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ORIGINAL RESEARCH

Small Left Ventricle and Clinical Outcomes After Transcatheter Aortic Valve Replacement

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BACKGROUND: In patients undergoing transcatheter aortic valve replacement (TAVR), those with small left ventricle (LV) may have an increased risk of poor outcomes, because small LV is associated with low-flow (LF), left ventricular hypertrophy. However, the impact of small LV on patients undergoing TAVR remains unknown.

METHODS AND RESULTS: We examined 2584 patients who underwent TAVR between October 2013 and May 2017 using data from the Japanese multicenter registry. On the basis of the American Society of Echocardiography guidelines, small LV was defined as left ventricular end-diastolic dimension <42.0 mm for men or <37.8 mm for women. The 2-year clinical outcomes were compared between patients with and without small LV using multivariable Cox regression analyses and propensity score matching. Subgroup analyses by LF, left ventricular hypertrophy were performed. Of 2584 patients who underwent TAVR, 466 (18.0%) had small LV. Patients with small LV had smaller body size and less comorbidity, and were more likely to have LF status compared with those without. Small LV was associated with a higher 2-year all-cause (20.8% versus 14.3%; adjusted hazard ratio [HR],1.58 [95% CI, 1.20–2.09]; *P*=0.0013) and cardiovascular mortality (8.8% versus 5.5%; adjusted HR, 1.93 [95% CI, 1.25–2.98]; *P*=0.0028). Propensity score matching analysis showed consistent findings. In subgroup analyses, LF, left ventricular hypertrophy did not interact with small LV.

CONCLUSIONS: Small LV, determined by a simple echocardiographic parameter, was associated with poorer clinical outcomes after TAVR regardless of LF, left ventricular hypertrophy. LV size may be useful for assessing clinical outcomes after TAVR.

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Key Words: heart failure ■ left ventricular end-diastolic dimension ■ left ventricular hypertrophy ■ propensity score matching ■ transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is an established therapy for symptomatic severe aortic stenosis.[1–6] However, deaths and heart failure readmissions after TAVR are still common, and the risk stratification is important.

Left ventricular size is an important prognostic indicator in cardiac diseases. It is well known that a dilated left ventricle (LV) is associated with poor outcomes in a variety of cardiac diseases.[7–10] However, there are few studies on the impact of a small LV on clinical outcomes.

TAVR for patients with small LV poses some difficulty with respect to placing LV wires, and there is a higher risk of left ventricular perforation.[11] Moreover,

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CLINICAL PERSPECTIVE

What Is New?

- In patients undergoing transcatheter aortic valve replacement, the impact of small left ventricle (LV) remains unknown.
- On the basis of the American Society of Echocardiography guidelines, small LV was defined as left ventricular end-diastolic dimension <42.0 mm for men or <37.8 mm for women.
- Small LV, determined by a simple echocardiographic parameter, was associated with poorer clinical outcomes after transcatheter aortic valve replacement regardless of low-flow, left ventricular hypertrophy.

What Are the Clinical Implications?

- LV size may be useful for assessing clinical outcomes after transcatheter aortic valve replacement.
- Patients with small LV should be monitored carefully.

Nonstandard Abbreviations and Acronyms

ASE	American Society of Echocardiography
LF	low flow
LVEDD	left ventricular end-diastolic dimension
LVMI	left ventricle mass index
PVL	paravalvular leak
RWT	relative wall thickness
TAVR	transcatheter aortic valve replacement

it is well known that those with small LV are more likely to have low-flow (LF) status, left ventricular hypertrophy (LVH). Given that these factors are associated with poor clinical outcomes after TAVR,[12,13] patients undergoing TAVR with small LV may have an increased risk of clinical outcomes. However, there are no studies on the association between small LV and clinical outcomes after TAVR. Therefore, this study will (1) investigate the association between small LV and clinical outcomes after TAVR and (2) perform subgroup analyses in situations where small LV may have a more adverse effect.

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.

Data Source

We analyzed the data from the OCEAN-TAVI (Optimized Transcatheter Valvular Intervention–Transcatheter Aortic Valve Implantation) registry.[14] A total of 2588 patients were enrolled in the OCEAN-TAVI registry between October 2013 and May 2017. The OCEAN-TAVI registry is a prospective, multicenter, observational registry of patients who underwent TAVR at 14 centers in Japan. The OCEAN-TAVI registry was registered with the University Hospital Medical Information Network Clinical Trial Registry and accepted by the International Committee of Medical Journal Editors (UMIN-ID: 000020423). All study participants provided informed consent, and the registry was approved by the ethics committees of all participating institutions. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research. Patients were followed up annually at the participating institutions. The events were site reported from the participating institutions. For ensuring consistency, the database was regularly audited by the data committee members.

The American Society of Echocardiography (ASE) guidelines are widely used worldwide. According to ASE guidelines, the normal reference values of left ventricular end-diastolic dimension (LVEDD) are 42.0 to 58.4 mm for men and 37.8 to 52.2 mm for women.[15] Therefore, small LV was defined as LVEDD <42.0 mm for men or <37.8 mm for women. Patients with missing values for LVEDD were excluded from the analysis.

Outcomes

The primary outcomes were 2-year all-cause and cardiovascular mortality after TAVR. The secondary outcomes were readmission attributable to heart failure within 2 years and in-hospital outcomes and complications. All-cause mortality, cardiovascular mortality, and complications were defined on the basis of the Valve Academic Research Consortium-2 criteria.[16]

Echocardiography

Transthoracic echocardiography was performed at baseline, before hospital discharge, and at the annual follow-up. All transthoracic echocardiographic parameters were measured according to ASE guidelines.[15,17,18] In addition, according to ASE guidelines, LV mass, LV mass index (LVMI), and relative wall thickness (RWT) were calculated as follows: LV mass=0.80×1.04×[(LVEDD+interventricular septum thickness+posterior wall thickness)^3–LVEDD^3]+0.6 g, LVMI=LV mass÷body surface area,

and RWT=(2×posterior wall thickness)÷LVEDD. The normal reference values of LVMI were defined as <95 g/m^2 for women and <115 g/m^2 for men. LV geometry was divided into 4 groups, as follows: normal (normal LVMI with RWT ≤0.42), concentric remodeling (normal LVMI with RWT >0.42), eccentric LVH (increased LVMI with RWT ≤0.42), and concentric LVH (increased LVMI with RWT >0.42). LF status was defined as stroke volume index <35 mL/m^2.

Statistical Analysis

We compared baseline characteristics between patients with small LV and nonsmall LV. Continuous variables were presented as medians and 25th to 75th percentile and compared using Student *t* test or Mann-Whitney *U*-test. Categorical variables were presented as frequencies and percentages and compared by the Pearson χ^2 test or the Fisher exact test.

There were missing data for baseline variables. Percentage of missing data for baseline variables is shown in Table S1. Multiple imputation was performed. Missing continuous variables were imputed using the predictive mean matching method. Missing binary variables were imputed using logistic regression models. Twenty imputed data sets were created. The log-rank test was performed to compare all-cause and cardiovascular mortality between groups. Thereafter, multivariable Cox regression analyses were performed to examine variables that were independently associated with all-cause and cardiovascular mortality. In multivariable analysis, incorporated variables were determined according to clinical relevance and previous studies[12,13,19–24] (full list of incorporated variables in multivariable analysis Data S1). The results of analyses in each imputed data set were pooled according to the Rubin rule.

To ensure robustness of the results, propensity score matching after multiple imputation was performed for small LV versus nonsmall LV. The propensity scores were calculated within each imputed data set using logistic regression models to estimate the probability of a small LV. Then, the propensity scores were averaged across imputed data sets for each patient. One-to-one propensity score matching without replacement on the original data was performed by the average propensity score with a caliper width of 0.2 of the SD of the logit of the average propensity score. Balance between the 2 groups was assessed by absolute standardized mean difference. The covariates included in the propensity score matching are listed in Table S2. The cumulative incidences of all-cause and cardiovascular mortality were calculated using the Kaplan-Meier method. The log-rank test was performed to compare all-cause and cardiovascular mortality between patients with small LV and nonsmall LV in the overall cohort and the matched cohort. Landmark analyses at 6 months were also performed. In addition, for heart failure admission, the Fine and Gray competing risk model was used because all-cause death was considered a competing risk factor.

Subgroup analyses were performed because it was hypothesized that the mortality of the patients with small LV was strongly affected by the presence of LF status, LVH. In addition, because patients with small LV had small body size, the parameters of frailty were also considered important. Subgroup analyses were performed for age (≥85 or <85 years), sex, body mass index (≥22 or <22 kg/m^2), albumin levels (≥3.5 or <3.5 g/dL), clinical frailty scale (1–4, 5–6, or ≥7), stroke volume index (≥35 or <35 mL/m^2), left ventricular ejection fraction (LVEF) (>40% or ≤40%), and LV geometry (normal, eccentric LVH, concentric remodeling, or concentric LVH). Subgroup analysis was also performed by postprocedural valve sizes and types. Interaction tests between each covariate were performed.

Furthermore, we hypothesized that small LV is less tolerant of paravalvular leak (PVL) than nonsmall LV. Therefore, patients were stratified by the presence or absence of PVL in the overall and matched cohort. In addition, in the overall and matched cohort, we further stratified PVL by severity, according to the Valve Academic Research Consortium-2 criteria: none, trace or mild, moderate, or severe. Kaplan-Meier curves and log-rank test were performed in each group.

Finally, we performed the sensitivity analyses with LVEDD and LVEDD/body surface area as a continuous variable. Also, we performed the sensitivity analysis with a single cut point of LVEDD (<40 mm). Cox regression analyses were performed for all-cause and cardiovascular mortality.

All statistical analyses were performed using R software version 3.6.1. All tests were 2 sided, and $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

After excluding 4 patients with missingness for LVEDD, the remaining 2584 patients were divided on the basis of small LV or nonsmall LV at baseline. Among the 2584 patients, LV size in 466 (18.0%) was small. The differences in baseline characteristics are shown in Table 1. Patients with small LV had smaller body and fewer comorbidities compared with those without small LV. Echocardiography in patients with small LV showed greater LVEF, smaller left atrial dimension, lower rates of moderate or severe valvular disease, and

Table 1. Baseline Characteristics

Characteristics	Small LV (n=466)	Nonsmall LV (n=2118)	*P* Value
Clinical data			
Age, y	85 (82–88)	85 (81–88)	0.086
Men	150 (32.2)	643 (30.4)	0.44
Body mass index, kg/m^2	21.1 (18.5–23.5)	22.3 (20.0–24.6)	<0.001
Body surface area, m^2	1.36 (1.26–1.50)	1.41 (1.30–1.55)	<0.001
NYHA class 3 or 4	220 (47.2)	1098 (51.8)	0.07
Hypertension	353 (75.8)	1634 (77.1)	0.52
Dyslipidemia	177 (38.0)	935 (44.1)	0.015
Diabetes mellitus	83 (17.8)	472 (22.3)	0.033
Chronic kidney disease	288 (61.8)	1518 (71.7)	<0.001
Previous stroke	56 (12.0)	245 (11.6)	0.78
COPD	68 (14.6)	317 (15.0)	0.84
Peripheral artery disease	74 (15.9)	303 (14.3)	0.38
Coronary artery disease	163 (35.0)	788 (37.2)	0.37
Previous CABG	22 (4.7)	147 (6.9)	0.079
Atrial fibrillation	92 (19.7)	457 (21.6)	0.38
Permanent pacemaker	22 (4.7)	144 (6.8)	0.098
Active cancer	22 (4.7)	101 (4.8)	0.97
Clinical frailty scale score			0.27
1–4	334 (71.7)	1567 (74.0)	
5–6	108 (23.2)	474 (22.4)	
7–8	24 (5.2)	77 (3.6)	
STS risk score, %	6.59 (4.57–8.90)	6.54 (4.53–9.61)	0.34
Transfemoral approach	375 (80.5)	1788 (84.4)	0.037
Hemoglobin, g/dL	11.4 (10.1–12.6)	11.2 (10.1–12.4)	0.009
eGFR, mL/min per 1.73 m^2	54.9 (40.7–68.0)	49.8 (37.0–62.0)	<0.001
Albumin, g/dL	3.70 (3.40–4.00)	3.80 (3.50–4.10)	0.001
Albumin <3.5 g/dL	123 (26.4)	493 (23.3)	0.15
Brain natriuretic peptide, pg/mL	189 (91–442)	286 (127–598)	<0.001
Echocardiographic data			
Aortic valve area, cm^2	0.62 (0.50–0.72)	0.63 (0.50–0.75)	0.15
Peak velocity, m/s	4.40 (4.00–5.00)	4.54 (4.08–5.10)	0.007
Mean pressure gradient, mm Hg	46.0 (35.0–59.0)	48.2 (38.5–62.0)	0.003
LV end-diastolic dimension, mm	36.3 (35.0–37.5)	45.0 (42.0–49.0)	<0.001
LV end-systolic dimension, mm	23.0 (21.0–25.0)	29.0 (26.0–34.0)	<0.001
Left atrial dimension, mm	38.0 (33.0–42.1)	42.6 (38.9–47.0)	<0.001
IVS, mm	12.0 (11.0–13.0)	11.8 (10.2–13.0)	0.001
PWT, mm	11.5 (10.0–13.0)	11.0 (10.0–12.1)	0.017
Relative wall thickness, mm	0.63 (0.55–0.71)	0.49 (0.43–0.56)	<0.001
LV mass index, g/m^2	99.8 (84.3–117.9)	132.1 (110.6–154.7)	<0.001
LV geometry			<0.001
Normal	5 (1.1)	77 (3.6)	
Eccentric LVH	0 (0)	335 (15.8)	
Concentric LVH	220 (47.2)	1455 (68.8)	
Concentric remodeling	241 (51.7)	212 (10.0)	
LVEF, %	64.9 (60.0–69.0)	61.0 (50.7–67.7)	<0.001
LVEF ≤40%	9 (1.9)	235 (11.1)	<0.001
E/A	0.67 (0.56–0.80)	0.70 (0.57–0.90)	0.002

(*Continued*)

Table 1. Continued

Characteristics	Small LV (n=466)	Nonsmall LV (n=2118)	*P* Value
E/e′	19.2 (14.5–25.0)	19.9 (15.5–25.5)	0.028
Deceleration time, ms	248 (201–316)	239 (183–306)	0.009
SVi, mL/m^2	40.8 (30.5–50.4)	45.4 (36.9–54.4)	<0.001
SVi <35 mL/m^2	152 (36.0)	381 (19.7)	<0.001
Systolic pulmonary artery pressure, mm Hg	29.0 (25.0–36.0)	31.0 (25.2–39.0)	0.009
Aortic regurgitation ≥ moderate	29 (6.2)	243 (11.5)	0.001
Mitral regurgitation ≥ moderate	18 (6.0)	161 (12.4)	<0.001
Tricuspid regurgitation ≥ moderate	30 (6.4)	173 (8.2)	0.21

Data are shown as median (25th–75th percentile) for continuous variables and number (percentage) for categorical variables. CABG indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IVS, interventricular septum thickness; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; PWT, posterior wall thickness; STS, Society of Thoracic Surgeons; and SVi, stroke volume index.

higher rates of LF status compared with those without. Also, patients with small LV had stronger RWT but less LVMI.

In-Hospital Outcomes and Complications

In-hospital outcomes and complications are shown in Table 2. The 30-day death was more frequent in patients with small LV group than those without. Patients with small LV were implanted with a smaller valve and had a lower incidence of prosthesis-patient mismatch than patients with nonsmall LV.

All-Cause and Cardiovascular Mortality Within 2 Years

Kaplan-Meier curves of all-cause and cardiovascular mortality in overall cohort are shown in Figure 1A. The

Table 2. In-Hospital Outcomes and Postprocedural Echocardiographic Data

Variables	Small LV (n=466)	Nonsmall LV (n=2118)	*P* Value
Procedural outcomes			
30-d death	14 (3.0)	32 (1.5)	0.027
Procedural MI	2 (0.4)	17 (0.8)	0.393
Stroke	14 (3.0)	47 (2.2)	0.312
Bleeding	128 (27.5)	492 (23.2)	0.052
AKI	51 (10.9)	238 (11.2)	0.856
Vascular complication	40 (8.6)	193 (9.1)	0.716
New permanent pacemaker	32 (6.9)	179 (8.5)	0.258
New-onset atrial fibrillation	19 (4.1)	83 (4.0)	0.869
Conversion to open surgery	8 (1.7)	17 (0.8)	0.11
PPM	30 (7.0)	222 (11.2)	0.010
PVL ≥ moderate	12 (2.6)	37 (1.8)	0.224
Valve			0.035
Corevalve	38 (8.2)	157 (7.4)	
Evolut R	36 (7.7)	112 (5.3)	
Sapien XT	262 (56.2)	1136 (53.6)	
Sapien 3	130 (27.9)	713 (33.7)	
Valve size, mm			0.001
20	21 (4.5)	77 (3.6)	
23	273 (7.7)	112 (5.3)	
26	140 (30.0)	769 (36.3)	
29	32 (6.9)	220 (10.4)	

Data are shown as number (percentage). AKI indicates acute kidney injury; LV, left ventricle; MI, myocardial infarction; PPM, prosthesis-patient mismatch; and PVL, paravalvular leak.

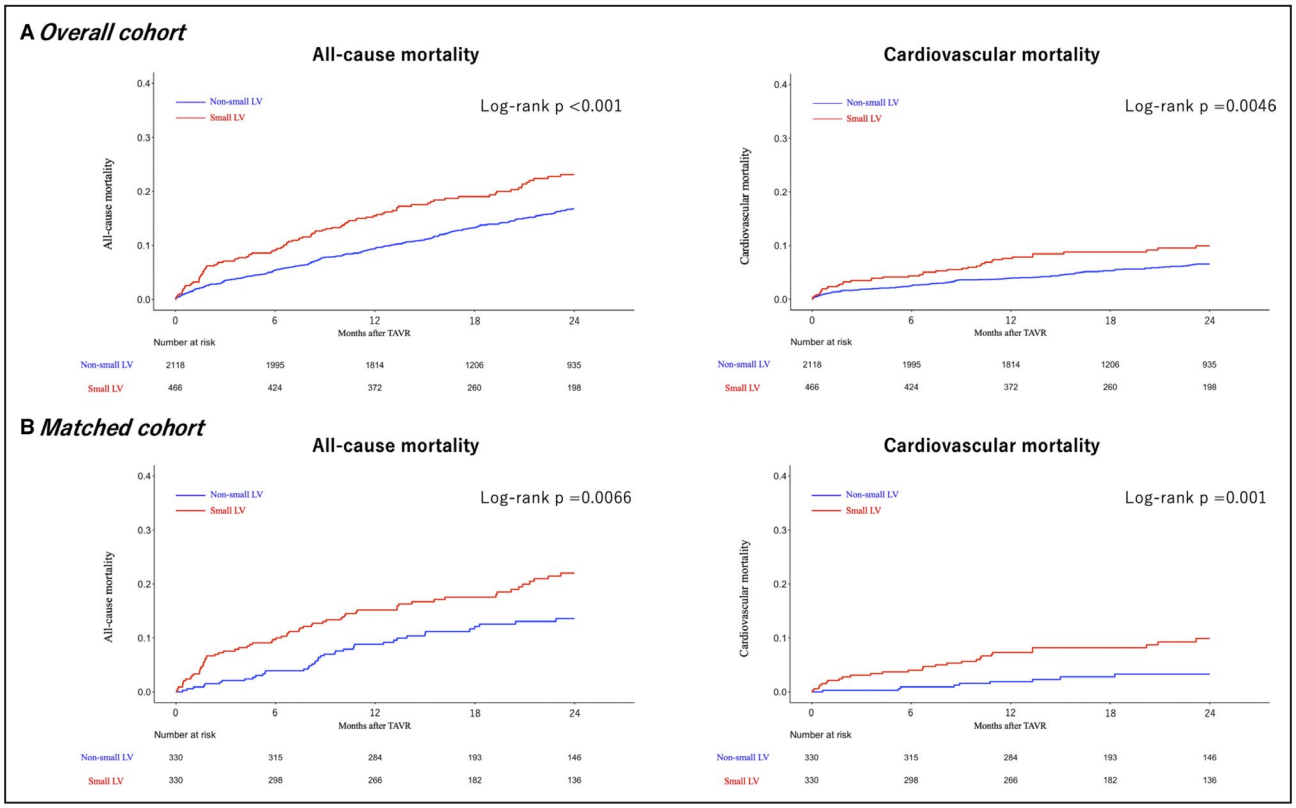

Figure 1. Kaplan-Meier curve of all-cause and cardiovascular mortality in overall cohort and the matched cohort.
The 2-year all-cause and cardiovascular mortality of patients with small left ventricle (LV) compared with those without in the overall cohort (**A**) and matched cohort (**B**). TAVR indicates transcatheter aortic valve replacement.

median follow-up period was 673 (25th–75th percentile, 381–865) days. There were 401 patients who died of all-cause mortality and 157 who died of cardiovascular causes, during the follow-up period. There was a significant difference between the 2 groups in 2-year all-cause (log-rank *P*<0.001) and cardiovascular mortality (log-rank *P*=0.0046).

After the adjustment for cofounders, small LV was still significantly associated with a higher risk of 2-year all-cause mortality (adjusted hazard ratio [HR], 1.58; 95% CI, 1.20–2.09; *P*=0.0013) and cardiovascular mortality (adjusted HR, 1.93; 95% CI, 1.25–2.98; *P*=0.0028) (Table 3). The full univariable and multivariable model results are shown in Tables S3 and S4.

Propensity score matching was performed, with a total of 660 patients matched (Table S2). Absolute standardized mean difference was <0.1 in all examined covariates in the matched cohort. In the matched cohort, there were significant differences between the 2 groups in 2-year all-cause mortality (log-rank *P*=0.0066) and cardiovascular mortality (log-rank *P*=0.001) (Figure 1B). For heart failure readmission, Fine and Gray competing risk models in the overall and matched cohort are shown in Figure 2. Small LV was significantly associated with a higher incidence of heart failure readmission (Gray *P*=0.032).

The results of landmark analyses for all-cause and cardiovascular mortality are shown in Figure S1. There was significant difference in all-cause and cardiovascular mortality within 6 months after TAVR, but the difference was not obvious afterwards. The result was consistent in both the overall and matched cohorts.

Table 3. Unadjusted and Adjusted All-Cause and Cardiovascular Mortality Within 2 Years

	Small LV			
	Unadjusted		Adjusted	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause mortality	1.51 (1.20–1.90)	<0.001	1.58 (1.20–2.09)	0.0013
Cardiovascular mortality	1.66 (1.17–2.38)	0.005	1.93 (1.25–2.98)	0.0028

HR indicates hazard ratio; and LV, left ventricle.

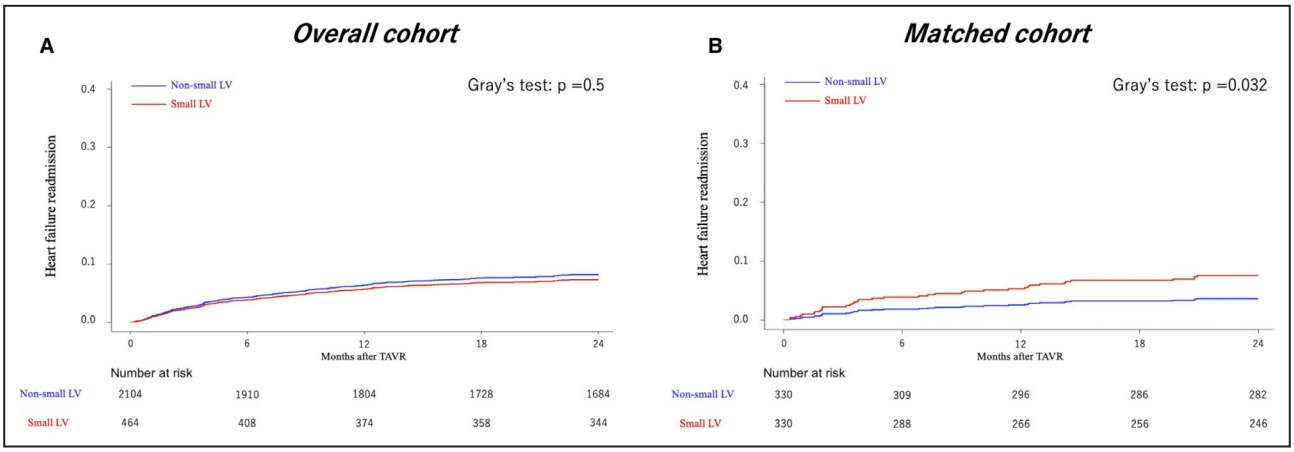

Figure 2. Heart failure readmission after transcatheter aortic valve replacement (TAVR).
Fine and Gray competing risk model for heart failure readmission after TAVR in patients with small left ventricle (LV) compared with those without in the overall (**A**) and matched cohort (**B**).

Subgroup Analyses

Subgroup analyses for all-cause and cardiovascular mortality are shown in Figures 3 and 4. There were no significant interactions between small LV and prespecified subgroups, except for age, including LF status, LV geometry, or frailty, in both all-cause and cardiovascular mortality. There were no significant interactions between small LV and valve sizes or valve types in both all-cause and cardiovascular mortality (Figure S2).

Subgroup	No. of patients	No. of event/total no. of patients		Hazard ratio (95% CI)	p for interaction
		Non-small LV	Small LV		
Overall	2554	304/2118	97/466	1.51(1.20-1.90)	
Age <85yrs	1249	131/1032	47/217	1.77(1.27-2.47)	p =0.2
Age ≥85yrs	1335	173/1086	50/249	1.31(0.96-1.80)	
Male	793	124/643	40/150	1.44(1.01-2.05)	p =0.79
Female	1791	180/1475	57/316	1.53(1.14-2.06)	
BMI <22kg/m²	1281	167/998	65/283	1.43(1.07-1.90)	p =0.89
BMI ≥22kg/m²	1303	137/1120	32/183	1.47(1.00-2.16)	
Alb <3.5 g/dl	616	126/493	47/123	1.58(1.13-2.21)	p =0.54
Alb ≥3.5 g/dl	1968	178/1625	50/343	1.37(1.00-1.88)	
CFS 1-4	1901	184/1567	51/334	1.33(0.98-1.82)	
CFS 5,6	582	93/474	34/108	1.73(1.17-2.56)	p =0.35
CFS ≥7	101	27/77	12/24	1.49(0.76-2.95)	
SVi <35 ml/m²	533	71/381	37/152	1.32(0.89-1.97)	p =0.87
SVi ≥35 ml/m²	1827	208/1557	48/270	1.38(1.01-1.89)	
LVEF ≤40 %	244	46/235	1/9	0.56(0.08-4.09)	p =0.29
LVEF >40 %	2340	258/1883	96/457	1.61(1.27-2.04)	
LV geometry					
Normal	119	24/114	2/5	2.29(0.54-9.69)	p =0.73
Eccentric LVH	335	58/335	0	NA	
Concentric remodeling	453	20/212	46/241	2.10(1.24-3.55)	
Concentric LVH	1675	201/1455	49/220	1.68(1.23-2.30)	

Figure 3. Subgroup analysis of all-cause mortality within 2 years.
Forest plot representing the hazard ratios of 2-year all-cause mortality in patients with small left ventricle (LV) compared with patients without, stratified by preprocedural characteristics. Alb indicates albumin; BMI, body mass index; CFS, clinical frailty score; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NA, not applicable; and SVi, stroke volume index.

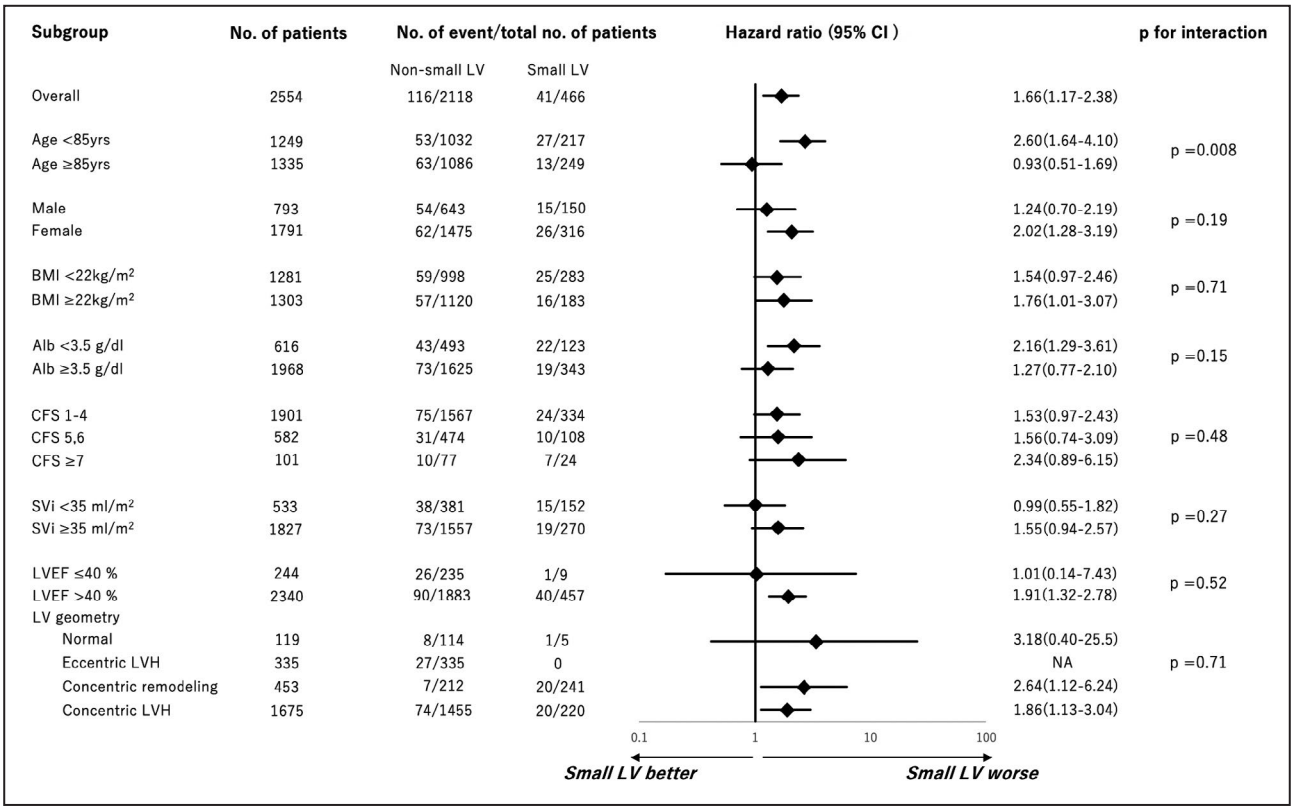

Figure 4. Subgroup analysis for cardiovascular mortality within 2 years.
Forest plot representing the hazard ratios of 2-year cardiovascular mortality in patients with small left ventricle (LV) compared with patients without, stratified by preprocedural characteristics. Alb indicates albumin; BMI, body mass index; CFS, clinical frailty score; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NA, not applicable; and SVi, stroke volume index.

All-Cause Mortality, Stratified by the Presence or Absence of PVL

Kaplan-Meier curves of all-cause mortality in each group are shown in Figure 5. In the overall cohort, there was a significant difference in all-cause mortality between the patients with and without small LV in the group with PVL (log-rank *P*=0.0017) (Figure 5A). However, there was no significant difference in all-cause mortality between patients with and without small LV in the group with no PVL (log-rank *P*=0.39). Findings were consistent in the analysis using the matched cohort (Figure 5B). Analysis by severity of PVL showed a significant difference in the rates of those with trace or mild PVL between those with small LV and nonsmall LV (Figure S3), whereas the difference in the rates of those with non-PVL and moderate or severe PVL was not apparent between groups, likely because of the small number of those with moderate or severe PVL.

Sensitivity Analyses

Results of the sensitivity analyses are shown in Tables S5 through S7. Smaller LVEDD and LVEDD/body surface area were consistently associated with increased all-cause and cardiovascular mortality, even when LVEDD and LVEDD/body surface area were treated as continuous variables. A single cut point of LVEDD <40 mm was also significantly associated with a higher risk of 2-year all-cause mortality (adjusted HR, 1.57; 95% CI, 1.21–2.07; *P*<0.001) and cardiovascular mortality (adjusted HR, 1.74; 95% CI, 1.18–2.56; *P*=0.005).

DISCUSSION

The impact of a small LV on patients undergoing TAVR remains unknown. The main findings of our study showed that small LV, determined by a simple echocardiographic parameter, was associated with poorer clinical outcomes. To the best of our knowledge, this study is the first to identify the association between small LV and clinical outcomes after TAVR.

There are few studies on the impact of a small LV on clinical outcomes. We hypothesized that a higher mortality of patients with small LV was strongly influenced by LF status, LVH, and frailty. Previous studies reported that LF status and frailty were associated with a high risk of mortality after TAVR,[12,20,21] whereas it is

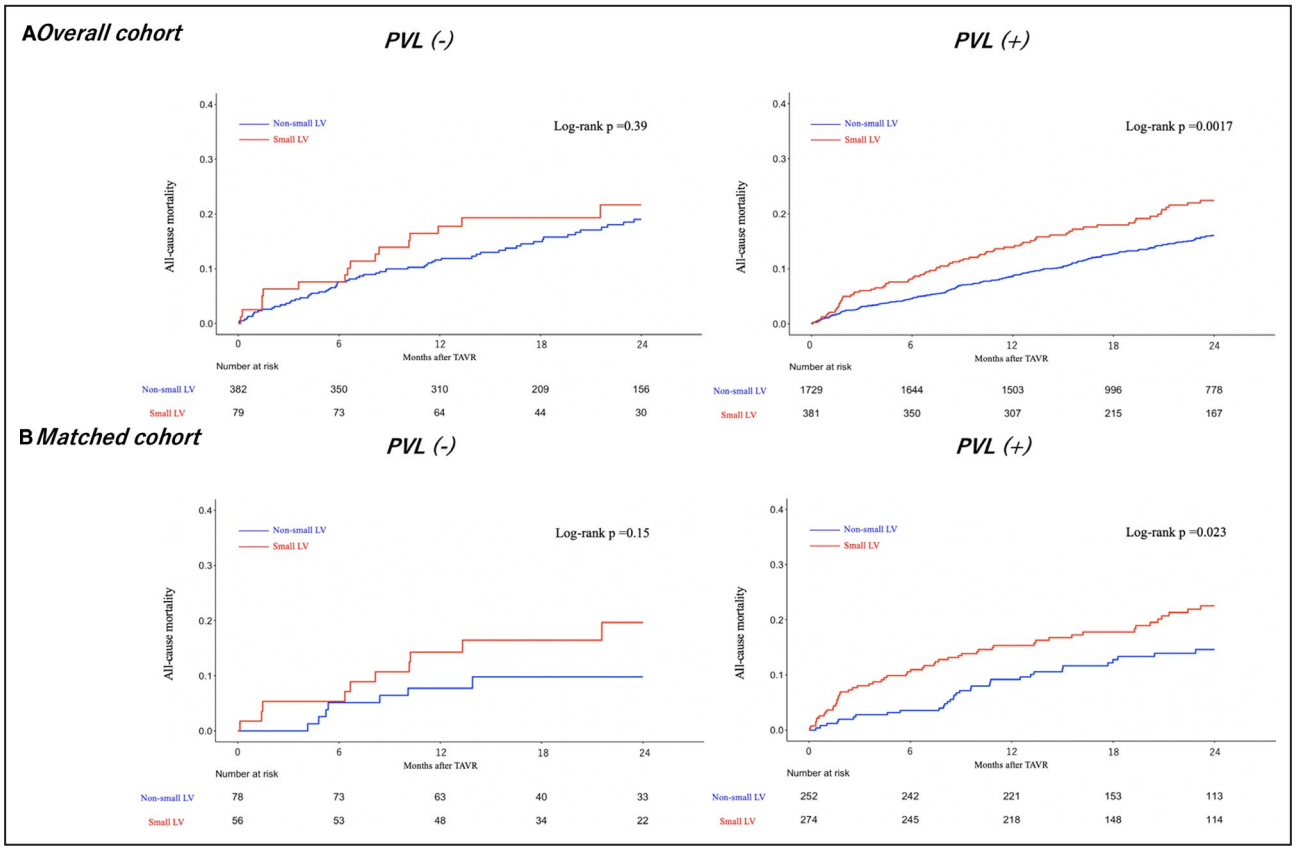

Figure 5. All-cause mortality, stratified by the presence or absence of paravalvular leak (PVL).
All-cause mortality of patients with small left ventricle (LV) compared with those without in groups with the absence and the presence of PVL in the overall (**A**) and matched cohort (**B**). TAVR indicates transcatheter aortic valve replacement.

not clear if baseline LVH has an impact on mortality in patients undergoing TAVR.[13,25,26] In our analysis, even after the adjustment for LF status, LVH, and frailty, small LV was associated with the increased risks of all-cause and cardiovascular mortality, and heart failure readmission. Furthermore, subgroup analyses showed that there was no interaction between small LV and LF status, LVH, and frailty.

There are some potential explanations for the association of small LV and poorer clinical outcomes. First, small LV may be more intolerant of volume overloads. Even with the same degree of PVL, small LV may have a stronger volume overload than nonsmall LV. As a result, patients with small LV readily develop heart failure, and are more likely to die because of the heart failure. In our study, patients with small LV had higher mortality in the group with PVL, and there was no significant difference in the group with no PVL. Colli et al reported that preoperative LV dilatation was associated with better outcomes in the cases with PVL.[27] Efforts to minimize PVL, such as the choice of an appropriate valve and postdilatation, may be necessary in patients with small LV. In addition, intraoperative transesophageal echocardiography to avoid missing PVL may be considered. Second, left ventricular outflow tract obstruction may more frequently occur in patients with small LV after improvement of afterload with severe aortic stenosis by TAVR. Third, there may be less benefit from regression of hypertrophy in patients with small LV. In our study, patients with small LV had a lower LV mass index and lower incidence of LVH at baseline than in those without. The absence of LVH was associated with worse outcomes because LV could not adequately respond to pressure overloads by severe aortic stenosis.[28] It was reported that lower LV mass regression was associated with worse clinical outcomes following TAVR.[29,30]

In our study, patients with small LV had higher LVEF and lower brain natriuretic peptide. Intuitively, the combination of higher LVEF and lower brain natriuretic peptide seems to contribute to better clinical outcomes; however, Chen et al reported, compared with patients with normal brain natriuretic peptide values, those with lower brain natriuretic peptide as well as higher were associated with worse prognosis after TAVR.[31] Also, Wehner et al showed that the HR of all-cause mortality was lowest at LVEF 60% to 65% and patients with LVEF ≥65% had a higher mortality.[32] In our study

population, half of patients with small LV have LVEF >65%. Given these previous reports, small LV may be an unfavorable factor in terms of prognosis after TAVR.

Given the robust association between small LV and the increased risk of mortality and heart failure readmission, LVEDD may be a useful marker of clinical outcomes after TAVR. There are advantages of using LVEDD as an indicator of clinical outcomes. LVEDD is often measured routinely in most patients with severe aortic stenosis. Furthermore, the measurement of LVEDD has a small error, unlike the measurement of stroke volume, which requires the measurement of left ventricular outflow tract diameter. Moreover, it does not require complex calculations, like LVMI. LVEDD is a simple indicator with high versatility.

Study Limitations

Our study has several limitations. First, this is a nonrandomized, retrospective study using data from a prospective multicenter cohort registry. There is a possibility that unknown and unmeasurable confounders exist. Second, there was no clear definition of small LV. In our study, small LV was defined according to the normal reference values of LVEDD of the ASE guidelines. Third, LV end-diastolic volume and LV end-systolic volume by the modified Simpson method were not used because of insufficient data in the registry. Fourth, the echocardiographic data were site reported from the participating institutions and not adjudicated by the clinical event adjudication committee. Thus, there may have been some variations in interpretation of the left ventricular dimension measurements between institutions. Fifth, there was not enough data of the other parameters of diastolic dysfunction, such as septal or lateral é, left atrial volume, and frailty markers, such as gait speed and strength of hand grip. The grade of diastolic dysfunction is associated with worse outcomes.[22–24] In addition, patients with small LV had small body size. Therefore, the markers of frailty were important. More meticulous studies that consider these should be our future targets.

CONCLUSIONS

Small LV, determined by a simple echocardiographic parameter, was associated with poorer clinical outcomes after TAVR. To stratify the risk after TAVR, the size of the LV may be important, and further investigation will be required to corroborate our findings.

ARTICLE INFORMATION

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Disclosures

Dr Yamamoto, Dr Tada, Dr Naganuma, Dr Shirai, Dr Mizutani, Dr Watanabe, Dr Tabata, and Dr Ueno are clinical proctors for Edwards Lifesciences and Medtronic. Dr Takagi, Dr Shimizu, and Dr Hayashida are clinical proctors of Edwards Lifesciences. The remaining authors have no disclosures to report.

Supplementary Material

Data S1
Tables S1–S7
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

In multivariable analysis of all-cause mortality, the variables used for model adjustment were age, sex, body mass index, New York Heart Association functional class 3 or 4, dyslipidemia, chronic kidney disease, atrial fibrillation, chronic obstructive pulmonary disease, peripheral artery disease, coronary artery disease, active cancer, clinical frailty scale, transfemoral approach, hemoglobin, albumin <3.5 g/dl, brain natriuretic peptide, peak velocity, mean pressure gradient, LV geometry, left ventricular ejection fraction ≤40%, deceleration time, SVi <35 ml/m2, systolic pulmonary artery pressure, mitral regurgitation ≥moderate, tricuspid regurgitation ≥moderate. In multivariable analysis of cardiovascular mortality, the variables used for model adjustment were age, sex, body mass index, New York Heart Association functional class 3 or 4, chronic kidney disease, atrial fibrillation, previous coronary artery bypass grafting, clinical frailty scale, transfemoral approach, albumin <3.5 g/dl, brain natriuretic peptide, LV geometry, left ventricular ejection fraction ≤40%, SVi <35 ml/m2, systolic pulmonary artery pressure, tricuspid regurgitation ≥moderate.

Table S1. Percentage of missing value.

Variables	Percentage of missing value (%)
Systolic pulmonary artery pressure	15.1
E/e'	13.1
Brain natriuretic peptide	12.8
Stroke volume index	8.7
Deceleration time	8.7
Left ventricular end-systolic dimension	0.27
Aortic valve area	0.08
Mean pressure gradient	0.08
Left ventricular geometry	0.08
Interventricular septum thickness	0.04
Posterior wall thickness	0.04
Aortic regurgitation	0.04

Table S2. Covariables before and after propensity score matching.

	Before propensity score matching			After propensity score matching		
	Small LV n = 466	Non-small LV n = 2118	Absolute SMD	Small LV n = 330	Non-small LV n = 330	Absolute SMD
Clinical data						
Age, yrs	85.0 (82.0-88.0)	85.0 (81.0-88.0)	0.089	85.0 (81.3-88.0)	85.0 (82.0-88.0)	0.016
Male	150 (32.2)	643 (30.4)	0.039	104 (31.5)	104 (31.5)	<0.001
Body mass index, kg/m^2	21.1 (18.5-23.5)	22.3 (20.0-24.6)	0.37	21.4 (19.0-24.0)	21.7 (19.2-23.7)	0.006
Body surface area, m^2	1.36 (1.26-1.50)	1.41 (1.30-1.55)	0.36	1.40 (1.29-1.50)	1.40 (1.28-1.50)	0.039
NYHA 3 or 4	220 (47.2)	1098 (51.8)	0.093	156 (47.3)	141 (42.7)	0.09
Hypertension	353 (75.8)	1634 (77.1)	0.033	225 (77.3)	252 (76.7)	0.014
Dyslipidemia	177 (38.0)	935 (44.1)	0.13	135 (40.9)	134 (40.6)	0.006
Diabetes mellitus	83 (17.8)	472 (22.3)	0.11	65 (19.7)	66 (20.0)	0.008
Chronic kidney disease	288 (61.8)	1518 (71.7)	0.21	219 (66.4)	210 (63.6)	0.057
Previous stroke	56 (12.0)	245 (11.6)	0.014	42 (12.7)	35 (10.6)	0.066
COPD	68 (14.6)	317 (15.0)	0.011	50 (15.2)	42 (12.7)	0.07
Peripheral artery disease	74 (15.9)	303 (14.3)	0.044	46 (13.9)	53 (16.1)	0.059
Coronary artery disease	163 (35.0)	788 (37.2)	0.046	116 (35.2)	116 (35.2)	<0.001

Previous CABG	22 (4.7)	147 (6.9)	0.095	20 (6.1)	18 (5.5)	0.026
Atrial fibrillation	92 (19.7)	457 (21.6)	0.045	63 (19.1)	69 (20.9)	0.045
Permanent pacemaker	22 (4.7)	144 (6.8)	0.089	18 (5.5)	13 (3.9)	0.072
Active cancer	22 (4.7)	101 (4.8)	0.002	13 (3.9)	18 (5.5)	0.072
Clinical frail score			0.079			0.017
1-4	334 (71.7)	1567 (74.0)		236 (71.5)	236 (71.5)	
5,6	108 (23.2)	474 (22.4)		83 (25.2)	82 (24.8)	
7,8	24 (5.2)	77 (3.6)		11 (3.3)	12 (3.6)	
STS score, %	6.59 (4.57-8.90)	6.54 (4.53-9.61)	0.051	6.47(4.57-8.90)	6.20(4.44-9.10)	0.078
Hemoglobin, g/dl	11.4 (10.1-12.6)	11.2 (10.1-12.4)	0.13	11.3 (10.0-12.7)	11.5 (10.2-12.7)	0.09
eGFR, ml/min/1.73m^2	54.95(40.75-68.00)	49.88 (37.0-62.09)	0.23	51.8 (38.6-65.4)	54.3 (40.5-65.3)	0.06
Albumin, g/dl	3.70 (3.40-4.00)	3.80(3.50-4.10)	0.15	3.70 (3.40-4.00)	3.80 (3.50-4.00)	0.045
Albumin <3.5g/dl	123 (26.4)	493 (23.3)	0.072	86 (26.1)	79 (23.9)	0.049
BNP, pg/ml	189.2 (91.1-442.3)	286.0 (127.6-598.4)	0.31	191 (97.2-443)	207 (98.7-417)	0.035
Transfemoral approach	375 (80.5)	1788 (84.4)	0.1	270 (81.8)	275 (83.3)	0.04
Echocardiographic data						
Aortic valve area, cm^2	0.62 (0.50-0.72)	0.63 (0.50-0.75)	0.081	0.63 (0.52-0.73)	0.62 (0,51-0.73)	0.025
Peak velocity, m/s	4.40 (4.00-5.00)	4.54 (4.08-5.10)	0.12	4.41 (4.00-5.03)	4.46 (4.00-4.96)	0.034
Mean pressure gradient, mmHg	46.0 (35.0-59.0)	48.2 (38.5-62.0)	0.14	46.0(36.0-60.0)	45.1 (37.0-58.9)	0.026

Left atrial dimension, mm	38.0 (33.0-42.1)	42.6 (38.9-47.0)	0.69	39.6 (35.0-43.1)	40.0 (36.0-44.0)	0.03
IVS, mm	12.0 (11.0-13.0)	11.8 (10.2-13.0)	0.2	12.0 (11.0-13.0)	12.0 (10.9-13.0)	0.099
PWT, mm	11.5 (10.0-13.0)	11.0 (10.0-12.1)	0.12	11.0 (10.0-13.0)	11.5 (10.2-12.4)	0.063
LVEF, %	64.9 (60.0-69.0)	61.0 (50.7-67.7)	0.49	64.0 (58.0-69.4)	64.0 (59.0-68.0)	0.026
LVEF ≤40%	9 (1.9)	235 (11.1)	0.38	7 (2.1)	5 (1.5)	0.045
E/A	0.67 (0.56-0.80)	0.70 (0.57-0.90)	0.16	0.68 (0.56-0.80)	0.65 (0.54-0.80)	0.095
E/e`	19.2 (14.5-25.0)	19.9 (15.5-25.5)	0.13	19.2 (14.6-24.2)	19.0 (14.5-24.3)	0.043
Deceleration time	248 (201-316)	239 (183-306)	0.11	248 (202-310)	255 (194-311)	0.046
SVi, ml/m^2	40.8 (30.5-50.4)	45.4 (36.9-54.4)	0.4	43.1 (33.6-50.9)	43.5 (34.1-52.9)	0.09
SVi <35ml/m^2	152 (36.0)	381 (19.7)	0.37	79 (26.5)	87 (28.8)	0.051
Systolic pulmonary artery pressure, mmHg	29.0 (25.0-36.0)	31.0 (25.2-39.0)	0.17	29.0 (25.0-36.0)	29.1 (25.0-36.0)	0.057
AR ≥moderate	29 (6.2)	243 (11.5)	0.19	23 (7.0)	23 (7.0)	<0.001
MR ≥moderate	18 (6.0)	161 (12.4)	0.22	24 (7.3)	29 (8.8)	0.056
TR ≥moderate	30 (6.4)	173 (8.2)	0.067	21 (6.4)	21 (6.4)	<0.001

Data are shown as median (25th-75th percentile) for continuous variables and number (percentage) for categorical variables. AR indicates aortic regurgitation; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IVS, interventricular septum thickness; LV, left ventricle; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PWT, posterior wall thickness; SMD, standardized mean difference; STS, Society of Thoracic Surgeons; SVi, stroke volume index; and TR, tricuspid regurgitation.

Table S3. Full univariable and multivariable model results of 2-year all-cause mortality.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Small LV	1.51 (1.20-1.90)	<0.001	1.58 (1.20-2.09)	0.0013
Age (per 1 yrs increase)	1.01 (0.99-1.03)	0.2	0.98 (0.96-1.00)	0.14
Male	1.65 (1.35-2.01)	<0.001	1.99 (1.59-2.48)	<0.001
Body mass index (per 1kg/m^2 increase)	0.93 (0.90-0.95)	<0.001	0.97 (0.94-0.99)	0.025
NYHA 3 or 4	1.86 (1.52-2.28)	<0.001	1.38 (1.11-1.72)	0.004
Dyslipidemia	0.69 (0.56-0.84)	<0.001	0.78 (0.63-0.97)	0.029
Diabetes mellitus	1.16 (0.92 (1.46)	0.2		
Chronic kidney disease	1.53 (1.21-1.92)	<0.001	1.33 (1.04-1.71)	0.023
Atrial fibrillation	1.41 (1.13-1.76)	0.003	0.96 (0.74-1.20)	0.65
COPD	1.59 (1.25-2.02)	<0.001	1.28 (1.00-1.67)	0.051
Peripheral artery disease	1.85 (1.46-2.33)	<0.001	1.28 (0.99-1.65)	0.054
Coronary artery disease	1.27 (1.04-1.55)	0.02	1.13 (0.91-1.40)	0.26
Previous CABG	1.37 (0.96-1.94)	0.082		
Active cancer	1.76 (1.22-2.52)	0.005	1.96 (1.34-2.84)	<0.001
Clinical frailty scale (per 1 group increase)	1.36 (1.27-1.46)	<0.001	1.25 (1.16-1.36)	<0.001
Transfemoral approach	0.65 (0.52-0.82)	<0.001	0.76 (0.59-0.97)	0.031
Hemoglobin (per 1g/dl increase)	0.82 (0.76-0.86)	<0.001	0.87 (0.81-0.93)	<0.001
Albumin <3.5g/dl	2.82 (2.31-3.44)	<0.001	1.71 (1.37-2.15)	<0.001
Brain natriuretic peptide (per 1pg/ml increase)	1.00 (1.00-1.00)	0.079	0.99 (0.99-1.00)	0.66
Peak velocity (per 1m/s increase)	0.77 (0.68-0.88)	<0.001	0.79 (0.54-1.15)	0.22
Mean pressure gradient (per 1mmHg increase)	0.99 (0.98-0.99)	<0.001	1.00 (0.99-1.02)	0.56

Left atrial dimension (per 1mm increase)	1.01 (0.99-1.03)	0.08		
Concentric Remodeling (for normal)	0.94 (0.72-1.22)	0.6	0.62 (0.38-1.02)	0.063
Concentric LVH (for normal)	0.88 (0.72-1.07)	0.2	0.79 (0.51-1.21)	0.28
Eccentric LVH (for normal)	1.16 (0.88-1.53)	0.3	0.84 (0.51-1.36)	0.47
LVEF ≤40%	1.38 (1.02-1.87)	0.04	0.80 (0.55-1.16)	0.23
E/e` (per 1 increase)	1.00 (0.99-1.01)	0.8		
Deceleration time (per 1sec increase)	0.99 (0.99-0.99)	0.02	0.99 (0.99-1.00)	0.5
SVi <35 ml/m^2	1.46 (1.17-1.82)	<0.001	1.17 (0.87-1.55)	0.29
Systolic pulmonary artery pressure (per 1mmHg increase)	1.02 (1.01-1.03)	<0.001	1.01 (0.99-1.02)	0.29
Mitral regurgitation ≥moderate	1.45 (1.10-1.91)	0.01	0.95 (0.69-1.30)	0.73
Tricuspid regurgitation ≥moderate	2.76 (2.12-3.59)	<0.001	2.12 (1.53-2.95)	<0.001

CABG indicates coronary artery bypass grafting; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; and SVi, stroke volume index.

Table S4. Full univariable and multivariable model results of 2-year cardiovascular mortality.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
small LV	1.66 (1.17-2.38)	0.005	1.93 (1.25-2.98)	0.0028
Age (per 1 yrs increase)	0.99 (0.96-1.02)	0.57	0.97 (0.95-1.01)	0.12
Male	1.85 (1.35-2.54)	<0.001	2.07 (1.48-2.89)	<0.001
Body mass index (per 1kg/m^2 increase)	0.95 (0.91-0.99)	0.034	0.98 (0.94-1.03)	0.39
NYHA 3 or 4	2.21 (1.58-3.09)	<0.001	1.68 (1.17-2.41)	0.005
Dyslipidemia	0.89 (0.65-1.23)	0.89		
Diabetes mellitus	1.33 (0.93-1.89)	0.11		
Chronic kidney disease	1.65 (1.13-2.42)	0.01	1.50 (1.00-2.23)	0.048
Atrial fibrillation	1.47 (1.03-2.08)	0.032	0.98 (0.68-1.40)	0.89
COPD	1.43 (0.97-2.12)	0.073		
Peripheral artery disease	1.97 (1.37-2.84)	<0.001		
Coronary artery disease	1.50 (1.10-2.06)	0.011		
Previous CABG	2.66 (1.72-4.12)	<0.001	2.02 (1.26-3.25)	0.0036
Active cancer	0.53 (0.20-1.43)	0.21		
Clinical frailty scale (per 1 group increase)	1.29 (1.15-1.45)	<0.001	1.19 (1.05-1.35)	0.0069
Transfemoral approach	0.60 (0.42-0.87)	0.007	0.71 (0.48-1.03)	0.073
Hemoglobin (per 1g/dl increase)	0.88 (0.80-0.97)	0.008		
Albumin <3.5g/dl	2.58 (1.88-3.54)	<0.001	1.71 (1.20-2.43)	0.003
Brain natriuretic peptide (per 1pg/ml increase)	1.00 (1.00-1.01)	0.066	1.00 (0.99-1.00)	0.94
Peak velocity (per 1m/s increase)	0.72 (0.59-0.89)	0.002		
Mean pressure gradient (per 1mmHg increase)	0.99 (0.98-1.00)	0.017		
Left atrial dimension (per 1mm increase)	1.01 (0.99-1.04)	0.2		

Concentric Remodeling (for normal)	0.99 (0.66-1.50)	0.98	0.68 (0.30-1.51)	0.34
Concentric LVH (for normal)	0.79 (0.58-1.09)	0.15	0.83 (0.41-1.68)	0.62
Eccentric LVH (for normal)	1.42 (0.94-2.15)	0.1	0.85 (0.39-1.88)	0.68
LVEF ≤40%	2.13 (1.41-3.23)	<0.001	1.09 (0.64-1.84)	0.75
E/e` (per 1 increase)	0.99 (0.98-1.01)	0.6		
Deceleration time (per 1sec increase)	0.99 (0.99-0.99)	<0.001		
SVi <35 ml/m^2	2.03 (1.45-2.84)	<0.001	1.35 (0.93-1.95)	0.11
Systolic pulmonary artery pressure (per 1mmHg increase)	1.02 (1.01-1.03)	<0.001	1.01 (0.99-1.02)	0.41
Mitral regurgitation ≥moderate	1.68 (1.10-2.56)	0.016		
tricuspid regurgitation ≥moderate	3.17 (2.13-4.73)	<0.001	2.47 (1.49-4.08)	<0.001

CABG indicates coronary artery bypass grafting; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; and SVi, stroke volume index.

Table S5. Univariable and multivariable Cox regression analysis in the model using continuous LVEDD.

	LVEDD (per 1 mm decrease)			
	Unadjusted		Adjusted	
	HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality	1.00 (0.99-1.01)	0.84	1.03 (1.01-1.05)	0.008
Cardiovascular mortality	0.99 (0.97-1.02)	0.48	1.04 (1.01-1.09)	0.026

CI indicates confidence interval; HR, hazard ratio; and LVEDD, left ventricular end-diastolic dimension.

Table S6. Univariable and multivariable Cox regression analysis in the model using continuous LVEDD/BSA.

	LVEDD/BSA (per 1 mm/m^2 decrease)			
	Unadjusted		Adjusted	
	HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality	1.00 (0.97-1.01)	0.47	1.03 (1.01-1.06)	0.025
Cardiovascular mortality	0.99 (0.95-1.02)	0.41	1.04 (1.00-1.09)	0.047

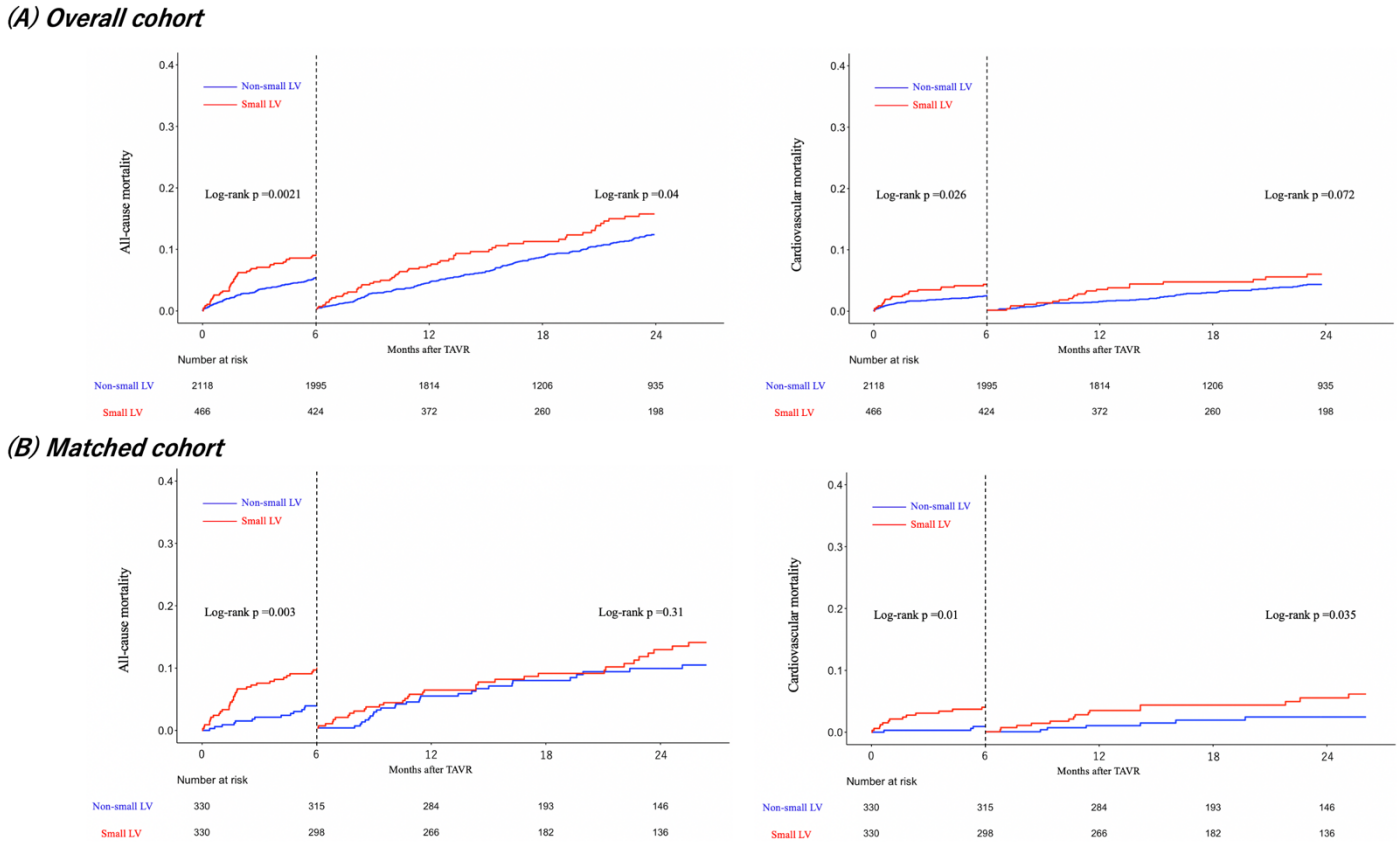
BSA indicates body surface area; CI, confidence interval; HR, hazard ratio; and LVEDD, left ventricular end-diastolic dimension.

Table S7. Univariable and multivariable Cox regression analysis in the model using LVEDD < 40mm.

	LVEDD < 40 mm			
	Unadjusted		Adjusted	
	HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality	1.23 (0.99-1.54)	0.064	1.57 (1.21-2.07)	<0.001
Cardiovascular mortality	1.33 (0.94-1.89)	0.10	1.74 (1.18-2.57)	0.005

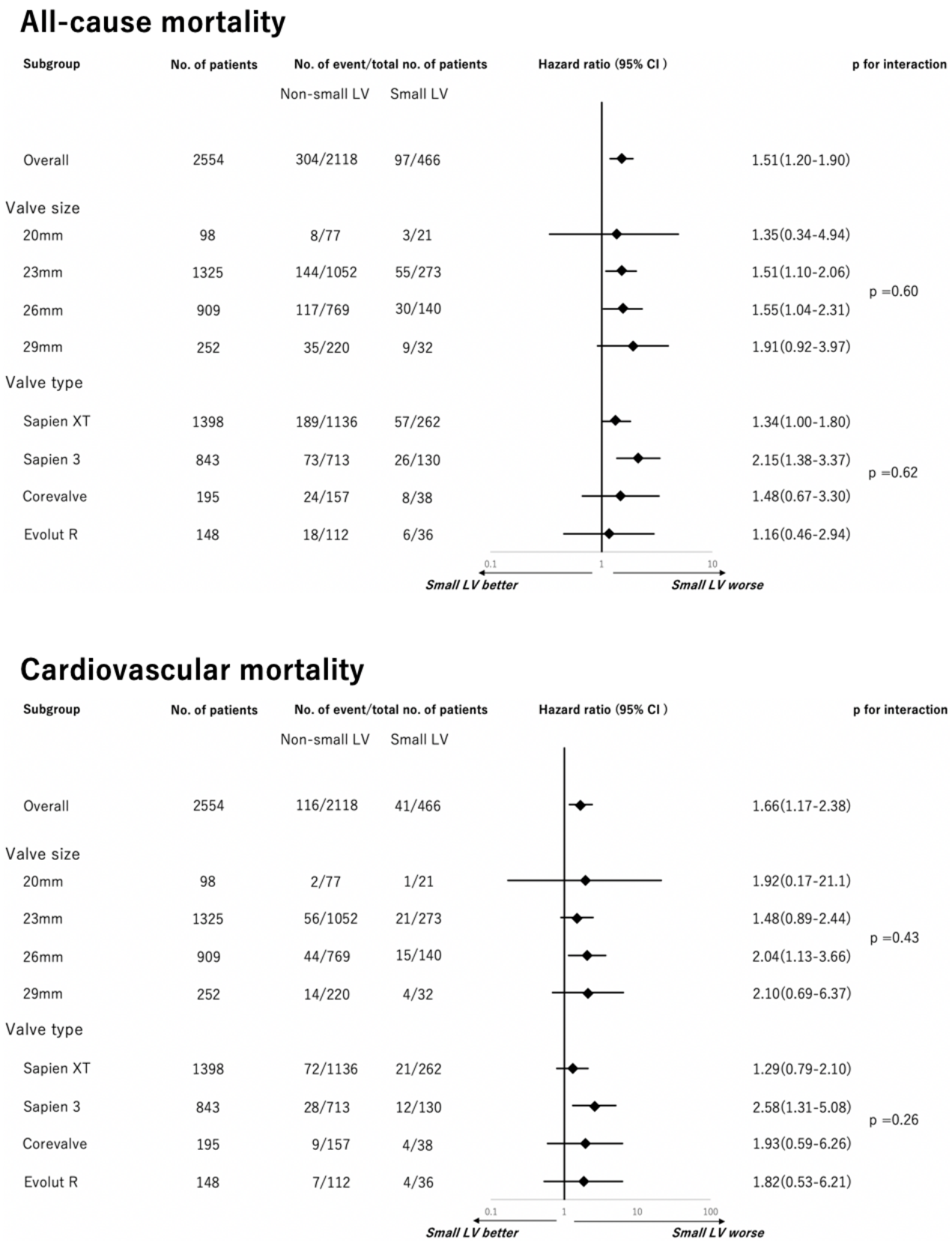
CI indicates confidence interval; HR, hazard ratio; and LVEDD, left ventricular end-diastolic dimension.

Figure S1. Landmark analysis at 6 months in the overall and matched cohort.



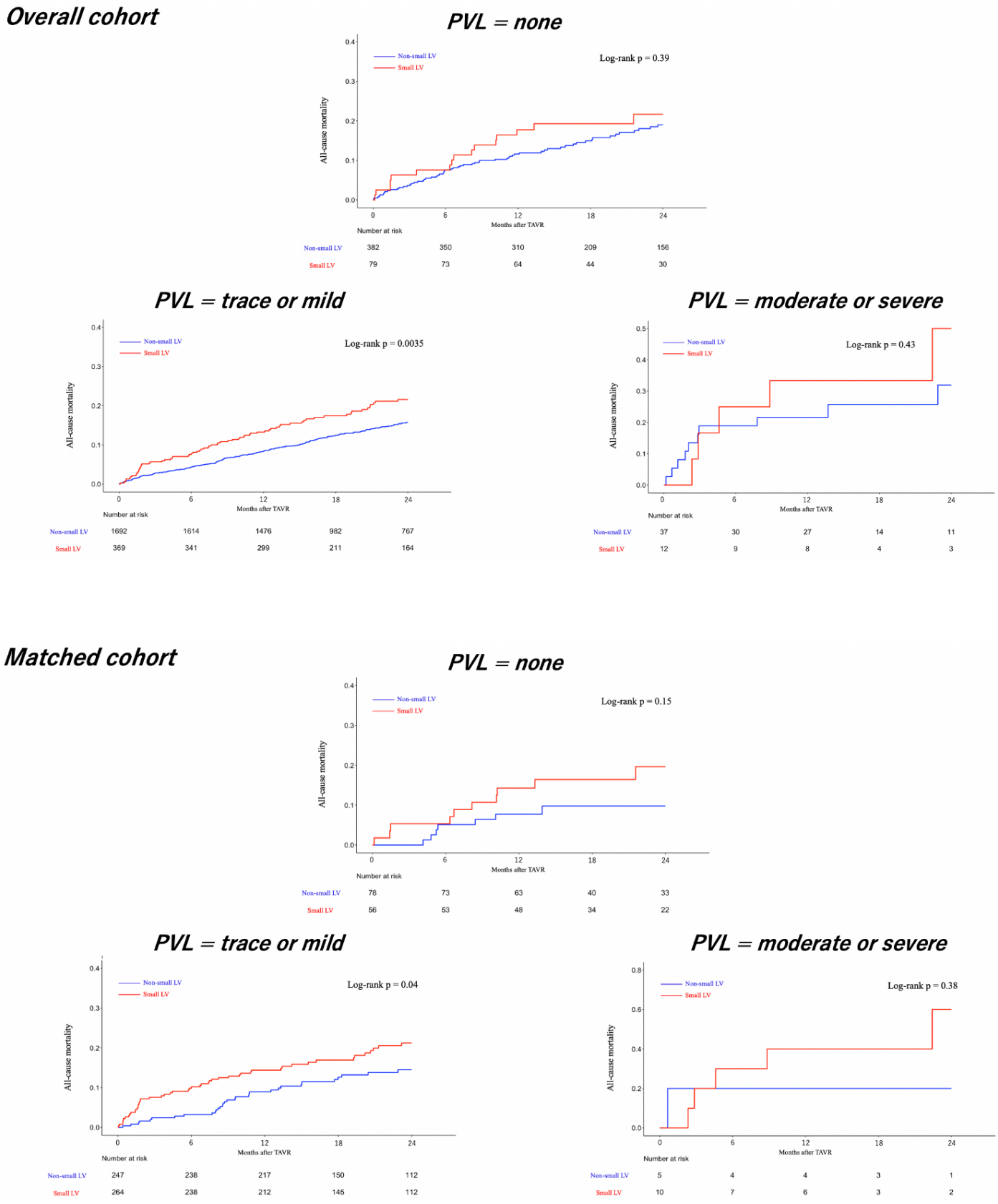
LV indicates left ventricle.

Figure S2. Subgroup Analyses of valve sizes and types.



LV indicates left ventricle.

Figure S3. Kaplan-Meier curves of all-cause and cardiovascular mortality stratified by the severity of PVL in the overall and matched cohort.



LV indicates left ventricle; and PVL, paravalvular leak.