



Prognostic assessment of relative apical sparing pattern of longitudinal strain for severe aortic valve stenosis



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ABSTRACT

Backgrounds: The relative apical sparing pattern (RASP) of left ventricular (LV) longitudinal strain (LS) is frequently associated with cardiac amyloidosis. Elderly patients with aortic valve stenosis (AS) complicated by transthyretin amyloid cardiomyopathy have poor prognosis. Furthermore, deteriorated basal LS in AS patients has been reported to be associated with adverse outcome. We investigated the association between RASP and outcomes in patients with severe AS.

Methods: We retrospectively studied 156 consecutive patients with severe AS and preserved LV ejection fraction. RASP was assessed by both of semi-quantitative (sRASP) and quantitative (qRASP) methods. sRASP was defined as a deterioration of LS ($\geq -10\%$) in ≥ 5 (of 6) basal segments, relative to preserved LS ($< -15\%$) in at least 1 apical segment. qRASP was calculated using the following formula: average apical LS/(average basal LS + average mid-ventricle LS); qRASP ≥ 1 was defined as positive. Patients were followed up to determine outcomes, which included sudden cardiac death or unexpected admission due to heart failure, over a median of 1.9 years.

Results: sRASP and qRASP were assessed in all patients, but 24 and 42 patients fulfilled the criteria for sRASP and qRASP, respectively. Both assessments were significantly associated with outcomes ($n = 44$; 28%). Furthermore, sRASP was significantly associated with outcome after adjusting for EuroSCORE, NYHA \geq II, or global longitudinal strain. A model based on these covariates for predicting outcomes significantly improved by adding sRASP.

Conclusion: RASP is observed in some patients with severe AS and provides additive prognostic information over conventional parameters.

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1. Introduction

Recent publications have shown that some patients with moderate-to-severe aortic valve stenosis (AS) (6–33%) have transthyretin amyloid cardiomyopathy (ATTR-CM) [1–4]. Their prognosis is poor, even after ameliorating pressure overload with aortic valve replacement (AVR) [4,5].

Compared to several echocardiographic indicators in patients with AS, left ventricular (LV) global longitudinal strain (GLS) is a sensitive identifier for subclinical LV dysfunction and is strongly associated with prognosis [6,7]. Recently, the relative “apical sparing” pattern (RASP) of LV longitudinal strain was identified on the

strain polar map during GLS measurement. The RASP finding can be used as a clue of cardiac amyloidosis including ATTR-CM [8–10]. In addition, in patients with AS, basal longitudinal strain can deteriorate because of increased wall stress and fibrosis associated with a large curvature in the basal part and pressure overload, which could be associated with the emergence of RASP [11,12]. Furthermore, this deteriorated basal longitudinal strain itself is reportedly more associated with adverse outcome than GLS [13,14].

Hence, we aimed to investigate the prevalence of RASP in patients with severe AS. Furthermore, we sought to determine the association between RASP and major adverse cardiac events (MACE), which may be independent of and incremental to clinical and echocardiographic parameters in such patients.

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2. Methods

2.1. Study participants

In this retrospective cohort study, we identified 192 consecutive patients, without duplication, presenting with severe AS (peak aortic jet velocity ≥ 4.0 m/s) and preserved LV ejection fraction ($>50\%$), among those who underwent clinically indicated echocardiography between April 2008 and December 2017. Patients who had previously undergone valve surgery at study enrolment were excluded based on their echocardiogram reports. Furthermore, patients who died within 30 days of the echocardiogram and those with an implanted pacemaker or cardioverter defibrillator were excluded during the chart review. Finally, after the exclusion of patients for whom strain could not be evaluated because of poor image quality, data obtained from 156 patients with severe AS were used for the final analysis (Fig. 1). Among them, 50 (32%) underwent AVR after echocardiographic examination. The median time from echocardiographic examination to AVR was 125 days (inter quartile range [IQR]: 35–343 days). Among those with AVR, 29 patients had a follow-up echocardiogram after >3 months, with good image quality after AVR (median time: 193 days, IQR: 104–334 days). Patient data were anonymized. This study was approved by the ethics committee of Ehime University Graduate School of Medicine (approval number: 1905015).

2.2. Clinical data

Clinical parameters one month before and after the echocardiographic examination (comorbidity, medical history, and serum markers) were collected by an investigator blinded to the findings. All types of atrial fibrillation (paroxysmal, persistent and perma-

nent) were defined as atrial fibrillation. Coronary artery disease was defined as a history of myocardial infarction, angioplasty, or angiographically documented coronary artery stenosis (A stenosis diameter $\geq 50\%$ in the left main trunk and $\geq 75\%$ in other segments) [15]. Additive EuroSCORE was calculated to predict the risk of post-operative mortality using clinical parameters [16]. The AVR treatment after enrollment was also determined.

2.3. Electrocardiography

Standard 12-lead electrography was performed with a paper speed of 25 mm/s and an amplification of 0.1 mV/mm. Low QRS voltage was defined as <0.5 mV peak-to-peak QRS amplitudes in each limb lead and <1.0 mV in each precordial lead [17]. The pseudoinfarction pattern was defined as a QS wave pattern in two contiguous leads in the absence of previous myocardial infarction. The Sokolow-Lyon index was calculated as the sum of the amplitudes of the S-wave in lead V₁ and the R-wave in leads V₅ or V₆ [18]. The electrocardiographic strain pattern was defined as coexistence, in leads I, II, aVL, or V3 to V6 of ST-segment horizontal or downward sloping depression ≥ 0.05 mV plus negative T-wave (Minnesota code 4–1 or 4–2 and 5–1 or 5–2) [19].

2.4. Standard echocardiography

Transthoracic echocardiography was performed by experienced sonographers using a commercially available ultrasound system (Vivid 7 or Vivid E9 or Vivid E95; GE Medical, Milwaukee, Wisconsin). Echocardiographic images were digitally recorded and downloaded as DICOM files for offline analysis. Conventional echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography [20–22]. LV mass was calculated according to the American Society of Echocardiography formula and normalized to body surface area. LV or left atrial volumes and LV ejection fraction were calculated with the biplane method of disks using two-dimensional images, and the volumes were indexed to body surface area. Transmitral early diastolic velocity (E) and E-wave deceleration time were obtained in the apical four-chamber view using pulsed-wave Doppler at the level of the mitral valve tip during diastole. Early diastolic mitral annular tissue velocity (e') was calculated as the average of septal and lateral mitral annular velocities, and E/e' was calculated.

For the quantification of AS severity, LV outflow tract diameter was measured on parasternal long-axis views. Pulsed-wave and continuous-wave Doppler methods were used to record velocities across the LV outflow tract and the aortic valve, respectively. Aortic jet velocities were measured by continuous-wave Doppler using multiple imaging views, including the apical long-axis, right parasternal, and suprasternal views, and the highest aortic velocity signal was used. Transaortic pressure gradients were estimated using the Bernoulli equation, and the aortic valve area was calculated with the continuity equation.

2.5. Speckle tracking imaging

We used standard methodologies for speckle tracking to measure GLS (EchoPAC PC BT13: GE Medical) [23]. After manual tracing of the LV endocardial border, the dedicated software automatically tracked the entire myocardium throughout the cardiac cycle in the apical four-chamber, two-chamber, and long-axis views. If two or more segments were not adequately tracked after two manual adjustments of the endocardial borders, strain analysis was judged as unacceptable [24]. GLS was obtained by averaging all values of segmental peak strain in the apical views [25]. The strain values for the 6 basal, 6 mid-, and 5 apical segments of the left ventricle

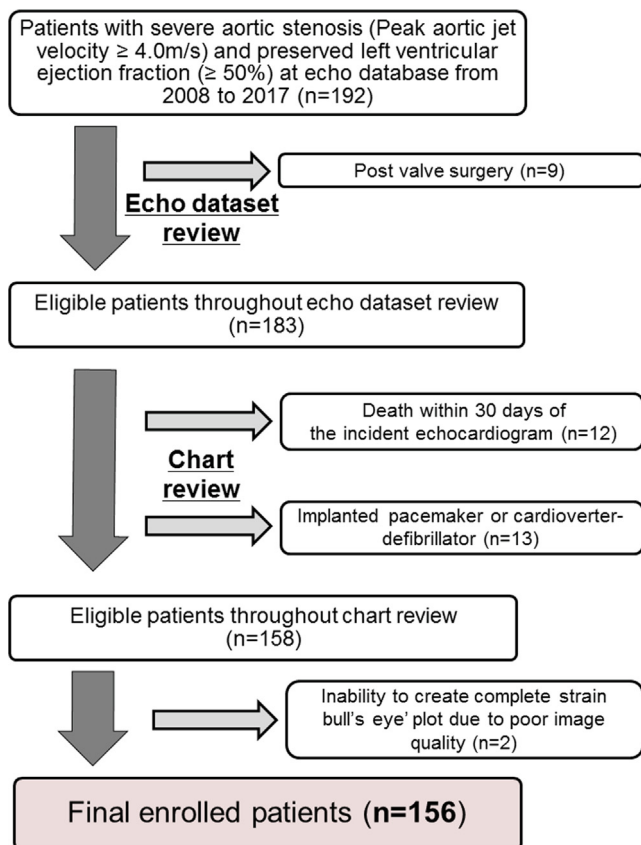


Fig. 1. Selection of patients based on the study protocol.

were averaged to obtain regional longitudinal strain (LS) values (basal, mid, and apical, respectively). During the measurement of GLS, a strain polar map including segmental LS values was automatically illustrated. The mean frame rate was 62 ± 9 frames/s. In patients with atrial fibrillation, strain parameters were estimated on the basis of index-beat method if the ratio of the preceding and pre-preceding intervals was close to 1 [26].

2.6. RASP

In accordance with a previous study, quantitative RASP (qRASP) was calculated using the following formula: (Average apical LS)/(Average basal LS + Average mid LS) [9]. Using the validated threshold, qRASP ≥ 1.0 was defined as positive [9]. Although the assessment of qRASP is concordant between observers, an offline analysis is required and is time-consuming. qRASP also depends on the values of mid-ventricular strain and may ignore the eccentricity of the strain because of the use of the average value. Furthermore, when the overall strain value was increased, false positives may have occurred because the increased value of the basal strain could have changed the color of the basal segments when a fixed color range is used. According to the potential limitation of qRASP assessment, we also semi-quantitatively assessed RASP with the following method. Currently, the manufacturers GE and Philips have adopted an eight equally-divided color range from -20% (red) to 20% (blue) when the strain value is represented on a strain polar map. In this context, RASP is represented with red at the apex together with pink or light blue at the base of the left ventricle. In other words, this pattern is composed of less than -15% LS, showing red at the apical segments, and more than -10% LS, showing pink or light blue at the basal segments [9,27,28]. Hence, semi-quantitative RASP (sRASP) was defined as reduction of LS ($\geq -10\%$) in ≥ 5 segments out of the 6 basal segments, relative to preserved LS ($< -15\%$) in at least 1 apical seg-

ment. A representative case is demonstrated in Fig. 2 Panel A. sRASP was independently assessed by two blinded sonographers. The concordance of this assessment was perfect ($\kappa = 1.00$).

2.7. MACE

The primary outcome was sudden cardiac death or unexpected admission due to heart failure. Medical records were used to conduct follow-up assessment of the patients. When the patient has been followed up by another clinic, the patient's event data was confirmed by the general practitioners' information. The patients were censored at the time of MACE or at the end of the follow-up period (January 1, 2019).

2.8. Statistical analysis

Overall, $<1\%$ of the observations were missing. Continuous variables were expressed as mean \pm standard deviation (SD) or median values (25th and 75th percentiles) according to their distributions, and qualitative data were presented as numbers or percentages. The significance of the differences between the groups was assessed using Student's *t*-test or the Mann-Whitney *U* test, as appropriate. The chi-square test was used for categorical variables. The repeated measurements were performed using a paired *t* test. Independent association between RASP and MACE was determined using univariate and multivariate Cox proportional hazards models. No significant violations of assumption of proportional hazards were noted. To increase external validation, the candidate covariates for the multivariate models were selected based on clinically relevant variables that were expected to confound the association between sRASP and MACE. Particularly, we refereed the covariates of the multivariate model used in the previous paper [7], because the cohort and study design in this referred paper were almost similar with our study. The variables were as follows: age, sex,

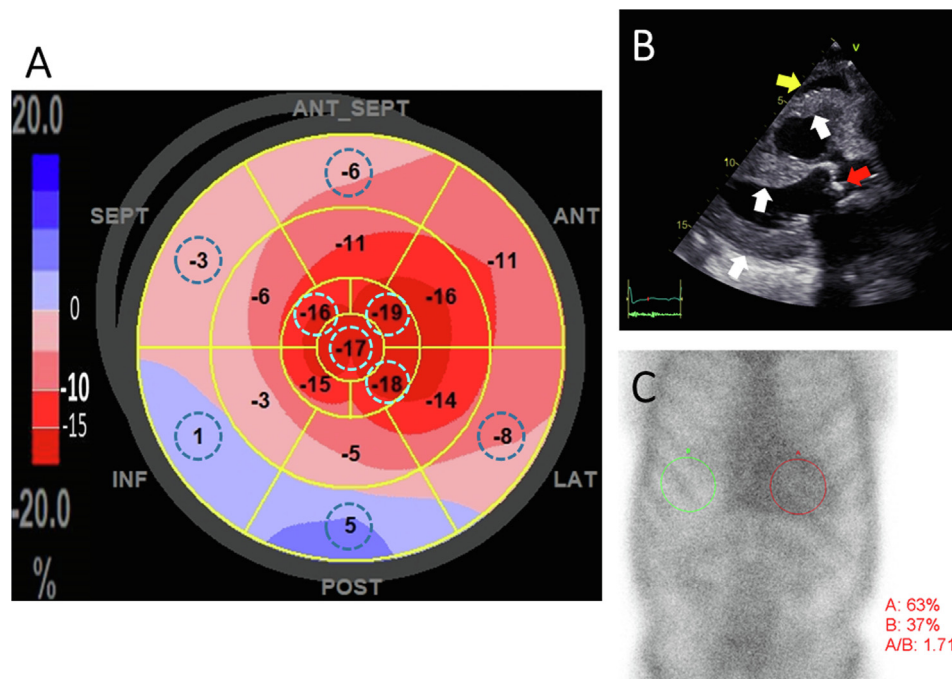


Fig. 2. A representative case of an 85-year-old male. Panel A shows the relative apical sparing pattern (RASP). The semi-quantitative RASP is positive because there is reduction in longitudinal strain ($\geq -10\%$) in 5 segments out of the 6 basal segments, relative to preserved longitudinal strain ($< -15\%$) at 4 apical segments. The quantitative RASP is calculated as 1.09 (>1.00); quantitative RASP is also positive. Panel B shows the parasternal long-axis view at late systole (see ONLINE MOVIE). The patient has increased wall thickness (**white arrows**) in both left and right ventricular wall with pericardial effusion (**yellow arrow**). The aortic valve is calcified (**red arrow**); peak aortic jet velocity was 4.1 m/s and calculated aortic valve area was 0.63 cm². Panel C shows 99mTc-pyrophosphate scintigraphy. Significant myocardial uptake was observed. RASP, relative apical sparing pattern. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

additive EuroSCORE, NYHA class, peak aortic jet velocity, AVR, LV mass index, left atrial volume index, and GLS. AVR was included as a time-dependent covariate in the analysis. Three models that could be used for the assessment of the independent association between sRASP and MACE were established to avoid overfitting. Furthermore, atrial fibrillation may have a significant impact on strain measurement. Accordingly, the association between sRASP and MACE was also confirmed only in patients without atrial fibrillation using similar multivariable models. In these analyses, the covariates were selected according to the number of events. The incremental value of the RASP was also assessed in four modeling steps using nested models. The first step consisted of fitting a multivariate model of an additive EuroSCORE as described previously [7]. Then, NYHA class ≥ 2 was included in the second step. Next, GLS or the ratio of LV ejection fraction and GLS (EFSR) was included in the third step. Finally, sRASP was included in the fourth step. The change in the overall log-likelihood ratio was used to assess the increase in predictive power. Harrell's C-statistic was used to evaluate model performance [29]. The interobserver variability of sRASP and the agreement of the methods for sRASP and qRASP were assessed using the kappa statistic. The Statistical Package for the Social Science software version 20.0 (SPSS Inc., Chicago, IL) was used to perform statistical analysis, and a p value < 0.05 (two-tailed) was considered statistically significant.

3. Results

3.1. Patient characteristics

The positive findings of sRASP and qRASP were found in 24 (15%) and 42 (27%) patients, respectively. Table 1 summarizes the baseline clinical and echocardiographic parameters of the enrolled patients with and without sRASP. Overall, the median age of the patients was 84 years. Nearly half of the patients were symptom-free (NYHA functional class I). The median additive EuroSCORE was 7. The mean values of LV ejection fraction and GLS were 67% and -16.7% , and the median peak aortic jet velocity and calculated aortic valve area were 4.2 m/s and 0.77 cm^2 , respectively. Also, the sRASP was significantly associated with slight built, lower blood pressure, higher heart rate, higher NYHA functional class, lower frequency of dyslipidemia, higher frequency of atrial fibrillation, higher EuroSCORE, higher brain natriuretic peptide, and more deteriorated LV systolic and diastolic functional parameters. However, the incidence of sRASP was not associated with the AS severity in this cohort.

Among the enrolled patients, two patients with sRASP underwent $^{99\text{mTc}}$ -pyrophosphate scintigraphy. Both patients had significant myocardial uptake of $^{99\text{mTc}}$ -pyrophosphate (Perugini grade ≥ 2) [30]. An example of one of the patients is shown in Fig. 2.

Patients with AVR ($n = 50$) were significantly younger than those without AVR (79 years [IQR 70–84] vs 86 years [IQR 81–89], $p < 0.01$). However, the proportion of male patients (33% vs 34%, $p = 0.90$), LV ejection fraction ($66 \pm 10\%$ vs $68 \pm 7\%$, $p = 0.26$), and GLS ($-16.4 \pm 4.0\%$ vs $-16.9 \pm 3.8\%$, $p = 0.41$) were not different between the two groups.

3.2. Outcomes

During follow-up (median: 1.9 years, IQR: 0.7–4.2 years), 44 (28%) patients presented MACE (13: sudden cardiac deaths; 31: unexpected admissions due to heart failure).

3.3. Associations between RASP and MACE

Of 24 patients presenting sRASP, 15 (63%) experienced MACE. In the univariate Cox regression analysis, the adverse outcome was

clearly associated with a higher prevalence of sRASP (hazard ratio [HR]: 3.66 [95% CI: 1.94–6.92], $p < 0.01$) and qRASP (HR: 2.29 [95% CI: 1.24–4.22], $p < 0.01$). To test the robustness of the association between sRASP and MACE, three different models were established (Table 2), resulting that sRASP was significantly associated with MACE in each model. Even in patients without atrial fibrillation, sRASP was associated with MACE after similar adjustments (Online Table 1).

3.4. Effect of AVR treatment on associations between sRASP and MACE

Online Table 2 shows the associations between RASP and MACE according to the requirement for AVR. Although the number of patients with AVR was small, the event rate was higher in patients with sRASP than in those without sRASP, irrespective of AVR treatment.

In addition, the qRASP values of 29 patients who underwent follow-up echocardiography significantly improved after AVR (0.86 ± 0.20 to 0.63 ± 0.19 , $p < 0.01$). Three of them had sRASP before AVR; among them, sRASP disappeared after AVR in two patients, and they did not have adverse events thereafter. Although the value of qRASP had improved from 1.63 to 1.08 in the remaining patient, sRASP was also observed, and MACE occurred.

3.5. Incremental value of sRASP over conventional risks for predicting MACE

In the sequential Cox models, the model based on the additive EuroSCORE for predicting MACE was significantly improved by the addition of the presence of symptoms, represented by NYHA functional class $\geq \text{II}$, and was furthermore improved by adding GLS. Finally, the addition of sRASP showed further incremental benefits (Fig. 3). Similarly, the model based on the additive EuroSCORE and the presence of symptoms was significantly improved by adding EFSR (chi-squared: 19.8 to 26.8, $p = 0.03$) and even further improved by adding sRASP (chi-squared: 26.8 to 36.1, $p = 0.02$).

4. Discussion

In our study, RASP was observed in some patients with severe AS and was associated with MACE, which was independent of and incremental to conventional clinical and echocardiographic parameters and GLS. The association between RASP and MACE might be significant, regardless of AVR.

4.1. Possible causes of the presence of RASP and its association with MACE in severe AS

The finding that RASP is frequently observed in patients with cardiac amyloidosis may be associated with the extent or severity of amyloid deposits (higher accumulation in basal segments than in apical segments) [10]. In a recent prospective clinical trial, 13.9% of patients with severe AS were complicated by ATTR-CM [2]. ATTR-CM is a life-threatening disease that results in poor quality of life of patients [31,32]. Accordingly, some patients with RASP in severe AS might be complicated by ATTR-CM, which might consequently confound the association between RASP and MACE.

Furthermore, this finding may also be affected by differences at the site of wall stress in patients with AS [11,12]. In some patients, qRASP values significantly improved after AVR. Interestingly, the patient whose sRASP remained the same after AVR had an adverse event and the patient whose sRASP improved after AVR had no event; however, it is a study that included a few cases. Possibly,

Table 1
Baseline characteristics in patients with and without semi-quantitative relative apical sparing pattern.

Variables	Number of available patients	All (n = 156)	sRASP (N = 24)	No sRASP (N = 132)	P (sRASP vs No sRASP)
Age, yrs	156	84 (76–89)	86 (82–90)	84 (75–88)	0.06
Male, n (%)	156	52 (33%)	5 (21%)	47 (36%)	0.16
Body mass index, kg/m ²	156	23.6 ± 4.3	21.8 ± 4.3	23.8 ± 4.3	0.04
Body surface area, m ²	156	1.46 ± 0.19	1.35 ± 0.18	1.48 ± 0.18	<0.01
Systolic blood pressure, mmHg	156	136 ± 21	126 ± 26	138 ± 19	<0.01
Diastolic blood pressure, mmHg	156	66 ± 12	64 ± 16	67 ± 11	0.31
Heart rate, beats/min	156	67 (57–77)	77 (64–87)	65 (56–74)	<0.01
NYHA functional class (I / II / III / IV), n (%)	156	74 (47%) / 64 (41%) / 15 (10%) / 3 (2%)	5 (21%) / 14 (58%) / 5 (21%) / 0 (0%)	69 (52%) / 50 (38%) / 10 (8%) / 3 (2%)	0.02
Comorbidities					
Hypertension, n (%)	156	109 (70%)	14 (58%)	95 (72%)	0.19
Dyslipidemia, n (%)	156	56 (36%)	4 (17%)	53 (40%)	0.02
Diabetes mellitus, n (%)	156	28 (18%)	7 (29%)	21 (16%)	0.10
Atrial fibrillation, n (%)	156	30 (19%)	9 (38%)	21 (16%)	0.01
Coronary artery disease, n (%)	156	23 (15%)	5 (21%)	18 (14%)	0.36
Cerebrovascular disease, n (%)	156	14(9%)	4 (17%)	10 (8%)	0.15
Additive EuroSCORE	156	7 (5–8)	8 (7–10)	7 (5–8)	0.02
Biochemical parameters					
Hemoglobin, g/dL	156	11.7 ± 2.0	11.8 ± 1.4	11.7 ± 2.0	0.86
Sodium, mEq/L	156	140 (138–142)	141 (138–142)	140 (138–142)	0.47
eGFR, mL/min/1.73 m ²	156	58 (42–74)	55 (38–65)	59 (42–74)	0.36
Albumin, g/dL	153	3.9 (3.5–4.2)	3.8 (3.5–4.2)	3.9 (3.5–4.2)	0.47
Brain natriuretic peptide, pg/mL	156	98 (46–223)	235 (98–443)	83 (43–178)	<0.01
Electrocardiographic parameters					
Low voltage or pseudoinfarct pattern, n (%)	156	15 (10%)	2 (8%)	13 (10%)	0.59
Left ventricular Sokolow index, mm	156	3.8 (3.0–4.5)	3.7 (3.1–4.3)	3.8 (3.0–4.5)	0.77
Strain pattern, n (%)	156	64 (41%)	10 (42%)	54 (41%)	0.86
QRS duration, ms	156	92 (85–100)	87 (81–97)	92 (86–100)	0.17
Echocardiographic parameters					
Left ventricular diastolic diameter, mm	156	46 ± 7	45 ± 10	46 ± 6	0.53
Left ventricular systolic diameter, mm	156	28 ± 6	29 ± 9	28 ± 5	0.40
Interventricular septum thickness, mm	156	10 ± 2	11 ± 2	10 ± 2	0.07
Posterior wall thickness, mm	156	10 ± 2	10 ± 2	10 ± 2	0.28
Left ventricular mass index, g/m ²	156	105 (87–129)	108 (95–136)	104 (85–126)	0.13
Left ventricular diastolic volume index, mL/m ²	156	43 (36–55)	41 (32–50)	44 (36–55)	0.28
Left ventricular systolic volume index, mL/m ²	156	13 (11–19)	17 (13–19)	13 (10–19)	0.13
Stroke volume index, mL/m ²	156	30 (23–36)	23 (20–33)	30 (25–36)	0.03
Left ventricular ejection fraction, %	156	67 ± 7	63 ± 6	68 ± 7	<0.01
e', cm/s	155	4.5 (3.8–5.8)	4.1 (2.8–5.4)	4.6 (3.9–5.8)	0.15
E/e'	155	17.9 (13.1–27.2)	28.4 (16.4–35.8)	17.5 (12.6–25.6)	<0.01
Deceleration time, ms	156	286 (223–345)	244 (209–314)	289 (239–360)	0.04
Left atrial volume index, mL/m ²	156	58 (45–80)	80 (54–105)	57 (45–73)	0.02
Global longitudinal strain, %	156	−16.8 ± 3.8	−13.0 ± 2.9	−17.4 ± 3.6	<0.01
EFSR	156	4.2 ± 1.0	5.0 ± 1.0	4.1 ± 1.0	<0.01
Aortic valve parameters					
Peak aortic jet velocity, m/s	156	4.2 (4.0–4.9)	4.3 (4.0–5.0)	4.2 (4.0–4.9)	0.47
Aortic valve mean gradient, mmHg	156	44 (37–57)	44 (36–65)	44 (37–55)	0.95
Calculated aortic valve area, cm ²	156	0.77 (0.52–1.00)	0.62 (0.42–1.00)	0.78 (0.57–1.00)	0.11
RASP					
Quantitative RASP	156	0.90 ± 0.25	1.15 ± 0.40	0.86 ± 0.18	<0.01
Quantitative RASP > 1.00, n (%)	156	42 (27%)	16 (67%)	26 (20%)	<0.01

Data are expressed as mean ± standard deviation, median (IQR), or number (%). **Bold** indicates p < 0.05.

EFSR, Ejection fraction strain ratio; eGFR, Estimated glomerular filtration rate; RASP, Relative apical sparing pattern; sRASP, Semi-quantitative relative apical sparing pattern.

the patient whose sRASP remained the same after AVR may have worse cardiac function because of distribution of amyloid deposits and fibrosis with long-standing afterload, which resulted in the cardiac event.

4.2. Additive value of RASP over GLS in predicting MACE

In this study, RASP showed an incremental benefit over GLS in predicting MACE in patients with severe AS. GLS is mostly

Table 2
Characteristics independently associated with the primary outcome (multivariable Cox regression).

Variables	Comorbidity model n = 156, Events = 44 Chi-square = 47.0, c-statistics = 0.78 HR (95% CI), p-Value	Valve model n = 156, Events = 44 Chi-square = 23.3, c-statistics = 0.72 HR (95% CI), p-Value	Echo model n = 156, Events = 44 Chi-square = 34.7, c-statistics = 0.70 HR (95% CI), p-Value
Age (per 1-year increase)	1.07 (1.01–1.13) p = 0.02	1.04 (0.99–1.09) p = 0.13	
Male	1.15 (0.56–2.40) p = 0.70		
Additive EuroSCORE (per 1 increase)	0.93 (0.77–1.13) p = 0.48		
NYHA functional class (per 1 increase)	2.50 (1.63–3.81) p < 0.01		
Peak aortic jet velocity (per 1 m/s increase)		1.17 (0.70–1.95) p = 0.55	
Aortic valve replacement (Time-dependent covariate analysis)		0.32 (0.10–0.98) p = 0.04	
Left ventricular mass index (per 10 g/m ² increase)			1.08 (0.99–1.18) p = 0.09
Left atrial volume index (per 10 mL/m ² increase)			1.07 (1.02–1.13) p < 0.01
Global longitudinal strain (per 1% increase)			1.02 (0.93–1.13) p = 0.56
sRASP	2.36 (1.21–4.58) p = 0.01	3.22 (1.61–6.46) p < 0.01	2.42 (1.06–5.50) p = 0.04

Bold indicates p < 0.05.

CI, Confidence interval; HR, Hazard ratio; sRASP, Semi-quantitative relative apical sparing pattern.

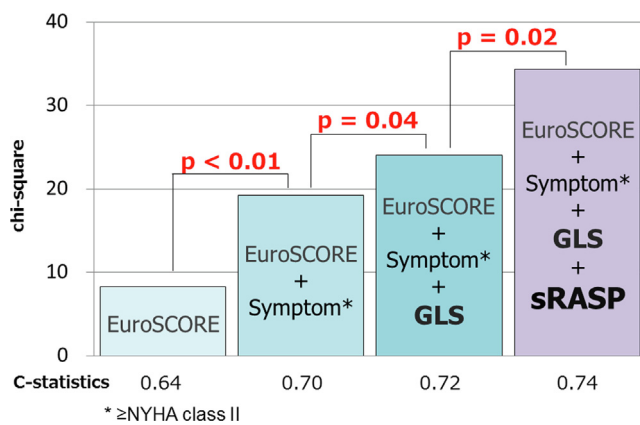


Fig. 3. Incremental value of semi-quantitative relative apical sparing pattern over the conventional risk model in predicting adverse cardiac events. Symptom indicates NYHA functional class \geq II. GLS, global longitudinal strain; sRASP, semi-quantitative relative apical sparing pattern.

deteriorated in patients with severe AS because of sustained pressure overload. Possibly, RASP might have additive information that reflects amyloid accumulation and fibrosis with uneven increased afterload other than left ventricular dysfunction as indicated by GLS, which could result in an incremental benefit over GLS in predicting outcome. Furthermore, it has been reported that the decrease in basal longitudinal strain (in other words, the appearance of RASP) was more sensitively associated with poor prognosis rather than GLS in patients with moderate to severe AS [13,14]. For a similar reason, RASP may provide prognostic value to EFSR, which can contribute to predict cardiac amyloidosis [33]. Moreover, the higher reproducibility of sRASP over EFSR may associate with this result.

However, a previous study have clearly found the prognostic significance of GLS in patients with aortic stenosis [6,7,34]. The results of this study have not been validated yet. Therefore, GLS may still be an important prognostic factor unless our results are confirmed in other cohorts.

4.3. Difference between RASP measurements

In this study, we assessed RASP using semi-quantitative and quantitative methods. Although both assessments were associated with the adverse outcome, sRASP seemed to be more associated

with the outcome rather than qRASP. To clarify the cause of this result, we have created a 2×2 tables with sRASP and qRASP (Fig. 4). The agreement between both methods was fair ($\kappa = 0.36$). The discordant cases included 8 patients with positive sRASP and negative qRASP and 26 patients with negative sRASP and positive qRASP. In cases with positive sRASP and negative qRASP, midventricular longitudinal strain was relatively preserved; consequently quantitative RASP seemed to be low. In contrast, in cases with negative sRASP and positive qRASP, the whole longitudinal strain (particularly apical longitudinal strain) was preserved; consequently sRASP seemed to become negative and quantitative RASP seemed to become positive. In this group, global longitudinal strain was maintained, there was no visually apparent RASP, and a few events occurred. This seemed to explain the results of this study, that is, sRASP was more useful for event prediction than qRASP.

qRASP is consistent but time consuming, and some concerns remain regarding the equation, that is, (1) dependency on the mid-ventricular strain value, (2) offset of the variation of the strain value based on the use of average value, (3) false positive because of increased strain value of the entire left ventricle, and (4) no established threshold for the assessment. On the other hand, sRASP is simple and does not rely on the shortcomings of the quantitative method. Currently, GLS and its bull's eye plot can be quickly found online at the patient's bedside; such assessment may help to refine risk stratification in patients with severe AS readily. However, sRASP depends on absolute strain values. Therefore, determining sRASP may depend on the device used and the manufacturer. This is because vendor differences in strain measurement have been reported [23]. This may affect the cutoff values of LS in preserved and deteriorated segments, which could affect the generalization of sRASP. Therefore, verifying the validity of this method for all vendors is necessary.

4.4. Limitations

Our data should be interpreted keeping in mind the limitations. First, a major limitation is that histological assessment was not performed in this study. Therefore, patients with RASP might not necessarily exhibit ATTR-CM. However, the previous study demonstrated that RASP was sensitively associated with cardiac amyloidosis regardless of its types [35]. Second, according to recent studies, ATTR-CM seemed to be more frequent in paradoxical AS [1,36]. The present study enrolled only patients with true severe AS. Therefore, the association between RASP with MACE remains to be defined in paradoxical AS and in patients with earlier stage

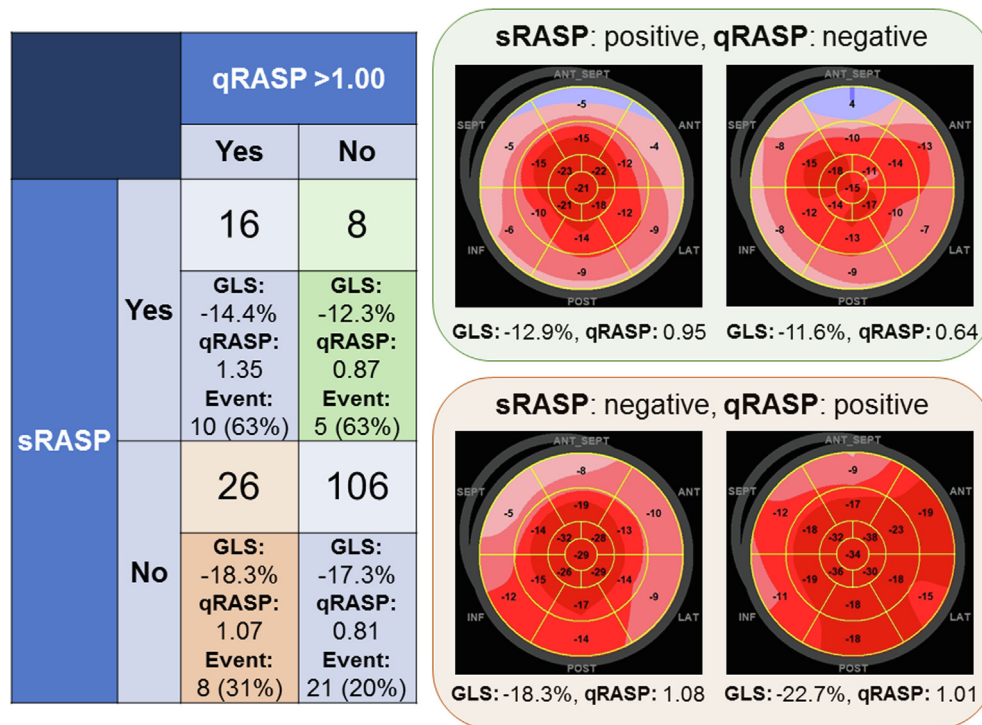


Fig. 4. Relationship between relative apical sparing pattern measurements. GLS, global longitudinal strain; qRASP, quantitative relative apical sparing pattern; sRASP, semi-quantitative relative apical sparing pattern.

AS. Finally, this was a retrospective study from a single, large, tertiary referral center. Thus, the external generalizability of the results may be limited.

5. Conclusions

The assessment of RASP is readily available in clinical settings. RASP is observed in some patients with true severe AS and provides incremental benefit in predicting MACE, over conventional clinical and echocardiographic parameters and GLS. This noninvasive diagnostic procedure may be useful for risk stratification and the allocation of appropriate medical resources in AS patients. However, larger multicenter prospective studies among several types and stages of AS should be conducted to confirm the results of the present study.

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CRediT authorship contribution statement

Makoto Saito: Conceptualization, Methodology, Formal analysis, Writing - original draft. **Misaki Imai:** Data curation, Investigation. **Daisuke Wake:** Data curation, Investigation. **Rieko Higaki:** Data curation, Project administration, Resources. **Yasuhisa Nakao:** Visualization. **Hiroe Morioka:** Supervision. **Takumi Sumimoto:** Supervision. **Katsuji Inoue:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2020.100551>.

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