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ORIGINAL ARTICLE
Valvular Heart Disease

Left Ventricular Hypertrophic Change Indicating Poor Prognosis in Patients With Normal-Flow, Low-Gradient Severe Aortic Stenosis With Preserved Left Ventricular Ejection Fraction

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Background: Risk stratification of normal-flow, low-gradient (NFLG) severe aortic stenosis (SAS) with preserved left ventricular (LV) ejection fraction (EF) remains unclear.

Methods and Results: Of 289 consecutive patients diagnosed with SAS by aortic valve area <1.0 cm^2, 66 with NFLG-SAS (stroke volume index >35 mL/m^2, mean pressure gradient <40 mmHg, LVEF ≥50%) were enrolled in this study; patients with bicuspid aortic valve, acute coronary syndrome, hemodialysis, or a history of aortic valve replacement (AVR) were excluded. Adverse events (AEs) were defined as cardiovascular death, hospitalization for heart failure, and deteriorating condition requiring AVR. Factors associated with AEs were investigated using a Cox proportional hazards model. Over a median of 675 days of follow-up, 25 AEs were recorded: 4 cardiovascular deaths, 12 hospitalizations for heart failure, and 9 patients requiring AVR. In addition, there were 14 events of progression to high-gradient SAS. Multivariable analysis showed significant associations between AEs and the presence of symptoms (hazard ratio [HR] 10.276; 95% confidence interval [CI] 3.724–28.357; P<0.001), LV hypertrophy (LV mass index >115 and >95 mg/m^2 for males and females, respectively; HR 3.257; 95% CI 1.172–9.050; P=0.024), and tricuspid regurgitation (TR) velocity (HR 2.761; 95% CI 1.246–6.118; P=0.012).

Conclusions: The presence of symptoms, LV hypertrophy, and high TR velocity could be reliable prognostic indicators and may require watchful waiting for timely AVR in patients with NFLG-SAS.

Key Words: Left ventricular hypertrophy; Normal-flow, low-gradient severe aortic stenosis; Preserved left ventricular ejection fraction; Prognosis

Aortic stenosis (AS) is the most frequent valvular disease in clinical practice and is considered a severe health issue, especially in the elderly.[1] As the aortic valve stenosis progresses, the aortic valve area (AVA) decreases, and transvalvular flow velocity and pressure gradient increase. Therefore, a diagnosis of severe AS is determined according to echocardiographic criteria, including AVA <1.0 cm^2, peak transvalvular flow velocity ≥4.0 m/s, and mean pressure gradient (MPG) ≥40 mmHg.[2–4] However, 30–40% of patients with severe AS have lower transvalvular flow velocity or pressure gradient despite the presence of small AVA (<1.0 cm^2).[5–8] According to the current guidelines,[2–4] these patients are categorized as having low-gradient severe AS (LG-SAS). In classical LG-SAS with reduced left ventricular ejection fraction (LVEF; i.e., <50%), aortic valve replacement (AVR) is known to have a beneficial effect on survival, as in patients with high-gradient severe AS (SAS; MPG ≥40 mmHg). In contrast, patients with LG-SAS and preserved LVEF pose major challenges when selecting interventions for AS, even though these patients describe suspected symptoms of AS.[2–4]

Previous studies reported a poor prognosis for LG-SAS with preserved LVEF and a low-flow condition (stroke volume [SV] index ≤35 mL/m^2), which has been called paradoxical AS,[9,10] and the timing for consideration of intervention for LG-SAS.[2–4] In contrast, some patients present

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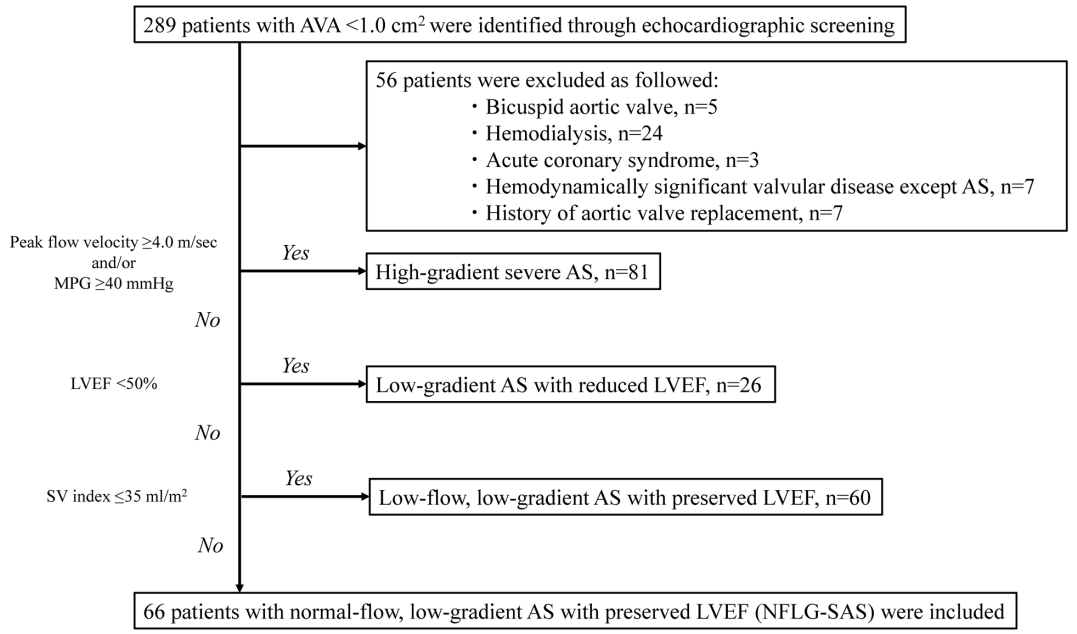

Figure 1. Derivation of study patients. Of the initial 289 patients, 56 were excluded for the reasons listed. A further 81 patients were excluded because peak transvalvular flow velocity was ≥4.0 m/s and/or mean pressure gradient (MPG) was ≥40 mmHg, 26 patients were excluded because of a reduced left ventricular ejection fraction (LVEF), and 60 patients were excluded because of low-flow conditions. AS, aortic stenosis; AVA, aortic valve area; NFLG-SAS, normal-flow, low-gradient severe aortic stenosis; SV, stroke volume.

with normal flow (SV index >35 mL/m^2) despite LG-SAS with preserved LVEF (NFLG-SAS). Because NFLG-SAS has comparable clinical outcomes to moderate AS under appropriate medical management,[11,12] the current guidelines recommend considering these patients as those with a likelihood of pseudo-SAS, although they meet the AVA criteria for severe AS.[2–4] However, evidence that NFLG-SAS can be treated as moderate AS is lacking, particularly in the Japanese population. Therefore, in this study we sought to elucidate the characteristics and clinical outcomes of Japanese patients with NFLG-SAS.

Methods

Study Population and Data Collection

We retrospectively screened 289 consecutive patients aged ≥20 years who had a small AVA (<1.0 cm^2) evaluated by echocardiography with the continuity equation between January 2013 and December 2015. The derivation of study patients is shown in the flow diagram in **Figure 1**. First, 56 patients were excluded due to the following criteria: bicuspid aortic valve, hemodialysis, acute coronary syndrome, hemodynamically significant mitral regurgitation due to mitral valve prolapse, mitral stenosis, and/or aortic regurgitation, and a history of AVR. Second, another 81 patients diagnosed with high-gradient SAS based on the criteria of peak transvalvular flow velocity ≥4.0 m/s and/or MPG ≥40 mmHg were excluded. Third, 26 LG-SAS patients with reduced LVEF (<50%) were also excluded. Thus, of 126 patients who had LG-SAS with preserved LVEF (≥50%), 66 patients with SV index >35 mL/m^2 were classified as NFLG-SAS and included in this study population.

Demographic data, laboratory values, medication, and echocardiographic findings related to AS at the time of enrollment in the study, when study patients were first diagnosed with SAS with small AVA (<1.0 cm^2), were collected. The assessment of symptoms related to AS was up to the attending cardiologists. Symptomatic patients were defined as those with dyspnea on mild exertion (New York Heart Association [NYHA] functional class greater than II) or those requiring administration of loop diuretics to ameliorate their dyspnea and peripheral edema.

This study was conducted in full accordance with the Declaration of Helsinki, and was approved the Institutional Review Board and Ethics Committee of the Nagoya City University Graduate School of Medical Sciences, Japan.

Echocardiographic Assessment

All patients received comprehensive echocardiographic screening, including a Doppler flow study using commercially available ultrasound systems. Furthermore, all echocardiographic measurements were carefully reviewed by 2 cardiologists (Y.K. and S. Kitada) following the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging to determine the classifications of AS type.[13] Peak transvalvular flow velocity was assessed using continuous-wave Doppler imaging, and the fastest velocity obtained in several acoustic windows was used. MPG was also evaluated using continuous-wave Doppler imaging. SV was calculated by multiplying the left ventricular outflow tract (LVOT) area by the time–velocity integral of LVOT, and was also indexed for body surface area (BSA). Valvuloarterial impedance (Zva), which represents global left ventricular (LV) afterload

Table 1. Characteristics of the Entire Patient Cohort and Comparisons of Patients With and Without AEs

	All patients (n=66)	AEs		P value
		No (n=41)	Yes (n=25)	
Age (years)	82±8	82±8	83±7	0.822
Female sex	50 (75.8)	31 (75.6)	19 (76.0)	0.999
BSA (m^2)	1.40±0.19	1.38±0.18	1.42±0.20	0.359
Symptoms	25 (37.9)	7 (17.1)	18 (72.0)	<0.001*
SBP (mmHg)	133±21	131±20	136±23	0.374
Heart rate (beats/min)	69±13	68±13	71±14	0.464
Comorbidity				
Hypertension	47 (71.2)	27 (65.9)	20 (80.0)	0.270
Diabetes	13 (19.7)	8 (19.5)	5 (20.0)	0.999
Hyperlipidemia	33 (50.0)	18 (43.9)	15 (60.0)	0.310
Atrial fibrillation	11 (16.7)	6 (14.6)	5 (20.0)	0.735
CAD	14 (21.2)	6 (14.6)	8 (32.0)	0.124
Laboratory data				
BNP (pg/mL)	149.5 [68.6–320.6]	127.9 [40.3–372.8]	181.8 [101.7–317.2]	NA
Log[BNP]	4.94±1.19	4.80±1.38	5.15±0.82	0.279
eGFR (mL/min/1.73 m^2)	54.4±24.9	59.0±25.8	47.0±21.9	0.059
Hemoglobin (mg/dL)	11.8±2.0	11.7±2.0	11.9±2.1	0.701
Echocardiographic findings				
Peak velocity (m/s)	3.23±0.48	3.17±0.45	3.33±0.52	0.190
Mean PG (mmHg)	23.6±7.7	22.3±7.1	25.6±8.3	0.093
AVA index (cm^2/m^2)	0.63±0.12	0.63±0.11	0.63±0.14	0.955
AVA index <0.6 cm^2/m^2	28 (42.4)	17 (41.5)	11 (44.0)	0.999
Zva ($mmHg \cdot m^{-2} \cdot mL^{-1}$)	3.59±0.67	3.62±0.67	3.54±0.67	0.657
LVEDD (mm)	42.6±6.0	41.6±5.6	44.2±6.5	0.098
LVESD (mm)	26.1±5.3	25.5±4.7	27.0±6.1	0.292
LAD (mm)	40.6±7.3	39.8±5.7	42.0±9.3	0.245
LVEF (%)	69.6±7.8	69.6±7.4	69.6±8.5	0.999
SV index (mL/m^2)	44.7±7.5	43.6±7.1	46.5±7.9	0.120
LVMI (g/m^2)	121.7±32.8	115.7±31.3	131.5±33.4	0.056
LV hypertrophy	43 (65.2)	24 (58.5)	19 (76.0)	0.188
RWT	0.50±0.10	0.50±0.10	0.50±0.09	0.736
TR velocity (m/s)	2.62±0.51	2.52±0.46	2.79±0.55	0.045*
E/e′	18.6±7.1	17.9±6.9	19.8±7.5	0.472
IVC (mm)	13.8±3.5	13.5±3.6	14.3±3.5	0.362
Medications				
ACEI/ARB	31 (47.0)	19 (46.3)	12 (48.0)	0.999
β-blocker	15 (22.7)	8 (19.5)	7 (28.0)	0.547
CCB	38 (57.6)	22 (53.7)	16 (64.0)	0.451
Statin	29 (43.9)	16 (39.0)	13 (52.0)	0.321

Data are expressed as n (%), the mean±SD, or as the median [interquartile range]. *Statistically significant, P<0.05. ACEI, angiotensin-converting enzyme inhibitor; AEs, adverse events; ARB, angiotensin II receptor blocker; AVA, aortic valve area; BNP, B-type natriuretic peptide; BSA, body surface area; CAD, coronary artery disease; CCB, calcium channel blocker; E/e′, ratio of early diastolic velocity to early diastolic annular velocity; eGFR, estimated glomerular filtration rate; IVC, inferior vena cava diameter; LAD, left atrial diameter; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVMI, LV mass index; PG, pressure gradient; RWT, relative wall thickness; SBP, systolic blood pressure; SV, stroke volume; TR, tricuspid regurgitation; Zva, valvuloarterial impedance.

taking into account both valvular and arterial loads in AS, has been reported to predict adverse events in asymptomatic patients with moderate to severe AS and to differentiate SAS from moderate AS.[7,14,15] In the present study, Zva was calculated according to the following formula:[5,14]

$$\text{Zva} = (\text{SBP at the time of echocardiography} + \text{MPG}) / \text{SV index}$$

where SBP is systolic blood pressure. Zva was included in this study as a clinical variable. AVA was calculated by the equation continuity and indexed for BSA. We classified AVA <1.0 cm^2 into SAS. In addition, an AVA index <0.6 cm^2/m^2 was used as another criterion of SAS in this study. Based on the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging,[16] relative wall thickness (RWT) was calculated by dividing the sum of the interventricular septum wall thickness and LV posterior wall thickness by the LV end-diastolic diameter. In addition, LV mass was assessed with the linear method formula, with comparisons

Table 2. AEs Among Patients With Normal-Flow, Low-Gradient SAS

	No. patients with AEs (%)
Cardiovascular death	4 (16)
Hospitalization for HF	12 (48)
AVR according to guidelines	9 (36)
Progression to high-gradient SAS (n)	8/9
Reduction of LVEF <50% (n)	1/9
AE within 1 year	10 (40)
Progression to high-gradient SAS among all events	14 (61[A])
Reduction of LVEF <50% among all events	3 (13[A])

Adverse events were documented in 25 patients. [A]Proportion of events after exclusion of 2 events due to sudden cardiac death. AVR, aortic valve replacement; HF, heart failure; SAS, severe aortic stenosis. Other abbreviations as in Table 1.

made of LV mass index (LVMI). LV hypertrophy was defined as an upper threshold of normal LVMI of 115 mg/m^2 for men and 95 mg/m^2 for women.[16] When patients were in atrial fibrillation, at least 5 cardiac cycles were averaged for all measures.

Clinical Outcome Analysis

The study endpoint was defined as a composite of cardiovascular death, unplanned hospitalization due to acute decompensated heart failure (HF), or deteriorating condition requiring an AVR according to current guidelines.[2–4] Cardiovascular death was defined as death from congestive HF deterioration, coronary artery disease, cardiac arrest, cardiac arrhythmia, myocardial infarction, stroke, or sudden death. Deaths due to end-stage malignancy, severe infection, or major gastrointestinal bleeding were considered non-cardiovascular deaths and were not included in the study endpoint. In addition, echocardiographic data were collected at the time when patients experienced adverse events, except for sudden cardiac death. We then confirmed whether the adverse events were associated with a progression to high-gradient SAS and/or a reduction in LVEF below 50%. When patients survived without an adverse event during the follow-up period, we used the time from the enrollment to the occurrence of a terminal endpoint or the last censoring as the duration of observations in our prognosis study. When patients died because of any other cardiovascular disease, these patients were considered censored cases at the time of non-cardiovascular death. The duration between enrollment and the time of censoring was used as the observation period for these patients.

First, we evaluated the contributions of clinical variables to the relative hazard of experiencing the composite endpoint of this study using a multivariable Cox proportional hazards model with a stepwise procedure. Second, using the clinical variables that were found to be statistically significant in the multivariable analysis, we classified all patients into subgroups and compared event-free survival among the subgroups using the Kaplan-Meier method with the log-rank test.

Statistical Analysis

Continuous data are presented as the mean±SD and categorical variables are presented as frequencies and percentages. The Cox proportional hazards model used to estimate the contribution of clinical variables to the study endpoint included variables that were statistically significant in the univariable analysis. In all cases, $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 23.0 (SPSS Japan, Tokyo, Japan).

Results

Clinical Characteristics of Study Patients

The clinical characteristics of all 66 patients in this study are provided in **Table 1**. The mean age was 82 years, and 75.8% of the patient cohort were women. Although the mean AVA index was 0.63 cm^2 and 42.4% of the study patients had an AVA index <0.6 cm^2/m^2, peak transvalvular flow velocity was 3.23 m/s, MPG was 23.6 mmHg, and mean Zva was 3.59 mmHg·m^{-2}·mL^{-1}. Among the 66 patients, 25 (37.9%) were symptomatic, 13 (52%) of them required loop diuretic therapy. Median plasma B-type natriuretic peptide (BNP) concentrations were 149.5 pg/mL (interquartile range [IQR] 68.6–320.6 pg/mL). Mean tricuspid regurgitation (TR) velocity was 2.62 m/s, the mean E/e′ was 18.6, and mean LVMI was 121.7 g/m^2. LV hypertrophy was found in 43 patients (65.2%): 37.5% of men (n=6) and 74.0% of women (n=37). An increase in LVMI was more frequently observed in female than male patients (P=0.014).

Contribution of Clinical Parameters to Cardiovascular Events in NFLG-SAS

During the follow-up period (median 675 days; IQR 170–1,090 days), 25 adverse events were documented, including 4 cardiovascular deaths, 12 hospitalizations for HF, and 9 patients requiring AVR (**Table 2**). Of all adverse events, 40% occurred within 1 year after the first diagnosis of NFLG-SAS. In addition, progression from low- to high-gradient SAS was documented in 14 events (61% of events after exclusion of 2 sudden cardiac deaths), consist of 88.9% of AVRs (8/9) and half the hospitalizations for HF (6/12). In contrast, a reduction in LVEF below 50% was observed in only 3 events.

Comparing clinical characteristics between patients with and without adverse events (**Table 1**) revealed that patients with adverse events more frequently had symptoms and had a significantly higher TR velocity. They also had a tendency to have lower estimated glomerular filtration rate, higher MPG, larger LV end-diastolic dimension, and larger LVMI. In a univariable Cox proportional hazards model analysis (**Table 3**), the presence of symptoms, LV hypertrophy, and TR velocity were significantly associated with the primary endpoint. In contrast, plasma BNP concentrations and Zva were not associated with adverse events. Furthermore, a multivariable Cox proportional hazards model revealed that the presence of symptoms, LV hypertrophy, and TR velocity were independently associated with the primary endpoint.

Optimal Cut-Off Value of TR Velocity to Predict Poor Prognosis

According to receiver operating characteristic curve analysis of TR velocity to predict adverse events, the optimal cut-off for TR velocity was 2.8 m/s, which had a sensitivity of 59.1% and a specificity of 76.9% (area under the curve 0.672; P=0.026). Compared with patients with a TR velocity ≤2.8 m/s, those with a TR velocity >2.8 m/s had significantly worse event-free survival (log-rank test, P=0.003; **Figure 2**).

Table 3. Multivariable Cox Proportional Hazards Model Analysis

	Univariable	Multivariable	
	P value	HR (95% CI)	P value
Age	0.339		
Female sex	0.771		
BSA	0.838		
Symptoms	<0.001*	10.276 (3.724–28.357)*	<0.001*
SBP	0.834		
Heart rate	0.409		
Hypertension	0.631		
Diabetes	0.473		
Dyslipidemia	0.312		
Atrial fibrillation	0.493		
CAD	0.069		
Log[BNP]	0.123		
eGFR	0.077		
Hemoglobin	0.379		
Peak velocity	0.160		
Mean PG	0.063		
AVA index	0.582		
AVA index <0.6 cm^2/m^2	0.844		
Zva	0.167		
LVEDD	0.166		
LVESD	0.316		
LAD	0.173		
LVEF	0.992		
SV index	0.128		
LV hypertrophy	0.049*	3.257 (1.172–9.050)*	0.024*
RWT	0.746		
TR velocity	0.036*	2.761 (1.246–6.118)*	0.012*
E/e′	0.928		
IVC	0.877		
ACEI/ARB	0.951		
β-blockers	0.542		
CCB	0.561		
Statin	0.416		

*Statistically significant, P<0.05. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Prognostic Impact of LV Hypertrophy and High TR Velocity on Asymptomatic Patients With NFLG-SAS

The patient cohort was divided into 2 groups according to the presence of symptoms. Furthermore, asymptomatic patients were divided into 4 subgroups based on the presence of LV hypertrophy and/or TR velocity >2.8 m/s. Then, event-free survival curves were compared among these groups (**Figure 3**). Because there were only 2 patients among the asymptomatic patients with TR velocity >2.8 m/s and without LV hypertrophy, the data for this group, which did not experience any adverse events during the follow-up period, are not shown. Symptomatic patients had the worst event-free survival, whereas the best event-free survival was found for asymptomatic patients without LV hypertrophy and high TR velocity (>2.8 m/s). In addition, among asymptomatic patients, those with LV hypertrophy regardless of TR velocity had significantly worse event-free survival than patients without LV hypertrophy and high TR velocity (log-rank test, P<0.001).

Figure 4 shows a comparison of event-free survival among subgroups defined according to the presence of symptoms and LV hypertrophy. Although there was no significant difference between patients with and without LV hypertrophy among the entire study cohort, significant differences were found among asymptomatic patients (log-rank test, P=0.034). In addition, there was no significant difference in prognosis between patients who had LV hypertrophy but not symptoms and patients who had symptoms but not LV hypertrophy (log-rank test, P=0.117). Furthermore, compared with patients with both symptoms and LV hypertrophy, those who had LV hypertrophy but not symptoms had significantly better event-free survival (log-rank test, P=0.013).

Discussion

In the current study, we demonstrated the following major findings. First, in patients diagnosed with NFLG-SAS, the presence of symptoms, LV hypertrophy, and high TR velocity were significantly associated with future cardiovascular events after adjusting for clinical background. In particular, symptomatic patients with NFLG-SAS were at

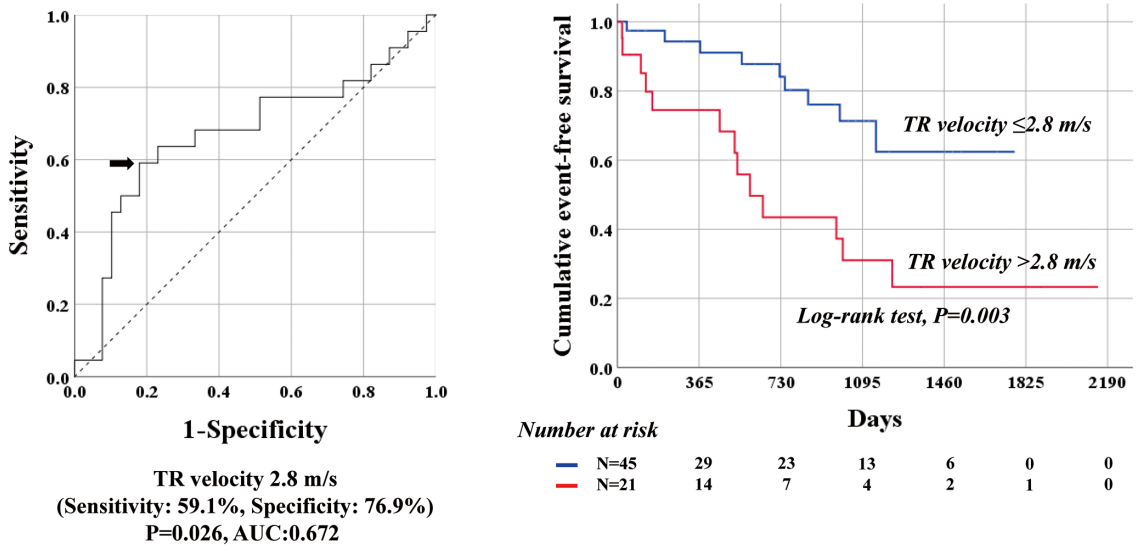

Figure 2. Receiver operating characteristic curve analysis of tricuspid regurgitation (TR) velocity to predict adverse events. (**Left**) The optimal cut-off value of TR velocity was 2.8 m/s, with a sensitivity of 59.1% and a specificity of 76.9% (area under the curve [AUC] 0.672; P=0.026). (**Right**) Comparison of event-free survival between patients with TR velocity ≤2.8 m/s and those with TR velocity >2.8 m/s. Compared with patients with a TR velocity ≤2.8 m/s, those with a TR velocity >2.8 m/s had significantly worse event-free survival (log-rank test, P=0.003).

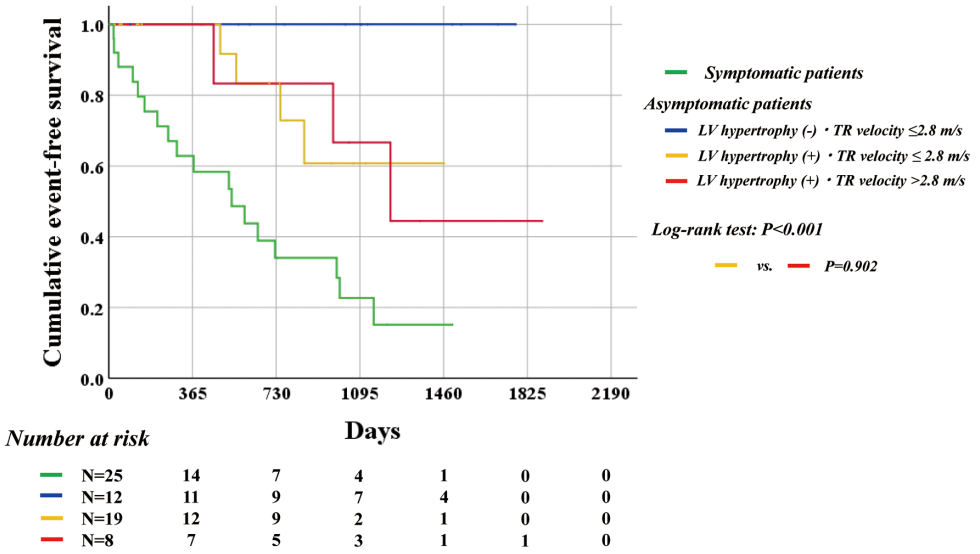

Figure 3. Comparison of event-free survival among 4 subgroups classified according to the presence of symptoms, left ventricular (LV) hypertrophy, and high tricuspid regurgitation (TR) velocity (>2.8 m/s). Among the asymptomatic patients, only 2 had TR velocity >2.8 m/s and no LV hypertrophy. Symptomatic patients had the worst event-free survival, whereas the best event-free survival was seen for asymptomatic patients without LV hypertrophy and with a low TR velocity (log-rank test, P<0.001). There was no significant difference in prognosis between asymptomatic patients with LV hypertrophy but not high TR velocity and asymptomatic patients with LV hypertrophy and high TR velocity (log-rank test, P=0.902).

the highest risk of future cardiovascular events. Even in the patients without symptoms, LV hypertrophic change requires watchful waiting for the onset of a cardiovascular event. Second, 60% of adverse events in patients with NFLG-SAS occurred more than 1 year after the diagnosis of SAS, showing the progression from low- to high-gradient SAS during the follow-up period.

In the present study, 43.6% of patients who underwent echocardiographic examinations showed LG-SAS with preserved LVEF, and 22.8% of screened patients were clas-

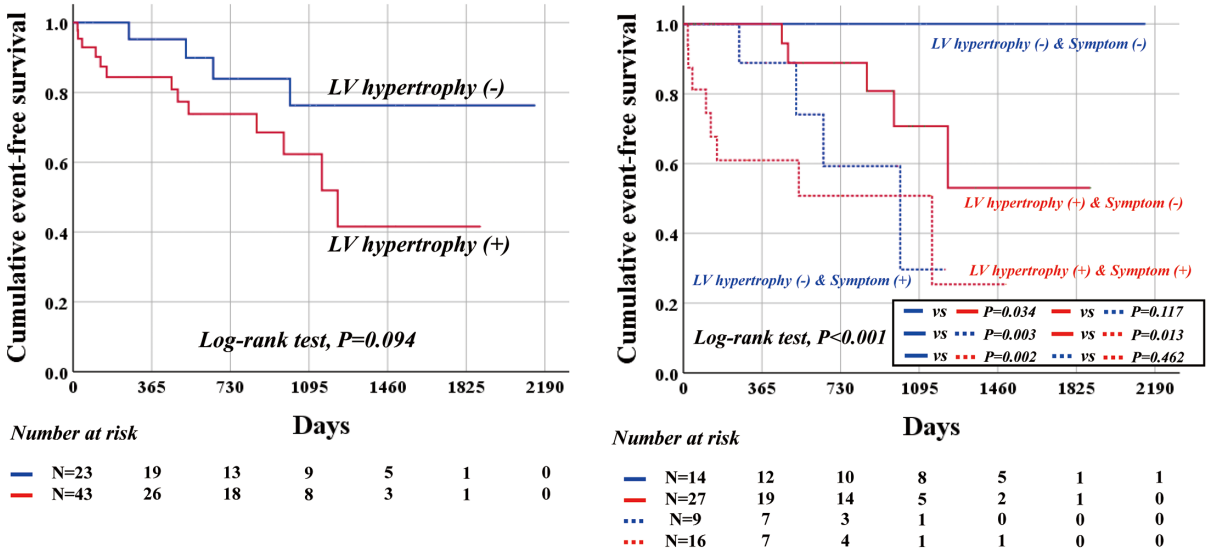

Figure 4. Comparison of event-free survival focusing on the presence of symptoms and left ventricular (LV) hypertrophy. (**Left**) Survival curves in patients with and without LV hypertrophy for the entire study cohort. The difference in event-free survival did not reach statistical significance (log-rank test, P=0.094). (**Right**) Event-free survival in the 4 subgroups classified according to the presence of symptoms and/or LV hypertrophy. Patients with both symptoms and LV hypertrophy had the worst event-free survival, whereas asymptomatic patients without LV hypertrophy had the best event-free survival (log-rank test, P<0.001). Significant differences were found between patients with and without LV hypertrophy among asymptomatic patients (log-rank test, P=0.034). There was no significant difference in prognosis between asymptomatic patients with LV hypertrophy and those with symptoms but not LV hypertrophy (log-rank test, P=0.117). Furthermore, event-free survival was significantly better among asymptomatic patients with LV hypertrophy than among patients with both symptoms and LV hypertrophy (log-rank test, P=0.013).

sified as NFLG-SAS. Previous studies reported that up to 40% of patients with a small AVA (<1.0 cm^2) suggesting SAS had a discordant low transvalvular pressure gradient.[5–8] In addition, NFLG-SAS is the most prevalent form of LG-SAS.[17] According to recent studies, 20–30% of patients diagnosed with SAS according to AVA <1.0 cm^2 had NFLG-SAS.[7,18] Thus, our cohort data are consistent with the previously reported prevalence.

The prognosis and management of NFLG-SAS continue to be matters of debate. Previous reports have suggested that NFLG-SAS may be a more advanced disease because of a worse prognosis under medical treatment when AS-related symptoms appear.[19–21] In contrast, other reports have suggested that the prognosis of NFLG-SAS is similar to that of moderate AS and that watchful waiting under appropriate medical treatment has a similar effect on the survival of patients with NFLG-SAS as compared to early AVR.[11,12] Even in the guidelines and a consensus paper, there are some differences in the recommended management of NFLG-SAS between Europe and the US.[2–4] Therefore, among NFLG-SAS patients, a robust prognostic indicator, which can differentiate high-risk patients who need an intervention in the near future, is required. In this regard, it is clinically crucial that the present study has demonstrated that symptoms, LV hypertrophy, and high TR velocity may be prognostic indicators.

First, as described in the current guidelines that the presence of AS-related symptoms is helpful in identifying the timing of AVR,[2–4] the present study demonstrated symptoms to have a prognostic value for future cardiovascular events in patients with NFLG-SAS. For asymptomatic patients with SAS, their postoperative survival rates were reported to be similar whichever strategy was chosen between AVR after watchful waiting and initial AVR, except in the case of SAS with a higher peak flow velocity, such as ≥4.5 m/s, at diagnosis.[22] In the clinical setting, determining whether SAS patients, not just those with NFLG-SAS, have symptoms due to SAS is challenging in the elderly population.[23–25] In this context, in addition to careful patient interviews, stress tests, including exercise stress echocardiography examinations and cardiopulmonary exercise tests, play a critical role in identifying the presence of symptoms, as also recommended by the Japanese guideline.[26]

Second, LV hypertrophy had a significant prognostic value in patients with NFLG-SAS even in the absence of symptoms. In the present study, we defined LV hypertrophy as an LVMI >115 g/m^2 in men and >95 g/m^2 in women, which are usually considered the upper threshold of normal LVMI in the clinical setting, rather than the threshold determined in SAS populations.[16] LV hypertrophy is a typical LV remodeling response that occurs as the LV adapts to reduce LV wall stress and maintain cardiac output.[27–29] In contrast, LV hypertrophy is also well known as a significant prognostic factor in patients with SAS.[30–32] In addition, our findings suggest that even slight LV hypertrophic change heralds the early transition from adaptive to maladaptive LV remodeling against AS and could be a prognostic indicator in NFLG-SAS.

Finally, high TR velocity suggesting pulmonary hypertension (PH) was a sign of a poor prognosis in NFLG-SAS. This finding is consistent with previous studies.[33–36] However, the cut-off value of TR velocity to predict adverse events in NFLG-SAS (2.8 m/s; the estimated sys-

tolic pulmonary artery pressure was around 30 mmHg) was a little lower as a surrogate value for the presence of PH.[37] We cannot determine the pathophysiological changes underlying such mild PH, including an increase in pulmonary vascular resistance or reduced pulmonary artery capacitance, based on the estimated systolic pulmonary artery pressure. However, as a speculation, PH may be worsened under exercise, which is observed in stress tests. Therefore, the significance of mild PH at rest should be investigated in future stress test studies.

The present study revealed the relationship between the progression of AS and cardiac events in NFLG-SAS. In general, a progression of AS is irreversible and eventually requires AVR. On an annualized average, the peak transvalvular flow velocity increases by 0.1–0.3 m/s. An increase in the MPG of 3–10 mmHg and a decrease in AVA of 0.1 cm^2 has been seen among patients with mild to moderate AS.[38] Risk factors associated with the progression of tricuspid aortic valve stenosis are similar to those for atherosclerosis.[39] Regarding the progression of NFLG-SAS, the latest report by Chadha et al[40] demonstrated that 48% of patients diagnosed with NFLG-SAS progressed to high-gradient SAS during a median follow-up of 25 months. In addition, a propensity-matched study of NFLG-SAS conducted by Chadha et al[12] demonstrated that patients with NFLG-SAS required AVR significantly earlier than those with moderate AS during a 24-month follow-up. The rate of progression of low-gradient AS was reported to be slower than that of high-gradient AS.[41] In fact, 60% of adverse events among patients in the present study occurred more than 1 year after the diagnosis of NFLG-SAS. Thus, variabilities in the progression of NFLG-SAS were shown. However, our findings suggest that close observation would be essential for patients with NFLG-SAS to detect progression to high-gradient SAS and determine the timing of AVR for a beneficial effect on survival.

Study Limitations

This study had several limitations. First, because we conducted this retrospective study in a single center with a small cohort size, large-scale studies are needed to clarify the strength of our conclusions. Second, most of our study cohort consisted of Japanese patients with a smaller body size. Therefore, our findings may be affected by a selection bias of the study cohort due to its ethnic homogeneity. A worldwide survey concerning ethnic variations in clinical backgrounds underlying the progression of NFLG-SAS to predict future cardiovascular events is needed to confirm our conclusions.

Conclusions

In patients with NFLG-SAS, the presence of symptoms, LV hypertrophy, and high TR velocity were associated with cardiovascular events, including cardiovascular death, development of HF, or a deterioration of the condition requiring AVR. In addition, an increase in aortic valvular gradients may indicate progression to advanced AS during the observation period. In summary, there is concern that NFLG-SAS patients will be uniformly treated focusing on follow-up of the natural history of AS. NFLG-SAS patients with these risk factors should be carefully treated, and longitudinal follow-up is essential to decide the timing of AVR.

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IRB Information

This study was approved by the Institutional Review Boards and Ethics Committees of the Nagoya City University Graduate School of Medical Sciences, Japan (Approval no. 60-17-0028).

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