ORIGINAL RESEARCH ARTICLE

Calculated plasma volume status and outcomes in patients undergoing transcatheter aortic valve replacement

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Abstract

Aims   This study investigated the prognostic value of plasma volume status (PVS) in patients who underwent transcatheter aortic valve replacement (TAVR).

Methods and results   Plasma volume status was calculated in 2588 patients who underwent TAVR using data from the Japanese multicentre registry. All-cause mortality and heart failure hospitalization (HFH) within 2 years of TAVR were compared among the PVS quartiles (Q1, PVS < 5.5%; Q2, PVS 5.5–13.5%; Q3, PVS 13.5–21.0%; and Q4, PVS ≥ 21.0%). Subgroups were stratified by the PVS cut-off value combined with the New York Heart Association (NYHA) class as follows: low PVS with NYHA I/II (n = 959), low PVS with NYHA III/IV (n = 845), high PVS with NYHA I/II (n = 308), and high PVS with NYHA III/IV (n = 476). The cumulative all-cause mortality and HFH within 2 years of TAVR significantly increased with increasing PVS quartiles [8.5%, 16.8%, 19.2%, and 27.0% (P < 0.001) and 5.8%, 8.7%, 10.3%, and 12.9% (P < 0.001), respectively]. The high-PVS group regardless of the NYHA class had a higher all-cause mortality and HFH [9.6%, 18.2%, 24.5%, and 30.4% (P < 0.001) and 6.1%, 10.4%, 14.1%, and 11.3% (P < 0.001)]. In a Cox regression multivariate analysis, the PVS values of Q3 and Q4 had independently increased all-cause mortality [hazard ratio (HR), 1.50 and 1.64 (P = 0.017 and P = 0.008), respectively], and Q4 had independently increased HFH (HR, 1.98, P = 0.005). The low PVS with NYHA III/IV, high PVS with NYHA I/II, and high PVS with NYHA III/IV also had significantly increased all-cause mortality [HR, 1.45, 1.73, and 1.86 (P = 0.006, P = 0.002, and P < 0.001), respectively] and HFH [HR, 1.52, 2.21, and 1.70 (P = 0.049, P = 0.002, and P = 0.031), respectively].

Conclusions   Plasma volume status is useful for predicting all-cause mortality and HFH after TAVR.

Introduction

With the introduction of transcatheter aortic valve replacement (TAVR), the management of aortic stenosis (AS) has evolved substantially.[1–3] However, many patients still experience adverse outcomes.[4,5] Worsening of heart failure (HF) is one of the major adverse events even after a successful TAVR. Previous investigations show that the HF

hospitalization (HFH) rates reach 11% and 24% within 60 days and 1 year after TAVR, respectively, despite initial haemodynamic improvements.[6,7] Concerning the balance between risk and cost-effectiveness of TAVR, identifying specific predictive factors associated with the worsening of HF is important.

Previous studies have reported that plasma volume (PV) expansion underlies systemic congestion and worsening of HF in patients with cardiac disease.[8,9] Greater degrees of congestion are associated with greater morbidity and mortality; therefore, relieving congestion is a fundamental therapeutic goal in patients with cardiac disease.[10,11] However, most PV measurement methods are clinically impractical and/or have several limitations.[12,13] Because PV is closely associated with body weight and haematocrit levels, validated equations based on these indices can be utilized to objectively estimate PV levels.[14] In a prior analysis, these calculated PV levels were correlated with corresponding optimally measured PV values.[15] Moreover, calculated PV status (PVS), a measure of the degree to which patients have deviated from their ideal PV, has been shown to strongly predict the prognosis of patients with HF and cardiac surgery.[15–17] However, no report has assessed the prognostic utility of PVS in patients who have undergone TAVR. Therefore, we aimed to assess the prognostic implication of calculated PVS in patients undergoing TAVR.

Methods

Subjects

This study evaluated data from the Optimized CathEter vAlvular iNtervention (OCEAN)-Transcatheter Aortic Valve Implantation (TAVI) registry, an ongoing multicentre registry collecting data from 14 Japanese medical centres including Kishiwada Tokushukai Hospital. Enrolled patients were determined as eligible candidates for TAVR by a consensus among surgeons at the individual centres and through discussions among cardiologists managing patients with multiple co-morbidities. Altogether, 2588 patients underwent baseline, perioperative, and post-operative data collection before undergoing TAVR between October 2013 and May 2017; follow-up outcomes were prospectively collected. Blood sampling was performed while they were in the hospital ward after they were admitted for the TAVR procedure, unless there were no special circumstances. Patients were followed up through clinical visits or telephone consultations after procedure. This study protocol was approved by the local institutional review board. All patients provided informed consent before participation.

Plasma volume equations

Plasma volume status was calculated by the estimated and ideal PV levels. For calculating the estimated PV, we used the Kaplan–Hakim formula as follows[14]:

$$\text{Estimated PV} = ([1 - \text{haematocrit}] \times [a + (b \times \text{weight [kg]})]),$$

where a (1530 in men and 864 in women) and b (41 in men and 47.9 in women) were used as adjustment values.

For calculating the haematocrit, we used a haemoglobin-based formula[18]:

$$\text{Haematocrit} = 2.941 \times \text{haemoglobin (g/dL)}.$$

Ideal PV was calculated from the following equation[19]:

$$\text{Ideal PV} = c \times \text{weight (kg)},$$

where c = 39 in men and 40 in women.

Subsequently, the estimated PVS was calculated using the following equation:

$$\text{PVS} = (\text{estimated PV} - \text{ideal PV}) \times 100/\text{ideal PV}.$$

First, we assessed the calculated PVS values as categorical variables for the survival analysis. To simplify the prognostic associations, patients were stratified into PVS quartiles (Model 1): Q1 (PVS < 5.5%; n = 646), Q2 (5.5% ≤ PVS < 13.5%; n = 652), Q3 (13.5% ≤ PVS < 21.0%; n = 646), and Q4 (PVS ≥ 21.0%; n = 644) (Figure 1). As a subgroup analysis, we performed survival classification and regression tree (CART) analysis for determining the PVS cut-off that best discriminated mortality. CART analysis is an empirical and statistical method used to create decision rules based on data rather than on speculation to determine a risk stratification model.[20] CART analysis identified that 19.0% (accurately 19.015%) was an adequate cut-off value of PVS. We also divided patients into two risk groups according to the cut-off value: low-PVS group (PVS below cut-off value; n = 1805) and high-PVS group (PVS above cut-off value; n = 783). Thereafter, the prognostic value of PVS in addition to the New York Heart Association (NYHA) class was assessed (Model 2). We divided patients into four risk groups: low PVS with NYHA I/II (n = 959), low PVS with NYHA III/IV (n = 845), high PVS with NYHA I/II (n = 308), and high PVS with NYHA III/IV (n = 476). We also assessed the calculated PVS values and haematocrit as continuous variables for the survival analysis. Additionally, the receiver operating characteristic (ROC), net reclassification improvement (NRI) (continuous), and integrated discrimination improvement (IDI) analyses were performed to compare the incremental predictive value of the calculated PVS and haematocrit in all-cause mortality and HF hospitalization within 2 years.

Figure 1 Distribution of the plasma volume status (PVS) in the OCEAN-TAVI registry cohort (*n* = 2588).
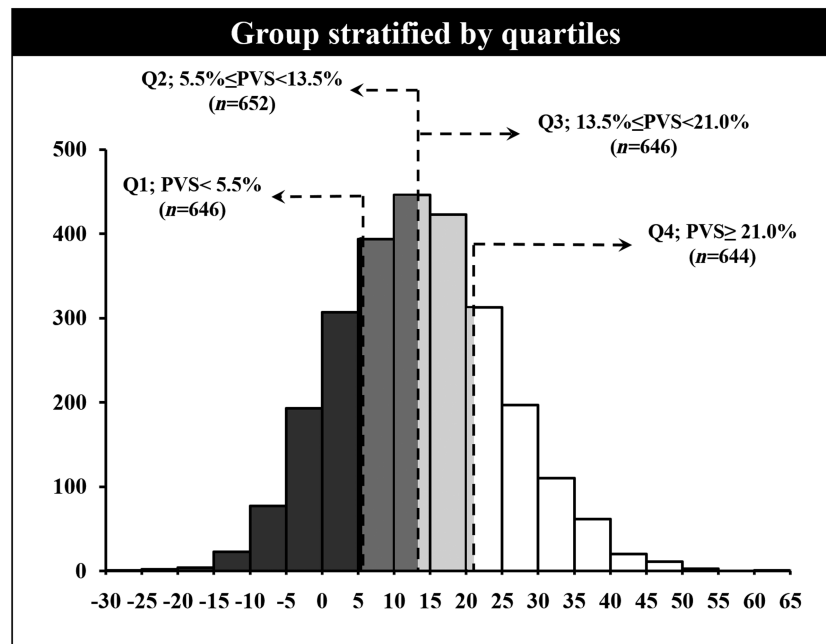
Outcomes

The study endpoints were all-cause mortality and HFH after TAVR. Chronic kidney disease was identified based on the Kidney Disease Improving Global Outcomes guidelines (estimated glomerular filtration rate of <60 mL/min/1.73 m²).[21] Procedural outcomes and complications during TAVR were evaluated according to the Valve Academic Research Consortium-2 criteria.[22] We defined 'hospitalization' as a patient being admitted to a hospital ward/intensive care unit. Medical records were used to determine the main cause of hospitalization. HFH was defined as hospitalization by clinical and/or radiological signs of HF. The medical records of all-cause death and HFH that did not include the hospitalization date were excluded from this study (all-cause death 0/493 and HFH 22/255).

Statistical analysis

All statistical analyses were performed using IBM SPSS software Version 22 (IBM Corp., Armonk, NY), MedCalc Software Version 17.4 (MedCalc Software bvba., Ostend, Belgium), and R software packages Version 3.0.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Differences were considered statistically significant at a *P* value <0.05. Continuous variables were expressed as mean ± standard deviation or median (with inter-quartile range) according to the variable distributions. Categorical valuables were expressed as percentages. Comparisons among the four groups were performed using Pearson's bivariate test and the χ^2 test for categorical covariates, one-way analysis of variance for continuous covariates that were listed as mean value and standard deviation, and the Kruskal–Wallis test for continuous variables that were listed as medians with inter-quartile range. The comparisons of the PVS groups and NYHA class were analysed using Spearman's correlation coefficient. The Kaplan–Meier method and log-rank test were used to evaluate the differences in mortality among the four groups. A univariable Cox regression analysis was performed to evaluate the associations between clinical parameters and all-cause mortality and HFH. Thereafter, a multivariable analysis was performed using the baseline clinical characteristics and variables with *P* values <0.05 of the univariable analysis to examine the independent associations of the calculated PVS with all-cause mortality and HFH after TAVR. The ROC, NRI (continuous), and IDI analyses were performed to compare the incremental predictive value of the calculated PVS and haematocrit.

Results

Study population

Table 1 presents the baseline characteristics of the groups. Significant intergroup differences were observed in the mean

Table 1 Baseline characteristics of study

	PVS < 5.5% (n = 646)	PVS 5.5–13.5% (n = 652)	PVS 13.5–21.0% (n = 646)	PVS ≥ 21.0% (n = 644)	P value
Baseline clinical characteristics					
Age (years)	82.5 ± 5.0	83.9 ± 5.0	85.0 ± 5.2	86.0 ± 5.0	<0.001
Gender (male)	226 (35.0%)	168 (25.8%)	168 (26.0%)	233 (36.2%)	<0.001
Height (cm)	153.1 ± 9.0	149.7 ± 8.6	148.8 ± 8.5	148.5 ± 9.6	<0.001
Weight (kg)	58.8 ± 10.1	51.3 ± 7.8	47.7 ± 8.1	42.8 ± 7.7	<0.001
BMI (kg/m^2)	25.0 ± 3.5	22.9 ± 2.9	21.5 ± 2.9	19.4 ± 2.7	<0.001
STS score (%)	4.76 (3.48–4.76)	6.24 (4.30–8.63)	7.12 (5.16–10.47)	8.11 (5.64–12.18)	<0.001
NYHA class (III/IV)	251 (38.9%)	310 (47.5%)	364 (56.3%)	396 (61.5%)	<0.001
Clinical Frailty Scale	3.60 ± 1.18	3.90 ± 1.18	4.03 ± 1.27	4.21 ± 1.30	<0.001
Use of diuretics, n	275 (42.6%)	331 (50.8%)	387 (59.9%)	416 (64.6%)	<0.001
Pre-procedural laboratory data					
BNP (pg/mL, n = 2256)	172.8 (81.2–377.1)	255.2 (108.1–509.6)	310.5 (132.5–663.5)	367.4 (186.1–730.9)	<0.001
Creatinine (mg/dL)	0.91 ± 0.33	0.98 ± 0.41	1.08 ± 0.59	1.16 ± 0.66	<0.001
Albumin (g/dL)	3.96 ± 0.38	3.82 ± 0.46	3.68 ± 0.49	3.50 ± 0.52	<0.001
Alb < 3.5 (g/dL)	58 (9.0%)	113 (17.3%)	184 (28.5%)	262 (40.7%)	<0.001
Haemoglobin (g/dL)	13.1 ± 1.2	11.6 ± 1.0	10.7 ± 1.0	9.7 ± 1.2	<0.001
Haematocrit (%)	38.5 ± 3.4	34.2 ± 3.0	31.4 ± 3.1	28.4 ± 3.4	<0.001
Co-morbidity					
Peripheral artery disease, n	80 (12.4%)	86 (13.2%)	110 (17.0%)	101 (15.7%)	0.064
Coronary artery disease, n	241 (37.3%)	223 (34.2%)	261 (40.4%)	229 (35.6%)	0.11
Atrial fibrillation, n	133 (20.6%)	152 (23.3%)	132 (20.4%)	132 (20.5%)	0.51
Prior stroke, n	84 (13.0%)	68 (10.4%)	80 (12.4%)	69 (10.7%)	0.39
Prior CABG, n	45 (7.0%)	40 (6.1%)	56 (8.7%)	28 (4.3%)	0.017
Prior PMI, n	30 (4.6%)	43 (6.6%)	43 (6.7%)	50 (7.8%)	0.14
Chronic kidney disease, n	396 (61.3%)	453 (69.5%)	475 (73.5%)	485 (75.3%)	<0.001
Hypertension, n	507 (78.5%)	508 (77.9%)	487 (75.4%)	488 (75.8%)	0.46
Diabetes mellitus, n	170 (26.3%)	156 (23.9%)	120 (18.6%)	109 (16.9%)	<0.001
Pulmonary disease, n	152 (23.5%)	147 (22.5%)	146 (22.6%)	171 (26.6%)	0.29
Liver disease, n	20 (3.1%)	11 (1.7%)	22 (3.4%)	23 (3.6%)	0.17
Active cancer, n	41 (6.3%)	28 (4.3%)	32 (5.0%)	23 (3.6%)	0.12
Echocardiographic data					
Prior LVEF (%)	60.3 ± 11.9	59.0 ± 13.4	58.7 ± 13.0	59.0 ± 12.3	0.12
Prior LVEF < 40%, n	42 (6.5%)	66 (10.1%)	70 (10.8%)	56 (8.7%)	0.035
AVA (cm^2)	0.66 ± 0.17	0.64 ± 0.16	0.62 ± 0.17	0.60 ± 0.17	<0.001
Indexed AVA (cm^2/m^2)	0.43 ± 0.11	0.44 ± 0.11	0.45 ± 0.12	0.45 ± 0.13	0.002
AV mean gradient (mmHg)	49.7 ± 16.9	49.6 ± 18.6	50.7 ± 18.5	52.4 ± 18.8	0.021
AV peak velocity (m/s)	4.53 ± 0.73	4.52 ± 0.81	4.58 ± 0.81	4.65 ± 0.80	0.011
AR ≥ moderate, n	60 (9.3%)	61 (9.4%)	75 (11.6%)	78 (12.1%)	0.21
MR ≥ moderate, n	50 (7.7%)	77 (11.8%)	72 (11.1%)	92 (14.3%)	0.003

AR, aortic regurgitation; AV, aortic valve; AVA, aortic valve area; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PMI, perioperative myocardial infarction; PVS, plasma volume status; STS, Society of Thoracic Surgeons.
Values are numbers (%) or mean ± standard deviation.

age, height, body weight, body mass index, Society of Thoracic Surgeons risk score, NYHA Class III/IV, Clinical Frailty Scale, diuretic usage rate, co-morbidities, laboratory data, and echocardiographic parameters (all $P < 0.05$). *Table 2* shows the peri-procedural and post-procedural data and early outcomes that included significant intergroup differences in the approach site, elective TAVR rate, cause of acute kidney injury, bleeding, and length of post-TAVR hospitalization (all $P < 0.05$). The associations among the PVS groups and NYHA class are shown in *Figure 2*. The associations among the PVS groups and NYHA class differed significantly among the four groups (all $P < 0.001$). The PVS groups and NYHA classification showed a significant correlation (Spearman's $\rho = 0.19$, $P < 0.001$).

Calculated plasma volume status and outcomes in the transcatheter aortic valve replacement cohort

After a median follow-up of 660 (range: 381–860) days, 493 patients died and 233 were hospitalized for worsening HF. The Kaplan–Meier analyses of the cumulative all-cause mortality and HFH in the PVS class stratified by quartiles are presented in *Figure 3A* and *3B*. The cumulative 2 year all-cause mortality rates significantly increased across all four groups (8.5%, 16.8%, 19.2%, and 27.0%, respectively; $P < 0.001$). The 2 year HFH rate gradually increased across the four groups (5.8%, 8.7%, 10.3%, and 12.9%, respectively; $P < 0.001$). The Kaplan–Meier analysis in the survival CART model also indicated a significantly higher all-cause mortality

Table 2 Peri-procedural and post-procedural patient characteristics and early outcomes

	PVS < 5.5% (n = 646)	PVS 5.5–13.5% (n = 652)	PVS 13.5–21.0% (n = 646)	PVS ≥ 21.0% (n = 644)	P value
Peri-procedural variables					
Non-transfemoral approach	83 (12.8%)	98 (15.0%)	110 (17.0%)	130 (20.2%)	0.003
Balloon expandable valve	563 (87.2%)	567 (87.0%)	566 (87.6%)	549 (85.2%)	0.62
Non-elective (for elective)	24 (3.7%)	35 (5.4%)	42 (6.5%)	50 (7.8%)	0.015
Post-procedural variables					
Device success (%)	589 (91.6%)	603 (92.9%)	603 (94.1%)	591 (91.8%)	0.30
Acute coronary obstruction, *n*	3 (0.5%)	4 (0.6%)	10 (1.5%)	8 (1.2%)	0.15
Disabling stroke, *n*	9 (1.4%)	11 (1.7%)	10 (1.5%)	10 (1.6%)	0.98
Acute kidney injury, *n*	53 (8.2%)	63 (9.7%)	87 (13.5%)	86 (13.4%)	0.003
Major vascular complication, *n*	18 (2.8%)	31 (4.8%)	27 (4.2%)	37 (5.7%)	0.069
All vascular complication, *n*	46 (7.1%)	62 (9.5%)	53 (8.2%)	72 (11.2%)	0.066
Life-threatening/disabling bleeding, *n*	14 (2.2%)	38 (5.8%)	35 (5.4%)	42 (6.5%)	0.002
Major bleeding, *n*	48 (7.4%)	61 (9.4%)	71 (11.0%)	102 (15.8%)	<0.001
All bleeding, *n*	81 (12.5%)	135 (20.7%)	179 (27.7%)	225 (34.9%)	<0.001
Pacemaker implantation in hospital, *n*	61 (9.4%)	45 (6.9%)	52 (8.0%)	53 (8.2%)	0.42
Cardiac tamponade, *n*	3 (0.5%)	12 (1.8%)	6 (0.9%)	12 (1.9%)	0.060
Conversion to open surgery, *n*	3 (0.5%)	9 (1.4%)	5 (0.8%)	8 (1.2%)	0.30
Early outcomes					
Length of stay in hospital after TAVR (days)	9.0 (6.0–14.0)	10.0 (7.0–15.5)	10.0 (7.0–16.0)	11.0 (7.0–17.0)	<0.001
Intensive care unit stay (days)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–3.0)	0.93
30 day mortality (%)	8 (1.2%)	12 (1.8%)	8 (1.2%)	19 (3.0%)	0.070
In-hospital death (%)	11 (1.7%)	16 (2.5%)	17 (2.6%)	26 (4.0%)	0.073

PVS, plasma volume status; TAVR, transcatheter aortic valve replacement.
Values are numbers (%) or mean ± standard deviation.

Figure 2 Association between the New York Heart Association (NYHA) class and plasma volume status. The number of patients with NYHA class ≤II in each group tends to decrease across the four groups, whereas that of patients with NYHA Classes III and IV tends to increase.
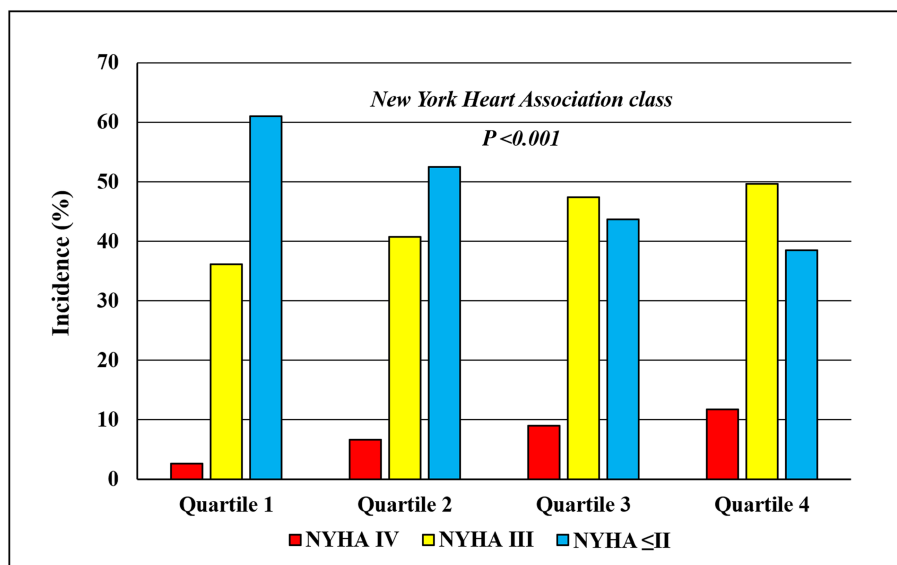
(*Figure 3C*: 28.0% vs. 13.6%, *P* < 0.001) and HFH in the high-PVS group than in the low-PVS group (*Figure 3D*: 12.6% vs. 8.0%, *P* = 0.002). The groups stratified by the PVS and NYHA class also showed increased all-cause mortality (*Figure 3E*: 9.6%, 18.2%, 24.5%, and 30.4%, respectively, *P* < 0.001) and HFH across the four groups (*Figure 3F*: 6.1%, 10.4%, 14.1%, and 11.3%, respectively, *P* < 0.001).

The all-cause mortality of the group with high PVS and NYHA I/II was significantly higher than that of the group with low PVS and NYHA III/IV (*P* = 0.047). In contrast, the HFH rates of the group with high PVS and NYHA I/II, and low PVS and NYHA III/IV, was similar (*P* = 0.75).

The landmark analysis showing the risk of HFH at 1 year and from 1 to 2 years is shown in *Figure 4*. The HFH rates

Figure 3 Kaplan–Meier curves showing the study endpoints in the plasma volume status (PVS) groups defined by two differential PVS classifications. (A) Kaplan–Meier curves showing cumulative all-cause mortality in PVS stratified by quartiles. (B) Kaplan–Meier curves showing the cumulative heart failure hospitalization (HFH) in PVS stratified by quartiles. (C) Kaplan–Meier curves showing the cumulative all-cause mortality in the classification and regression tree (CART) stratified by the PVS subgroups. (D) Kaplan–Meier curves showing the cumulative HFH in the CART stratified by the PVS subgroups. (E) Kaplan–Meier curves showing the CART mortality in the groups stratified by PVS and the New York Heart Association (NYHA) class. (F) Kaplan–Meier curves showing the cumulative HFH in the groups stratified by the PVS and the NYHA class.
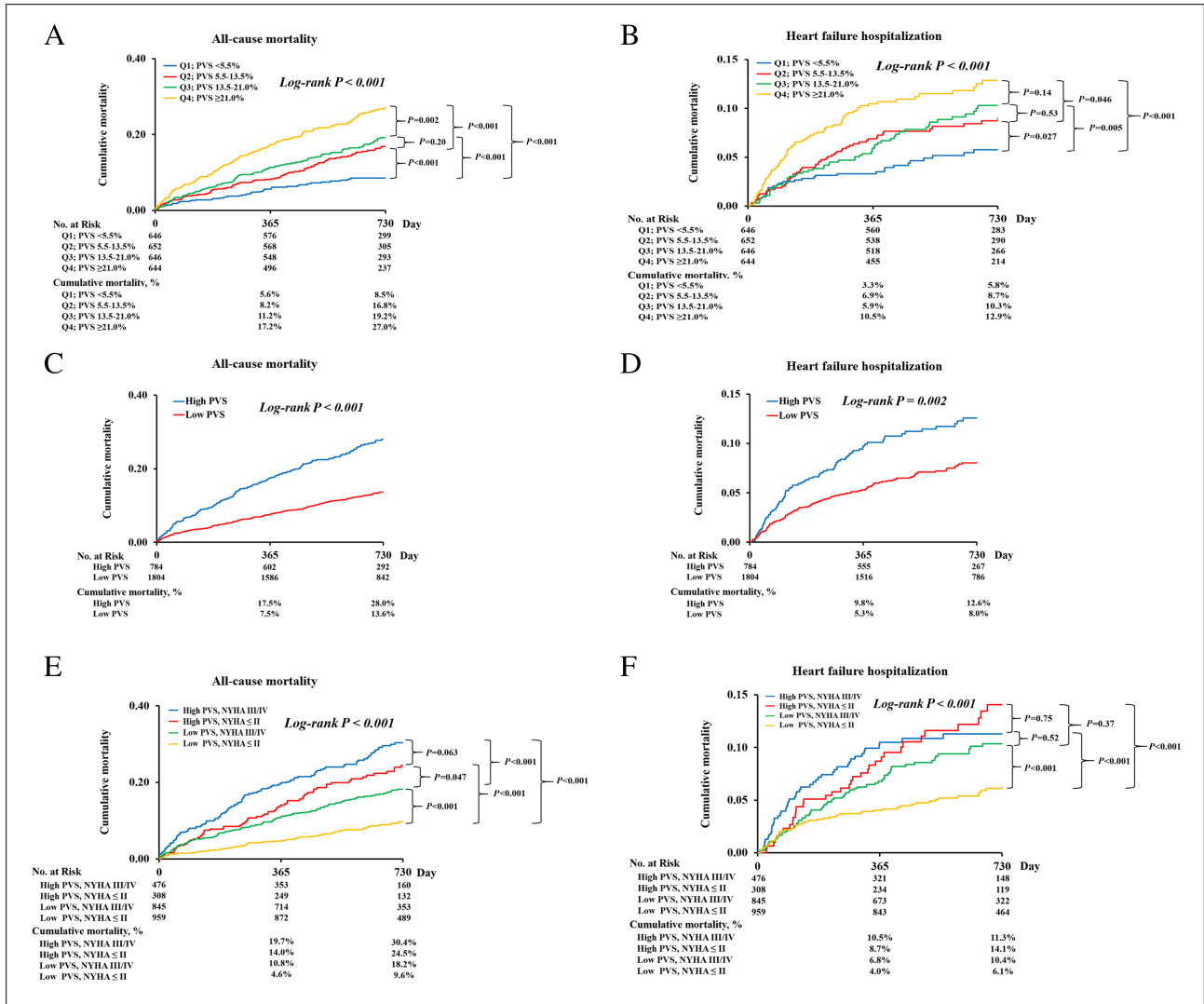
from 1 to 2 years after TAVR did not show a significant difference between the two groups (*Figure 4*: 3.1% vs. 2.9%, *P* = 0.54).
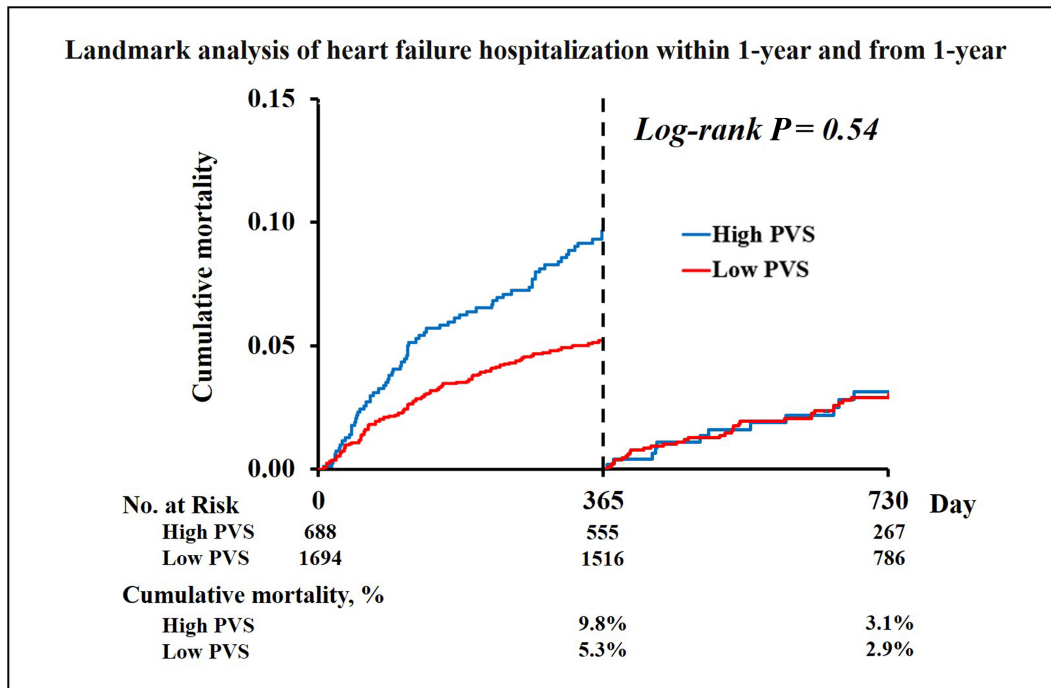
Independent predictors of all-cause mortality after transcatheter aortic valve replacement

The results of the Cox regression analysis for the association between all-cause mortality and clinical findings are presented in *Table 3*. In the univariate Cox regression, the PVS quartiles (Model 1) demonstrated a stepwise, incremental

increase in the mortality risk in the Q2, Q3, and Q4 groups relative to the Q1 group. After adjusting for multiple confounding factors, the Q3 [hazard ratio (HR), 1.50; 95% confidence interval (CI), 1.08–2.09; *P* = 0.017] and Q4 (HR, 1.64; 95% CI, 1.14–2.35; *P* = 0.008) groups were independently associated with all-cause mortality. These results were not attenuated even after body weight was adjusted for covariates instead of body mass index (Supporting Information, *Table S1*).

In Model 2, focusing on the PVS values and NYHA class, low PVS with NYHA III/IV (HR, 1.45; 95% CI, 1.11–1.90; *P* = 0.006), high PVS with NYHA ≤ II (HR, 1.73; 95% CI, 1.23–

Figure 4 Landmark analysis of the heart failure readmission at 1 year and from 1 to 2 years in high-plasma volume status (PVS) and low-PVS groups. Landmark analysis showing the risk of heart failure hospitalization within 1 year and from 1 to 2 years in patients with severe aortic stenosis who underwent transcatheter aortic valve implantation.

2.43; $P = 0.002$), and high PVS with NYHA III/IV (HR, 1.86; 95% CI, 1.36–2.53; $P < 0.001$) were independent predictors of increased all-cause mortality, relative to the low-PVS with NYHA ≤ II group. Additionally, the Cox regression analysis for the association between all-cause mortality and the calculated PVS (continuous variables) is shown in Supporting Information, *Table S2*. Similarly, the Cox regression analysis for the association between all-cause mortality and haematocrit is shown in Supporting Information, *Table S3*. Increasing PVS and haematocrit as continuous variables were also independently associated with all-cause mortality, even after adjusting for multiple confounding factors (HR, 1.02 and 0.96; 95% CI, 1.01–1.03 and 0.94–0.98; $P < 0.001$ and $P < 0.001$, respectively). However, the calculated PVS showed a better predictive value than haematocrit by the ROC (area under the curve, 0.62 vs. 0.59; $P = 0.0012$) (Supporting Information, *Figure S1A*), NRI (NRI, 0.2326; 95% CI, 0.1349–0.3302; $P < 0.001$), and IDI (IDI, 0.0173; 95% CI, 0.0111–0.0235; $P < 0.001$) analyses.

Independent predictors of heart failure hospitalization within 2 years after transcatheter aortic valve replacement

The clinical factors associated with HFH within 2 years after TAVR are presented in *Table 4*. In the univariate Cox

regression, the PVS groups (Model 1) demonstrated a stepwise incremental increase in mortality risk in the Q2, Q3, and Q4 groups relative to the Q1 group. After adjusting for multiple confounding factors, the Q4 group was independently associated with HFH (HR, 1.98; 95% CI, 1.23–3.20; $P = 0.005$). In Model 2, focusing on the PVS values and NYHA class, low PVS with NYHA III/IV (HR, 1.52; 95% CI, 1.00–2.31; $P = 0.049$), high PVS with NYHA ≤ II (HR, 2.21; 95% CI, 1.34–3.65; $P = 0.002$), and high PVS with NYHA III/IV (HR, 1.70; 95% CI, 1.05–2.75; $P = 0.031$) were independent predictors of increased HFH risk relative to the low-PVS with NYHA ≤ II group. Additionally, the Cox regression analysis for the association between HFH and the calculated PVS values as continuous variables is shown in Supporting Information, *Table S4*. Similarly, the Cox regression analysis for the association between HFH and haematocrit is shown in Supporting Information, *Table S5*. Increasing PVS and haematocrit as continuous variables were also independently associated with HFH, even after adjusting for multiple confounding factors (HR, 1.02 and 0.96; 95% CI, 1.00–1.03 and 0.93–0.99; $P = 0.014$ and $P = 0.014$, respectively). The ROC analysis showed no significant difference in the predictive value between the calculated PVS and haematocrit (area under the curve, 0.58 vs. 0.56; $P = 0.25$) (Supporting Information, *Figure S1B*). Similarly, the IDI analysis showed no significant difference in the predictive value between the calculated PVS and haematocrit (IDI, 0.0009; 95% CI, −0.0006 to 0.0023, $P = 0.2508$).

Table 3 Cox regression analysis for the association between long-term mortality and clinical findings

Variables	Univariable analysis			Multivariable analysis Model 1			Multivariable analysis Model 2		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Plasma volume status (stratified by quartiles)									
Q1: PVS < 5.5% (referent)	1.00	—	—	1.00	—	—			
Q2: PVS 5.5–13.5%	1.70	1.27–2.23	<0.001	1.33	0.95–1.84	0.094			
Q3: PVS 13.5–21.0%	2.01	1.50–2.69	<0.001	1.50	1.08–2.09	0.017			
Q4: PVS ≥ 21.0%	2.85	2.16–3.78	<0.001	1.64	1.14–2.35	0.008			
PVS and NYHA class									
Low PVS, NYHA ≤ II (referent)	1.00	—	—				1.00	—	—
Low PVS, NYHA III/IV	1.78	1.40–2.26	<0.001				1.45	1.11–1.90	0.006
High PVS, NYHA ≤ II	2.34	1.75–3.12	<0.001				1.73	1.23–2.43	0.002
High PVS, NYHA III/IV	3.08	2.40–3.94	<0.001				1.86	1.36–2.53	<0.001
Adjusting factors									
Age (per 1 year increase)	1.02	1.00–1.03	0.086						
Male (for female)	1.65	1.38–2.00	<0.001	1.70	1.38–2.11	<0.001	1.67	1.35–2.07	<0.001
BMI (per 1 kg/m^2 increase)	0.94	0.91–0.96	<0.001	0.98	0.95–1.01	0.21	0.98	0.95–1.01	0.14
NYHA Class III/IV (for I/II)	1.70	1.42–2.04	<0.001	1.28	1.04–1.58	0.020			
BNP	1.00	1.00–1.00	<0.001	1.00	1.00–1.00	0.50	1.00	1.00–1.00	0.58
CKD	1.51	1.23–1.86	<0.001	1.29	1.02–1.63	0.036	1.30	1.03–1.65	0.027
Hypertension	0.95	0.77–1.17	0.61						
Diabetes mellitus	1.19	0.97–1.46	0.092						
Pulmonary disease	1.49	1.23–1.80	<0.001	1.33	1.07–1.64	0.009	1.32	1.07–1.63	0.010
Liver disease	2.26	1.54–3.32	<0.001	2.05	1.31–3.22	0.002	1.98	1.26–3.10	0.003
Active cancer	1.54	1.09–2.17	0.014	1.60	1.07–2.40	0.023	1.58	1.05–2.37	0.028
Peripheral artery disease	1.80	1.46–2.22	<0.001	1.17	0.91–1.51	0.22	1.18	0.91–1.52	0.22
Atrial fibrillation	1.45	1.19–1.77	<0.001	1.15	0.91–1.44	0.24	1.14	0.90–1.43	0.27
Coronary artery disease	1.22	1.02–1.46	0.027	1.20	0.98–1.46	0.081	1.21	0.99–1.48	0.066
Prior CABG	1.37	1.00–1.87	0.050						
Prior PMI	1.11	0.79–1.55	0.57						
Prior stroke	1.27	0.98–1.64	0.08						
STS (per 1.0% increase)	1.04	1.03–1.04	<0.001	1.02	1.01–1.03	<0.001	1.02	1.01–1.03	<0.001
Clinical Frailty Scale (per 1 group increase)	1.32	1.24–1.41	<0.001	1.24	1.15–1.35	<0.001	1.24	1.15–1.35	<0.001
Prior LVEF < 40% (for prior LVEF ≥ 40%)	1.50	1.13–1.96	0.005	0.83	0.57–1.20	0.32	0.84	0.58–1.22	0.36
Non-elective TAVR (for elective TAVR)	1.62	1.15–2.28	0.006	0.69	0.42–1.13	0.14	0.69	0.43–1.13	0.14
Non-TF approach (for TF approach)	1.48	1.20–1.83	<0.001	1.28	1.00–1.63	0.055	1.25	0.98–1.60	0.078

BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; CI; confidence interval; CKD, chronic kidney disease; HR; hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PMI, perioperative myocardial infarction; PVS, plasma volume status; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TF, transfemoral.

However, the NRI analysis (continuous) revealed that the PVS had a better predictive value of HFH within 2 years compared with haematocrit (NRI, 0.1913; 95% CI, 0.0492–0.3334; *P* = 0.00832).

Discussion

In this study, we made several observations using a calculated PVS, which was based on a calculated haematocrit value derived from the haemoglobin levels. Our main findings are as follows: first, the mean calculated PVS in the elderly TAVR cohort was higher than that of the other cardiac disease cohorts.[15,17] Second, a high-PVS value was found to be an independent predictive factor for all-cause mortality and HFH within 2 years after TAVR even after adjusting for other confounding clinical factors. Third, the PVS value, in addition to the NYHA class, showed additional strength in predicting the all-cause mortality and HFH after TAVR.

In this study, the mean calculated PVS value was 13.6 ± 11.4%. The Valsartan in Heart Failure Trial (Val-HeFT) study consisting of 5002 chronic HF patients reported a mean PVS value of −9 ± 8%.[15] Moreover, the other study group comprised 1887 patients who underwent coronary artery bypass graft surgery, and their mean PVS value was −8.2 ± 9.1%.[17] Compared with those previous reports, the mean calculated PVS value in our registry was relatively high, indicating that several patients with severe AS had advanced stages of congestion and uneven PV expansion before TAVR compared with patients with other cardiac diseases. The proportion of patients with NYHA III/IV that was significantly correlated with the calculated PVS was also higher in our study than in previous studies.[15,17] The underlying cause for this result is that we included a cohort of surgically inoperable or high-risk candidates with severe AS in this study. Because severe AS is the terminal manifestation of AS and medical therapy is limited, PV may be difficult to control using diuretics or other medications before TAVR is performed. The rate of non-elective TAVR was higher in the high-PVS group than in

Table 4 Cox regression analysis for the association between HFH within 2 years and clinical findings

Variables	Univariable analysis			Multivariable analysis Model 1			Multivariable analysis Model 2		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Plasma volume status (stratified by quartiles)									
Q1: PVS < 5.5% (referent)	1.00	—	—	1.00	—	—			
Q2: PVS 5.5–13.5%	1.65	1.06–2.58	0.027	1.34	0.82–2.18	0.24			
Q3: PVS 13.5–21.0%	1.79	1.15–2.78	0.010	1.29	0.79–2.13	0.31			
Q4: PVS ≥ 21.0%	2.53	1.66–3.86	<0.001	1.98	1.23–3.20	0.005			
PVS and NYHA class									
Low PVS, NYHA ≤ II (referent)	1.00	—	—				1.00	—	—
Low PVS, NYHA III/IV	1.74	1.21–2.48	0.003				1.52	1.00–2.31	0.049
High PVS, NYHA ≤ II	2.31	1.50–3.55	<0.001				2.21	1.34–3.65	0.002
High PVS, NYHA III/IV	2.18	1.47–3.24	<0.001				1.70	1.05–2.75	0.031
Adjusting factors									
Age (per 1 year increase)	1.03	1.01–1.06	0.020	1.02	0.99–1.06	0.18	1.03	0.99–1.06	0.14
Male (for female)	1.45	1.09–1.92	0.010	1.23	0.88–1.71	0.22	1.25	0.90–1.74	0.19
BMI (per 1 kg/m² increase)	0.98	0.94–1.02	0.22						
NYHA class III/IV (for I/II)	1.45	1.10–1.91	0.008	1.15	0.83–1.61	0.40			
BNP	1.00	1.00–1.00	<0.001	1.00	1.00–1.00	0.19	1.00	1.00–1.00	0.17
CKD	2.13	1.49–3.04	<0.001	1.71	1.13–2.57	0.010	1.71	1.14–2.58	0.010
Hypertension	1.41	0.99–2.03	0.059						
Diabetes mellitus	1.46	1.08–1.97	0.015	1.29	0.90–1.84	0.17	1.28	0.90–1.82	0.18
Pulmonary disease	1.02	0.74–1.40	0.93						
Liver disease	1.24	0.58–2.63	0.58						
Active cancer	0.69	0.33–1.47	0.34						
Peripheral artery disease	1.61	1.15–2.26	0.006	1.13	0.75–1.71	0.56	1.09	0.73–1.65	0.67
Atrial fibrillation	1.94	1.45–2.59	<0.001	1.58	1.13–2.22	0.008	1.54	1.10–2.16	0.013
Coronary artery disease	1.45	1.10–1.91	0.008	1.21	0.86–1.69	0.28	1.21	0.87–1.70	0.26
Prior CABG	1.83	1.17–2.84	0.008	1.61	0.95–2.72	0.076	1.64	0.97–2.77	0.064
Prior PMI	1.65	1.05–2.58	0.031	1.32	0.81–2.17	0.27	1.31	0.80–2.14	0.29
Prior stroke	1.37	0.93–2.02	0.11						
STS (per 1.0% increase)	1.03	1.02–1.04	<0.001	0.99	0.96–1.01	0.28	0.99	0.97–1.01	0.35
Clinical Frailty Scale (per 1 group increase)	1.15	1.04–1.28	0.009	1.04	0.91–1.18	0.56	1.05	0.92–1.20	0.49
Prior LVEF < 40% (for prior LVEF ≥ 40%)	2.59	1.82–3.68	<0.001	1.81	1.14–2.87	0.012	1.79	1.13–2.85	0.014
Non-elective TAVR (for elective TAVR)	2.11	1.33–3.34	0.002	1.24	0.66–2.35	0.50	1.25	0.66–2.36	0.49
Non-TF approach (for TF approach)	1.92	1.41–2.62	<0.001	1.69	1.17–2.45	0.005	1.71	1.17–2.47	0.005

BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; CI; confidence interval; CKD, chronic kidney disease; HFH; heart failure hospitalization; HR; hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PMI, perioperative myocardial infarction; PVS, plasma volume status; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TF, transfemoral.

the low-PVS group, despite higher diuretic administration rates. Furthermore, surgically inoperable or high-risk patients were more inclined to be older and frailer and have multiple co-morbidities, as malnutrition and co-morbidities such as anaemia, cancer, chronic kidney disease, and liver disease substantially affect the haematocrit/haemoglobin levels and PV. Therefore, the PVS may have been elevated in patients with such conditions.

An elevated PV could adversely affect the prognosis.[15,17] Similarly, our present study revealed that a higher PVS value in these 2588 patients with severe AS was associated with long-term all-cause mortality and HFH within 2 years after TAVR. Moreover, the calculated PVS showed better predictive ability of these two outcomes than haematocrit, which was used for estimating the PVS value. To secure favourable prognoses in severe AS cohorts, TAVR would be better performed under a stable fluid balance condition. However, medical therapy has its limitations in patients with severe AS. The better way to secure favourable prognoses is to

perform TAVR before AS deteriorates. Recently, earlier interventions for severe AS have been increasingly advocated.[23,24] These studies suggest that the early treatment of severe AS results in more favourable outcomes, whereas delays in intervention only worsen the prognosis. Therefore, therapeutic interventions using an appropriate index are necessary. From this registry, we found that a PVS cut-off of 19% was best for predicting adverse outcomes. The prognosis of the low-PVS group was favourable in our study compared with that of the high-PVS group. However, the cut-off value determined by the CART analysis from this specific old-age Asian cohort is difficult to use broadly. Because the PV estimated in this registry was not validated by the actually measured PV, it is unclear how the estimated PV is correlated with the actual PV. Moreover, the calculated PVS and actually measured PV are found to be moderately correlated at best from the previous study.[25] Therefore, the prognostic PVS cut-off value determined in this registry should not be overstated.

We also found that the possibility of incorporating PVS information in addition to the NYHA class could allow for more accurate assessments of all-cause mortality and HFH up to 2 years after TAVR. The NYHA class is a traditional and simple classification of HF severity. The poor prognosis of patients with preoperative NYHA III/IV compared with those with NYHA I/II was globally proven in the TAVR cohorts.[26–28] However, the current study added the better accuracy in assessing PVS in conjunction with the NYHA classification for predicting the all-cause mortality and HFH after TAVR. The mortality rate of patients with high PVS and NYHA I/II was worse than that of patients with low PVS and NYHA I/II. Additionally, patients with high PVS and NYHA I/II had a worse prognosis than those with low PVS and NYHA III/IV. Similar trends of PVS utility were also confirmed in terms of HFH after TAVR. The NYHA classification can easily be used for all patients while being a subjective assessment. Calculating the PVS along with the traditional NYHA classification may help patient selection and outpatient monitoring.

The PVS value may have a potential of helping patient selection, timing of the procedure, and continuity of care after discharge for improving the patient's prognosis after TAVR.

Limitations

Several study limitations should be addressed. First, the PVS formula used in this study was not used for measuring actual values. Therefore, the accuracies of the calculated PV relative to the actual PV could not be ascertained in this study. Second, blood sampling was not performed under the same condition among patients. Moreover, hydration status would be different among patients. Because the haematocrit level changes with hydration status, the difference in hydration status among patients may cause a bias.[29] Third, in this registry, we used haemoglobin value because the haematocrit data were not included in the dataset. However, the PV values calculated using this alternative formula were still correlated with the NYHA class that reflected HF severities. It remains unclear whether the ideal PV can be calculated using body weight alone for this cohort of older adults. Fourth, the clinical outcomes including the information of death and HFH were prospectively recorded via self-audit by sites; thus, there is still the potential for under-reporting or over-reporting of data. Fifth, hospital stay was relatively longer in this study than in previous studies, reflecting the local Japanese practice for the TAVR procedure. This may affect the clinical outcomes including HFH. Further investigations are needed to clarify the impact of the length of hospital stay on clinical outcomes.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Supporting information.
Table S1. Cox regression analysis for the association between Long-term mortality and clinical findings.
Table S2. Cox regression analysis for the association between Long-term mortality and clinical findings.
Table S3. Cox regression analysis for the association between Long-term mortality and clinical findings.
Table S4. Cox regression analysis for the association between HFH within 2-year and clinical findings.

Table S5. Cox regression analysis for the association between HFH within 2-year and clinical findings.

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