HDS-R ≤23 were older, were more frail, were more likely to have peripheral artery disease, had lower serum albumin levels, had lower ejection fractions, and had smaller aortic valve areas than those with HDS-R >23. Patients with HDS-R ≤23 tended to have smaller body mass index (BMI) values, greater New York Heart Association functional class values, and higher pulmonary artery pressures than those with HDS-R >23. Fig. 1 demonstrates the distribution of HDS-R. By definition, 81 of the 455 patients (17.8%) were considered to have dementia (HDS-R ≤20) before TAVR. Other procedural outcomes are shown in Table 2. Patients with HDS-R ≤23 had longer stays in intensive care units and longer hospital stays than those with HDS-R >23. Patients >23 had trend toward higher discharge-to-home rate than those ≤23 (p = 0.133). There were no significant differences between the two groups in terms of device success, degree of paravalvular leak after TAVR, and early safety at 30 days including all-cause mortality and stroke. The discriminatory performance for predicting all-cause mortality at 3 years was greater in the cut-off point of 23/24 than that of 20/21 (AUC: 0.63, 95% CI: 0.50–0.76, p = 0.047 vs. AUC: 0.52, 95% CI: 0.39–0.65, p = 0.713) (Fig. 2).

Kaplan–Meier analysis

Fig. 3 demonstrates the all-cause mortality rate following TAVR that was stratified into two groups in the Kaplan–Meier analysis. Patients with HDS-R ≤23 had higher mortality than those with HDS-R >23 (log-rank p = 0.001). All-cause mortality rates in patients with HDS-R <23 and HDS-R >23 at 3 years were 86.8 ± 3.3% and 75.4 ± 4.7%, respectively.

Table 1
Baseline patient characteristics.

Characteristic (*n* = 455)	HDS-R ≤23 (*n* = 177)	HDS-R >23 (*n* = 278)	*p*-Value
Age, years	85.8 ± 4.5	83.6 ± 5.1	<0.001
Women, %	123 (69.4)	186 (66.9)	0.565
Body mass index (kg/m^2)	22.0 ± 3.8	22.5 ± 3.6	0.075
NYHA classification III/IV, %	94 (53.1)	123 (44.2)	0.065
Society of Thoracic Surgeons score, %	7.0 ± 3.9	6.0 ± 3.3	0.005
Clinical frailty scale (1–9)	4.5 ± 1.0	3.9 ± 1.0	<0.001
Diabetes mellitus, %	38 (21.4)	62 (35.0)	0.834
Hypertension, %	132 (74.5)	215 (77.3)	0.500
Dyslipidemia, %	81 (45.7)	151 (54.3)	0.075
Prior myocardial infarction, %	12 (6.7)	18 (6.4)	0.898
Prior bypass surgery, %	13 (7.3)	22 (7.9)	0.824
Peripheral artery disease, %	31 (17.5)	29 (10.4)	0.029
Prior stroke, %	16 (9.0)	25 (8.9)	0.986
Atrial fibrillation, %	46 (25.9)	59 (21.3)	0.239
COPD (moderate/severe), %	5 (2.8)	10 (3.5)	0.653
Hemoglobin level, g/dL	11.6 ± 1.3	11.7 ± 1.4	0.597
eGFR, mL/min/1.73 m^2	52.1 ± 18.1	52.7 ± 16.6	0.622
Serum albumin, g/dL	3.7 ± 0.4	3.8 ± 0.3	0.034
Ejection fraction, %	58.4 ± 9.5	60.1 ± 9.1	0.017
Aortic valve area, cm^2	0.63 ± 0.16	0.67 ± 0.13	0.002
Mean gradient, mmHg	54.7 ± 18.4	54.6 ± 17.8	0.671
MR (moderate/severe)	6 (3.3)	6 (2.1)	0.629
Pulmonary artery pressure, mmHg	27.8 ± 10.1	26.4 ± 9.9	0.136

Values are medians (interquartile ranges).
COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDS-R, revised Hasegawa's dementia scale; MR, mitral regurgitation; NYHA, New York Heart Association.

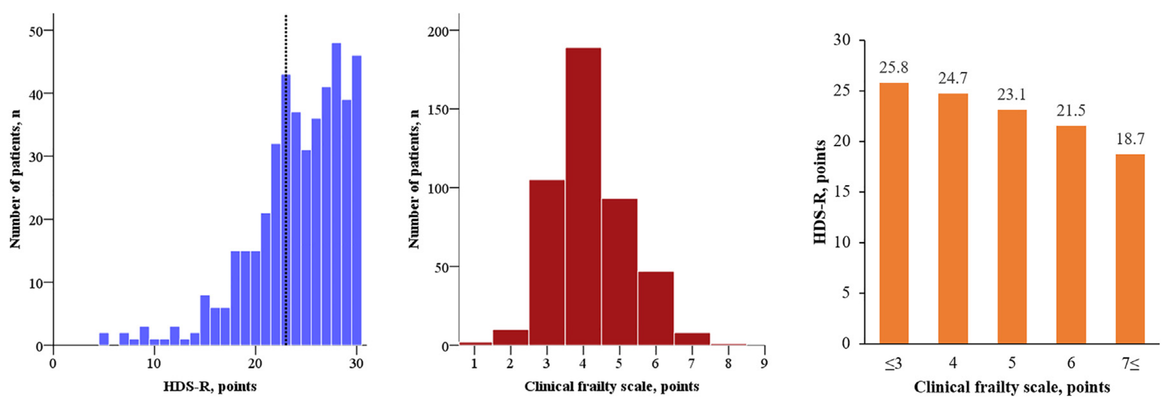

Fig. 1. Distribution of the revised Hasegawa's dementia scale (HDS-R). The dotted line indicates the cut-off point for dichotomization in the present study.

Table 2
Procedural outcomes.

Outcome (*n* = 455)	HDS-R ≤23 (*n* = 177)	HDS-R >23 (*n* = 278)	*p*-Value
Transfemoral approach, %	153 (86.4)	251 (90.2)	0.205
Current generation valve (SAPIEN 3/Evolut R)	113 (63.8)	177 (63.6)	0.990
Procedure time, min	97.5 ± 66.9	88.4 ± 48.9	0.030
Radiation time, min	22.9 ± 15.5	21.5 ± 10.3	0.356
Contrast media, mL	88.7 ± 53.6	82.9 ± 43.4	0.329
Device success, %	168 (94.5)	269 (96.7)	0.324
Stay in intensive care unit, days	1.7 ± 1.8	1.4. ± 1.5	0.001
Total hospital stay, days	20.5 ± 14.8	17.5 ± 12.5	0.001
Paravalvular leak, degree	1.2 ± 0.6	1.1 ± 0.6	0.264
Early safety at 30 days, %	19 (10.7)	21 (7.5)	0.243
Mortality, %	2 (1.1)	0 (0)	0.151
All stroke, %	9 (5.0)	6 (2.1)	0.088
Life-threatening bleeding, %	5 (2.8)	7 (2.5)	0.531
Acute kidney injury (AKIN stage 2 or 3), %	3 (1.6)	5 (1.7)	0.620
Coronary obstruction requiring intervention, %	3 (1.6)	1 (0.3)	0.166
Major vascular complication, %	5 (2.8)	10 (3.5)	0.653

Values are medians (interquartile ranges).
AKIN, acute kidney injury network; HDS-R, revised Hasegawa's dementia scale.

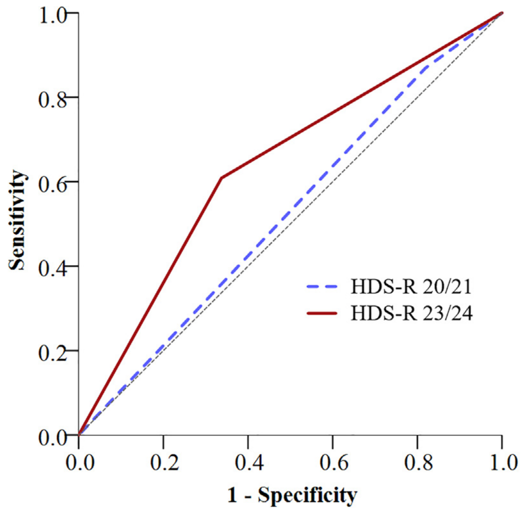

Fig. 2. Receiver operating characteristic analysis for all-cause mortality at 3 years. The discriminatory performance was greater in the cut-off point of 23/24 than that of 20/21 (AUC: 0.63, 95% CI: 0.50–0.76, $p = 0.047$ vs. AUC: 0.52, 95% CI: 0.39–0.65, $p = 0.713$). AUC, area under the curve; CI, confidence interval; HDS-R, revised Hasegawa's dementia scale.

Association between primary endpoint and clinical characteristics

After performing univariate analyses, the baseline variables (shown in Table 1) including women, BMI, New York Heart Association classification, HDS-R, clinical frailty scale, peripheral artery disease, prior stroke, atrial fibrillation, estimated glomerular filtration rate, serum albumin, and mitral regurgitation were entered into multivariate Cox regression analysis (Table 3). The analysis found that women, BMI, HDS-R, prior stroke, atrial fibrillation, and serum albumin were independently associated with all-cause mortality. On the other hand, the clinical frailty scale, which is a commonly used frailty marker, was not identified as a predictor of all-cause mortality by multivariate analysis. In sensitivity analysis, if STS score were entered into multivariate analysis, HDS-R was still independently associated with all-cause mortality after TAVR ($p = 0.018$, HR 1.97, 95% CI 1.12–3.46).

Discussion

The purpose of this study was to investigate the characteristics in patients with lower HDS-R scores and whether the HDS-R scores could independently predict mid-term outcomes following TAVR. Patients with HDS-R ≤23 were older, were more frail, were more likely to have peripheral artery disease, had lower serum albumin levels, had lower ejection fractions, and had smaller aortic valve areas than those with HDS-R >23. HDS-R was independently associated with all-cause mortality, with a median follow up of 523 days.

HDS-R

Patients with HDS-R ≤23 were older, were more frail, were more likely to have peripheral artery disease, had lower serum albumin levels, had lower ejection fractions, and had smaller aortic valve areas than those with HDS-R >23. Although the HDS-R was initially designed to exclude dementia in Japanese elderly patients, the present study demonstrates that patients with HDS-R ≤23 constitute a sicker and more frail population with greater cognitive impairment, which is in line with previous studies [11]. Historically, dementia has been defined as HDS-R ≤20 due to a previous study showing great sensitivity and specificity [10]. However, in the present study, ROC analysis demonstrated that the best cut-off point of HDS-R for predicting mid-term mortality was 23, not 20. This can be explained by the presumption that even mild

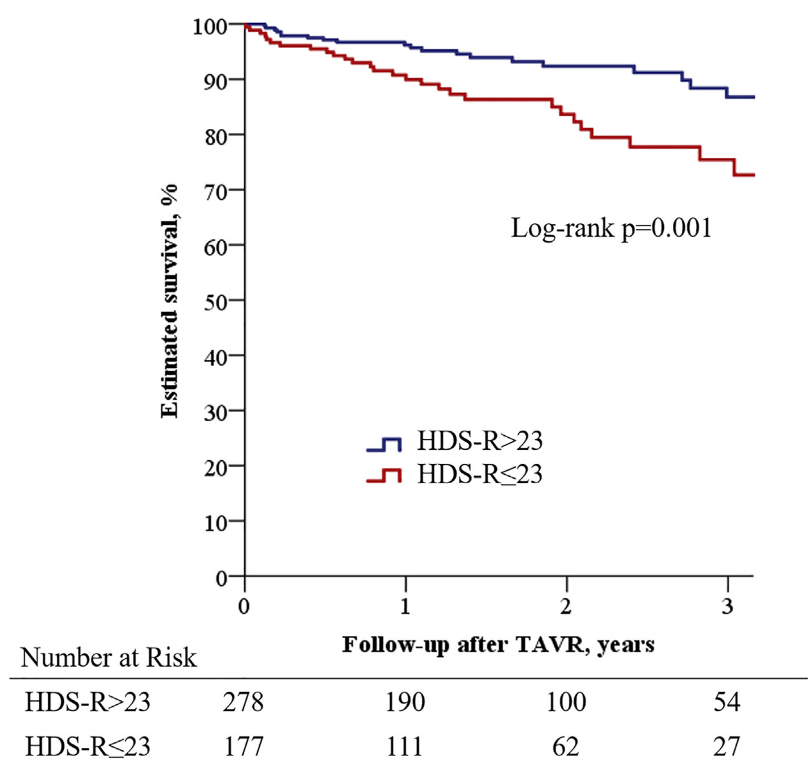

Fig. 3. Kaplan–Meier curves for all-cause mortality following transcatheter aortic valve replacement (TAVR). The all-cause mortality rate was 86.8 ± 3.3% in patients with HDS-R >23 (blue line) and 75.4 ± 4.7% in patients with HDS-R ≤23 (red line) (log-rank, $p = 0.001$). HDS-R, revised Hasegawa's dementia scale.

Table 3
Predictors of all-cause mortality in univariate and multivariate Cox regression analysis.

Parameters	Hazard ratio	95% CI	*p*-Value	Adjusted Hazard ratio	95% CI	*p*-Value
Age (every 10 years increase)	1.30	0.98–1.74	0.068			
Women	0.44	0.25–0.75	0.003	0.37	0.21–0.66	0.001
Body mass index (<20 kg/m^2)	1.76	1.02–3.15	0.041	2.15	1.19–3.89	0.010
NYHA classification (every degree increase)	1.65	1.06–2.57	0.025			
HDS-R	2.37	1.39–4.10	0.002	2.11	1.21–3.69	0.008
Clinical frailty scale (every score increase)	1.21	0.35–1.55	0.115			
Diabetes mellitus	1.24	0.65–2.26	0.497			
Hypertension	0.76	0.41–1.41	0.398			
Dyslipidemia	0.73	0.42–1.27	0.294			
Prior myocardial infarction	1.03	0.37–2.85	0.955			
Prior bypass surgery	0.98	0.41–2.31	0.981			
Peripheral artery disease	2.13	1.16–3.89	0.014			
Prior stroke	2.26	1.13–4.51	0.020	2.33	1.16–4.86	0.024
Atrial fibrillation	2.28	1.31–3.96	0.003	2.27	1.28–4.07	0.005
COPD	2.06	0.74–5.95	0.164			
Hemoglobin level (<11 g/dL)	1.13	0.65–1.96	0.646			
eGFR (every 15 mL/min/1.73 m^2 decrease)	1.32	0.99–1.77	0.058			
Serum albumin (<3.5 g/dL)	2.83	1.64–4.87	<0.001	2.48	1.42–4.34	0.001
Ejection fraction (every 10% decrease)	1.24	0.94–1.63	0.124			
Aortic valve area (every 0.1 cm^2 decrease)	1.04	0.89–1.26	0.619			
Mean pressure gradient (every 10 mm Hg decrease)	1.10	0.93–1.30	0.244			
MR (every degree increase)	1.42	0.93–2.17	0.100			
Pulmonary artery pressure (>40 mmHg)	1.00	0.39–2.01	0.999			
Transfemoral approach	0.71	0.36–1.38	0.322			
2nd vs. 1st generation valve	0.72	0.38–1.38	0.910			

CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDS-R, revised Hasegawa's dementia scale; MR, mitral regurgitation; NYHA, New York Heart Association.

cognitive impairment could affect outcomes in TAVR populations, or that their cognitive functions may be further deteriorated in the periprocedural period after TAVR, which could result in poorer outcomes over long-term periods [12,13]. Patients with HDS-R $\leq$23 actually had longer intensive care unit and hospital stays despite similar procedural complication rates between the two groups, although there is a lack of information regarding postprocedural cognitive impairment. Conversely, in a previous study showing the association between TAVR and the mini-Mental State Examination (MMSE), the best cut-off point of the MMSE for predicting mortality following TAVR was 25, which is almost equivalent to a score of 23 in the HDS-R [5,11]. Although it remains unclear as to which tests work better in the TAVR population, the HDS-R may be superior to the MMSE as a cognitive screening test in terms of the measure for memory [16,17].

In the present study, some patients with HDS-R<15 subsequently required TAVR. Although HDS-R is one of the useful tools for measuring cognitive function, it could underestimate them. For example, elderly patients are usually very nervous about answering questions a few days before their first transcatheter therapy, have difficulty hearing questions, or have difficulty concentrating on questions after informed consent including the issue regarding potential complications after TAVR. In addition, even patients with cognitive impairment suffer from severe symptoms such as shortness of breath or chest pain at rest, which potentially affect their quality of life. Furthermore, their close families usually hope for them to recover from severe aortic stenosis leading to poor outcomes including sudden death, and want them to have better quality of life as well. Therefore, in our heart team approach, selected patients with low HDS-R were considered eligible to undergo TAVR. Conversely, our heart team did not allow TAVR in a few immobile asymptomatic patients.

Predictors of mid-term outcomes after TAVR

The HDS-R was independently associated with all-cause mortality, with a median follow up of 523 days. As previous studies have reported, cognitive function is considered a part of frailty, which is one of the major predictors of mortality in patients following TAVR [4,11]. Frailty is easy to observe but hard to define [18]. This novel marker, HDS-R, is simple, is easy to perform, is objective, and has the power to predict mid-term outcomes following TAVR [9].

Women were identified as an independent protecting predictor of mortality in long-term outcomes in this study, as well. In a previous study, women were found to be more likely to develop major bleeding and vascular complications and more likely to need transfusions in the periprocedural period, likely due to anatomical disadvantages such as a smaller femoral artery diameter, a smaller left ventricle, or a smaller aortic annulus [19]. Conversely, in the longer-term, women have been considered to have better outcomes than men, which is in line with the results of the present study. This is because men tend to have vascular disease and comorbidities including hypertension, diabetes mellitus, coronary artery disease, prior revascularization, and lower left ventricular ejection fractions, as seen in a previous study [19]. BMI, atrial fibrillation, and low serum albumin levels have all been previously discussed as predictors of mortality in TAVR patients [20–22]. Although a prior stroke has been shown as a predictor of mortality in short-term periods, this is the first report demonstrating an association with mid-term outcomes [23]. At present, there are a lack of data in outcomes in TAVR patients with prior stroke because they have been excluded from most clinical trials. They were likely to have carotid artery disease, peripheral artery disease, and chronic kidney disease, which could affect longer-term outcomes, justifying our results [20]. Notably, there were no associations between HDS-R and the presence of a prior stroke in the present study. Nonetheless, this is the first study demonstrating the usefulness of the HDS-R in mid-term outcomes in TAVR patients [5,12].

Limitations

This study has a number of important limitations. First, this study was limited by its retrospective nature and by a relatively small number of enrolled patients. Therefore, a broad generalization of the findings cannot be supported. Second, this study does not include information regarding postprocedural HDS-R scores.

Conclusion

Our study offers several important conclusions. Herein, we demonstrate that patients with HDS-R ≤23 constitute a sicker and more frail population with greater cognitive impairment, and that the HDS-R can independently predict mid-term outcomes following TAVR.

Funding

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Conflict of interest

Tetsuya Tobaru, MD, PhD, is a proctor for Edwards Lifesciences and Medtronic.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.03.017.

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