Received: 23 March 2025 | Revised: 22 April 2025 | Accepted: 29 April 2025

DOI: 10.1002/joa3.70088

ORIGINAL ARTICLE

Journal of Arrhythmia Open Access WILEY

The HFA-PEFF score and outcomes in patients with sick sinus syndrome and preserved ejection fraction after pacemaker implantation

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Abstract

Background: Sick sinus syndrome (SSS) is associated with atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). However, diagnosing HFpEF in patients with SSS and determining its prognosis are challenging. The European Society of Cardiology has recommended the HFA-PEFF score for HFpEF diagnosis. In this study, we utilized the HFA-PEFF score to diagnose HFpEF in patients with SSS and preserved ejection fraction, comparing the prognosis and AF burden between those diagnosed with HFpEF and those without.

Methods: We identified 131 patients with symptomatic SSS and preserved ejection fraction who underwent pacemaker implantation between January 2019 and December 2021. Of these, 52 (39.7%) had an HFA-PEFF score ≥5 and met the diagnostic criteria for HFpEF.

Results: Patients with HFpEF experienced more cardiovascular events (28.8% vs. 11.4%; $p = .009$) within 3 years than those without HFpEF. The median duration of AF per day during the first year was significantly longer in the HFpEF group (10 vs. 30 min/day, $p < .001$). Additionally, these patients had a higher incidence of AF lasting for ≥7 days (32.9% vs. 16.9%; $p = .038$) within 3 years. A simplified HFA-PEFF score incorporating E/e′, tricuspid regurgitation peak gradient, left atrial volume index, and brain natriuretic peptide predicted cardiovascular events and AF burden.

Conclusions: Patients diagnosed with HFpEF using the HFA-PEFF score have a higher incidence of cardiovascular events and a greater AF burden within 3 years after pacemaker implantation for SSS. The HFA-PEFF score may be useful for risk stratification in these patients.

KEYWORDS
atrial cardiomyopathy, atrial fibrillation, heart failure with preserved ejection fraction, pacemaker, sick sinus syndrome

1 | INTRODUCTION

Sick sinus syndrome (SSS) is characterized by symptomatic sinus node dysfunction, which leads to reduced quality of life, syncope, and the need for a pacemaker. SSS is also associated with atrial fibrillation (AF). These conditions are not merely sinus node and pulmonary vein disorders but are manifestations of underlying atrial cardiomyopathy (AC).[1] AC is a structural, contractile, or electrophysiological atrial remodeling associated with increased cardiovascular events, such as heart failure, stroke, and myocardial infarction.[2,3] Many patients with AC have a preserved left ventricular ejection fraction (LVEF). Estimates suggest that approximately 10%–20% of patients with AF suffer heart failure with preserved ejection fraction (HFpEF), whereas 15%–40% of patients with HFpEF have concomitant AF. Therefore, these conditions are often referred to as "vicious twins."[4] Previous studies reported that exercise intolerance and chronotropic incompetence in HFpEF are associated with SSS.[5,6] However, only a few studies have examined the outcomes of patients with both SSS and HFpEF.[1,6]

The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) recommends the Heart Failure Association pre-test probability score for heart failure with preserved ejection fraction (HFA-PEFF score) as a diagnostic algorithm for HFpEF.[7] In addition to its diagnostic value, an association between the score and clinical outcomes has been demonstrated.[8,9] We previously reported that the HFA-PEFF score after catheter ablation for AF is associated with cardiovascular events and AF recurrence in patients with preserved LVEF and HFA-PEFF score improvement indicates atrial reverse remodeling.[9,10]

In this study, we utilized the HFA-PEFF score to diagnose HFpEF in patients with SSS and preserved ejection fraction, comparing the prognosis and AF burden between those diagnosed with HFpEF and those without.

2 | METHODS

2.1 | Study population

This retrospective single-center observational study consecutively recruited symptomatic SSS patients who underwent dual-chamber pacemaker (DDDR) implantation (Azure XT DR MRI, Medtronic Inc.) at Kurashiki Central Hospital from January 2019 to December 2021. The exclusion criteria were a history of persistent AF, previous AF ablation, previous cardiac surgery, hypertrophic cardiomyopathy, cardiac amyloidosis, and an LVEF <50%. Patients with the right atrial lead placed outside the right atrial appendage or who underwent conduction system pacing were also excluded. Blood tests and transthoracic echocardiography (TTE) were performed 2 days after pacemaker implantation. Cardiac sonographers performed TTE, and cardiologists trained in echocardiography interpreted the data. Current recommendations were used for measurements.[11] The Kurashiki Central Hospital Medical Ethics Committee approved this study, which was conducted according to the Declaration of Helsinki. All participants provided written informed consent.

2.2 | Device programming

Atrial rate stabilization, post-mode switch overdrive pacing, and reactive atrial-based antitachycardia pacing were started 1 month after pacemaker implantation in all patients. Specific device programming details are shown in Table S1. Sensed and paced atrioventricular delays were programmed by physicians to limit ventricular stimulation.

2.3 | HFA-PEFF score

The HFA-PEFF score has been detailed in previous research as part of the HFA-PEFF diagnostic algorithm for suspected HFpEF.[7] In brief, the HFA-PEFF diagnostic algorithm is a multistep tool that enhances the accuracy and efficiency of HFpEF diagnosis. Step 1 identifies patients suffering from HFpEF and excludes other specific causes of symptoms that mimic heart failure. Step 2 involves calculating the HFA-PEFF score.

The HFA-PEFF score comprises three domains: (1) function, (2) morphology, and (3) biomarker. Major and minor criteria are applied to each domain and contribute a maximum of 2 points. Thus, the highest score is 6. An HFA-PEFF score ≥5 is considered diagnostic of HFpEF, whereas a score <2 indicates an unlikely diagnosis of HFpEF and mandates investigation for alternative causes. Patients with an intermediate score (2–4 points) require further evaluation, including exercise echocardiography and heart catheterization. In this study, patients with an HFA-PEFF score ≥5 were diagnosed with HFpEF.

In patients with HFpEF and AF, the left atrial volume index (LAVI) was 35% greater than that in patients with HFpEF in sinus rhythm (SR). Additionally, average brain natriuretic peptide (BNP) levels were threefold higher in patients with AF than in patients with SR.[12] Therefore, separate cutoffs for LAVI and BNP in SR versus AF are recommended.[7] We calculated the preprocedural and postprocedural HFA-PEFF scores using the cutoff for LAVI and BNP in AF. Because global longitudinal strain (GLS) data were not measured, we calculated the score without the GLS.

2.4 | Simplified HFA-PEFF score

The original HFA-PEFF score includes numerous echocardiographic variables that can impede its use in daily practice. We created the AF-HFA-PEFF score, which is a simplified version of the HFA-PEFF score. The AF-HFA-PEFF score includes E/e′, tricuspid regurgitation peak gradient (TRPG), LAVI, and BNP levels as variables from the

TABLE 1 The atrial cardiomyopathy score.

Measurement	Criterion	Points	Score (form 0 to maximal 2 points per domain)
A. Functional Measurement Domain			
E/e′ as *major* criterion	E/e′ ratio ≥ 15	2	
Tricuspid regurgitation velocity (m/s)	Peak velocity >2.8	2	
E/e′ as *minor* criterion	E/e′ ratio 9–14	1	
B. Morphological measurement domain			
Left atrial volume index (LAVI) (mL/m^2) as *major* criterion	LAVI >40	2	
Left atrial volume index (mL/m^2) as *minor* criterion	LAVI 34–40	1	
C. Natriuretic peptide domain			
Serum concentration of BNP or NT-proBNP (pg/mL or ng/L)	BNP > 240 BNP 105–240 NT-proBNP >660 NT-proBNP 375–660	2 1 2 1	

Abbreviations: BNP, brain natriuretic peptide; LAVI, left atrial volume index; NT-proBNP, N-terminal proBNP.

original HFA-PEFF score (Table 1). A methodology for transitioning from continuous to discrete variables and distinguishing major and minor criteria was adopted from the HFA-PEFF score. Major and minor criteria were applied to each domain with a maximum of 2 points each. The highest AF-HFA-PEFF score was 6. We previously reported that the postprocedural HFA-PEFF score and the AF-HFA-PEFF score are equally associated with 3-year cardiovascular events and AF recurrence. Recovery of these scores after AF ablation indicates atrial reverse remodeling in patients with preserved LVEF.[9,10] Therefore, we renamed the AF-HFA-PEFF score the AC score and defined a score ≥4 as the cutoff value for stratifying prognosis and AF burden according to a previous study.[10]

2.5 | Follow-up

A remote monitoring system assessed the AF outcomes every month with device interrogation every 6 months in the outpatient clinic. A clinician confirmed AF episodes to verify the diagnostic accuracy and rule out far-field R-wave sensing, atrial lead oversensing, pacemaker-mediated arrhythmia, and/or electrical/mechanical interference. AF burden was derived from pacemaker counters.

Clinical data, age, sex, comorbidities, echocardiographic data, and medications were obtained from medical records. Cardiovascular events were defined as cardiac hospitalization for HF or acute ischemic events, ischemic stroke or transient ischemic attack (TIA), and cardiovascular mortality. Anticoagulant therapy was administered to patients with a history of AF and a CHA_2DS_2-VASc score ≥2 or to those with AF lasting more than 1 h with a CHA_2DS_2-VASc score ≥2 detected during follow-up.

2.6 | Statistical analysis

Normally distributed continuous variables are presented as means ± standard deviation. Non-normally distributed data are presented as medians and interquartile range (IQR). Between-group comparisons were made with parametric (Student's *t*) or nonparametric (Mann–Whitney *U*) tests. We compared categorical variables with the χ^2 test and Fisher's exact test as needed. Event-free survival was estimated with the Kaplan–Meier method. We developed multivariable Cox proportional hazard regression models for cardiovascular events and the duration of AF. Variables with a $p < .1$ in the univariate analysis were entered in the multivariate Cox regression model and considered statistically significant when $p < .05$. All statistical analyses were performed with SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

3 | RESULTS

We evaluated 191 potentially eligible patients with SSS who underwent dual-chamber pacemaker implantation. We excluded 12 patients with persistent AF, 16 with a history of AF ablation or cardiac surgery, 2 with a history of hypertrophic cardiomyopathy (HCM), 14 with an LVEF <50% (1 of whom had amyloidosis and 8 underwent conduction system pacing), 12 with right atrial lead placement in the right atrial septum, and 6 without sufficient clinical or echocardiographic data. Finally, 131 were enrolled in the analysis.

Table 2 presents the baseline characteristics of the study population. Their mean age was 80.2 ± 7.7 years. Overall, 47.3% of patients were women, and 57.3% had a history of paroxysmal AF

TABLE 2 Baseline characteristics.

	Total ($n=131$)	no HFpEF ($n=79$)	HFpEF ($n=52$)	p value
Demographics and comorbidities				
Age (years)	80.2±7.7	78.9±6.9	82.1±8.4	.026
Sex, female, *n* (%)	62 (47.3)	32 (40.5)	30 (57.7)	.054
Body mass index (kg/m^2)	22.6±3.2	23.0±3.2	22.1±3.0	.107
History of paroxysmal AF, *n* (%)	75 (57.3)	40 (50.6)	35 (67.3)	.059
Tachy-brady syndrome	49 (37.4)	28 (35.4)	21 (40.3)	.217
CHA_2DS_2-VASc score	4 (3–4)	3 (3–4)	4 (3–4)	.148
Hypertension, *n* (%)	92 (70.2)	57 (72.2)	35 (67.3)	.553
Diabetes, *n* (%)	33 (25.2)	19 (24.1)	14 (24.1)	.711
Coronary artery disease, *n* (%)	23 (17.6)	14 (17.7)	9 (17.3)	.951
Prior hospitalization for HF, *n* (%)	15 (11.5)	5 (6.3)	10 (19.2)	.023
Prior stroke/TIA, *n* (%)	16 (12.2)	9 (11.4)	7 (13.5)	.723
HFA-PEFF score	4 (3–5)	3 (3–4)	5 (5–6)	<.001
Atrial cardiomyopathy score	4 (2–5)	3 (1–4)	5 (4–6)	<.001
Medications, *n* (%)				
ACE-I/ARB	64 (48.9)	40 (50.6)	24 (46.2)	.616
MRA	23 (17.6)	8 (10.1)	15 (28.8)	.006
Loop diuretics	31 (23.7)	13 (16.5)	18 (34.6)	.017
SGLT2 inhibitor	17 (13.0)	8 (10.1)	9 (17.3)	.231
Beta-blocker	49 (37.4)	28 (35.4)	21 (40.3)	.217
Verapamil/diltiazem	2 (1.5)	0 (0)	2 (3.8)	.079
Digitalis	2 (1.5)	1 (1.3)	1 (1.9)	.764
Preprocedural antiarrhythmic drug, *n* (%)	18 (13.7)	11 (13.9)	7 (13.5)	.953
1a	8 (6.1)	5 (6.3)	3 (5.8)	.896
1c	7 (5.3)	5 (6.3)	2 (3.8)	.536
Amiodarone	3 (2.3)	1 (1.3)	2 (3.8)	.334
Preprocedural anticoagulant	74 (56.5)	38 (48.1)	36 (69.2)	.031
Vitamine K antagonist, *n* (%)	7 (5.3)	3 (3.8)	4 (7.7)	.332
Direct oral anticoagulant, *n* (%)	67 (51.1)	35 (44.3)	32 (61.5)	.054
Preprocedrual echocardiographic findings				
LVEF (%)	60 (56–64)	60 (55–65)	60 (56–64)	.295
IVS (mm)	11.2±1.9	11.0±1.7	11.4±2.2	.327
LVPW (mm)	10.6±1.8	10.5±1.7	10.8±2.0	.458
LVEDD (mm)	42.6±4.7	42.6±4.9	42.5±4.5	.918
LVESD (mm)	26.9±4.7	26.8±4.6	26.9±4.8	.941
Medial e′	5.2±1.5	5.4±1.4	4.8±1.6	.041
E/e′	12.9±5.7	11.8±4.4	14.7±7.0	.005
TRPG (mm Hg)	23.2±6.9	22.4±6.0	24.2±7.9	.149
LA diameter (mm)	38.9±6.1	37.5±6.0	41.0±5.6	.001
LAVI (mL/m^2)	45.6±17.0	38.5±12.0	56.4±17.7	<.001
LVMI (g/m^2)	103.7±26.2	99.0±21.9	110.8±30.4	.011
RWT	0.52±0.10	0.51±0.09	0.53±0.12	.422
Moderate or greater MR, *n* (%)	8 (6.1)	1 (1.3)	7 (13.5)	.004
Moderate or greater TR, *n* (%)	10 (7.6)	2 (2.5)	8 (15.4)	.007
Laboratory findings				
eGFR, mL/min/1.73 m^2	56.5 (42.7–70.6)	60.7 (44.8–73.8)	53.3 (33.1–66.6)	.036
BNP (pg/mL)	127.1 (59.6–275.5)	72.3 (45.2–117.2)	298.0 (186.4–419.2)	<.001

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; CA, catheter ablation; eGFR, estimated glomerular filtration rate; HF, heart failure; IVS, interventricular septum; LA, left atrium; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; OSA, obstructive sleep apnea; RWT, relative wall thickness; SGLT2, sodium-glucose cotransporter 2; TIA, transient ischemic attack; TR, tricuspid regurgitation; TRPG, tricuspid regurgitation peak gradient.

TABLE 3 Pacing characteristics.

	Total ($n = 131$)	No HFpEF ($n = 79$)	HFpEF ($n = 52$)	p value
Lower rate limit (bpm)	60 (60–60)	60 (60–60)	60 (60–60)	.624
Upper rate limit (bpm)	120 (120–130)	120 (120–130)	120 (120–130)	.134
Atrial pacing rate during the first year (%)	70 (50–84)	69 (45–81)	75 (52–93)	.079
Ventricular pacing rate during the first year (%)	1 (0–18)	1 (0–18)	1 (0–21)	.322
AF time during the first year, minutes/day	15 (0–84)	10 (0–53)	30 (13–108)	<.001

before pacemaker implantation. The median CHA_2DS_2-VASc score was 4 (IQR, 3–4). Of these, 52 (39.7%) had an HFA-PEFF score ≥5, meeting the diagnostic criteria for HFpEF. Patients with HFpEF were significantly older and more likely to be female.

Table 2 shows the echocardiographic findings 2 days after pacemaker implantation. Patients with HFpEF had a higher E/e′, left atrial (LA) diameter, LAVI, left ventricular mass index, and BNP levels. Moreover, they exhibited lower medial e′ and estimated glomerular filtration rate (eGFR). We also found more moderate or greater mitral regurgitation and tricuspid regurgitation in patients with HFpEF.

Table 3 illustrates the pacemaker characteristics of the study population. There were no significant differences between the HFpEF group and the non-HFpEF group in the lower limit rate, upper limit rate, atrial pacing rate, or ventricular pacing rate during the first year.

3.1 | Associations with cardiovascular events

Over a median follow-up of 36 months (IQR, 31–36), 24 patients experienced cardiovascular events: 16 hospitalizations for heart failure, 3 acute ischemic events, 1 TIA, 2 strokes, and 2 cardiac deaths.

The Kaplan–Meier analysis revealed that patients with HFpEF had a higher risk of cardiovascular events during follow-up. The 3-year risks were 28.8% and 11.4% for those with HFpEF and without HFpEF, respectively (Figure 1A). Univariate analysis revealed that the HFA-PEFF score (hazard ratio [HR] = 1.60; 95% confidence interval [CI] = 1.14–2.25; $p = .006$) was associated with the risk of cardiovascular events (Table S2). Moreover, multivariate analysis indicated that the association between the HFA-PEFF score and cardiovascular events was not modified even after introducing other relevant laboratory, clinical, and echocardiographic variables into the HFA-PEFF score (Table 4).

Similar to the original HFA-PEFF score, the AC score, a simplified HFA-PEFF score, was also associated with cardiovascular events. Kaplan–Meier analysis showed that an AC score ≥4 was associated with an increased risk of cardiovascular events at follow-up (Figure 1B). Univariate analysis revealed that the AC score (HR = 1.50; 95% CI = 1.13–1.98; $p = .005$) was associated with the risk of cardiovascular events (Table S1). The multivariate analysis indicated that the association between the AC score and cardiovascular events was not modified after introducing other relevant laboratory, clinical, and echocardiographic variables into the AC score (Table 5).

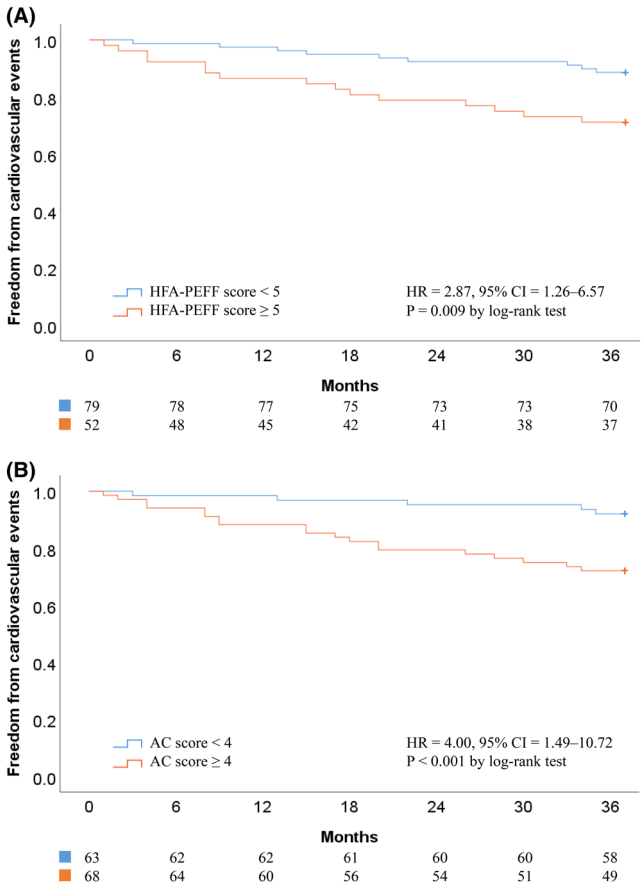

FIGURE 1 Kaplan–Meier cumulative rate of cardiovascular events stratified by HFA-PEFF and AC scores. (A) HFA-PEFF score. (B) AC score. AC, atrial cardiomyopathy.

3.2 | Associations with atrial fibrillation burden

Over 3 years, 84 patients had AF lasting ≥1 h, 49 patients had AF lasting ≥1 day, 29 patients had AF lasting ≥7 days, and 22 patients had AF lasting ≥30 days. The median duration of AF per day during the first year was significantly longer in the HFpEF group than in the non-HFpEF group (10 vs. 30 min/day, $p < .001$) (Table 3).

The Kaplan–Meier analysis showed that patients with HFpEF had a higher risk of AF episodes lasting ≥1 h, ≥1 day, ≥7 days, and ≥30 days during follow-up (Figure 2 and Figure S1). Furthermore, the univariate analysis indicated that the HFA-PEFF score was associated with

TABLE 4 Hazard ratio for the HFA-PEFF score for cardiovascular events with the inclusion of additional potentially relevant variables in multivariable Cox regression analysis.

	HR for additional variable		HR for HFA-PEFF score	
	Multivariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
+ Age	1.03 (0.97–1.10)	.285	1.54 (1.08–2.18)	.017
+ BMI	1.04 (0.91–1.18)	.615	1.63 (1.15–2.32)	.006
+ CHA_2DS_2–VASc score	1.08 (0.67–1.76)	.746	1.54 (1.08–2.18)	.017
+ Coronary artery disease	2.98 (1.30–6.80)	.01	1.55 (1.11–2.18)	.01
+ eGFR	0.98 (0.97–1.01)	.067	1.54 (1.09–2.17)	.0.013

Abbreviation: eGFR, estimated glomerular filtration rate.

TABLE 5 Hazard ratio for the AC score for cardiovascular events with the inclusion of additional potentially relevant variables in multivariable Cox regression analysis.

	HR for additional variable		HR for AC score	
	Multivariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
+ Age	1.03 (0.98–1.10)	.259	1.45 (1.09–1.94)	.011
+ BMI	1.03 (0.91–1.17)	.688	1.51 (1.14–2.01)	.004
+ CHA_2DS_2–VASc score	1.21 (0.89–1.65)	.234	1.46 (1.10–1.95)	.01
+ Coronary artery disease	2.99 (1.30–6.85)	.01	1.47 (1.11–1.94)	.007
+ IVS	1.11 (0.94–1.32)	.205	1.45 (1.10–1.92)	.008
+ LVPW	1.18 (0.99–1.41)	.069	1.43 (1.08–1.90)	.012
+ LVMI	1.01 (0.99–1.02)	.175	1.42 (1.07–1.90)	.017
+ RWT	3.12 (0.83–30.2)	.175	1.45 (1.09–1.91)	.01
+ eGFR	0.98 (0.97–1.01)	.091	1.43 (1.08–1.89)	.013

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; IVS, interventricular septum; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall; RWT, relative wall thickness.

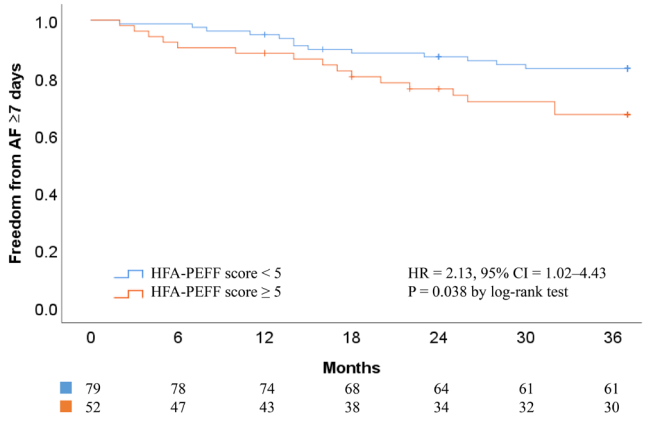

FIGURE 2 Kaplan–Meier cumulative rate of AF-free episodes lasting ≥7 days stratified by HFA-PEFF score. AC, atrial cardiomyopathy; AF, atrial fibrillation.

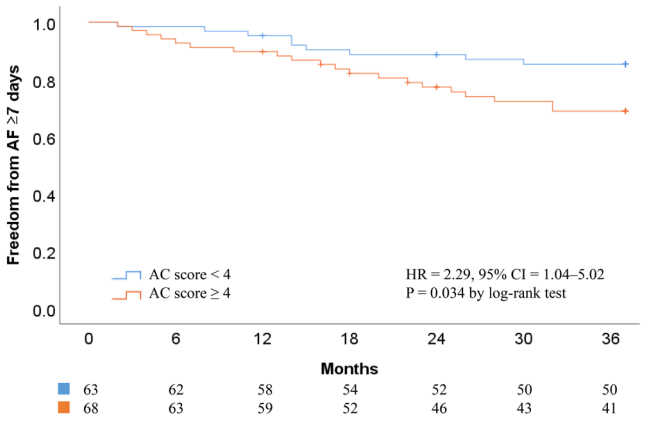

FIGURE 3 Kaplan–Meier cumulative rate of AF-free episodes lasting ≥7 days stratified by AC score. AC, atrial cardiomyopathy; AF, atrial fibrillation.

a risk of AF lasting ≥7 days (HR = 1.55; 95% CI = 1.14–2.11; $p = .006$) (Table S3). The multivariate analysis indicated that the association between the HFA-PEFF score and AF burden was not modified after introducing other relevant laboratory, clinical, and echocardiographic variables into the HFA-PEFF score (Table 6).

Similar to the original HFA-PEFF score, the AC score was associated with AF burden. The Kaplan–Meier analysis showed that an AC score ≥4 was associated with an increased risk of AF episodes lasting ≥1 h, ≥1 day, ≥7 days, and ≥30 days during follow-up (Figure 3

TABLE 6 Hazard ratio for the HFA-PEFF score for AF lasting ≥7 days with the inclusion of additional potentially relevant variables in multivariable Cox regression analysis.

	HR for additional variable		HR for HFA-PEFF score	
	Multivariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
+ History of paroxysmal AF	2.38 (0.94–6.02)	.066	1.43 (1.04–1.96)	.029
+ Tachy-brady syndrome	1.89 (0.87–4.10)	.109	1.43 (1.04–1.98)	.029
+ LVEF	0.95 (0.88–1.02)	.14	1.51 (1.11–2.06)	.009
+ Moderate or greater TR	2.13 (0.77–5.88)	.147	1.47 (1.06–2.02)	.019

Abbreviations: AF, atrial fibrillation; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation.

TABLE 7 Hazard ratio for the AC score for AF lasting ≥7 days with the inclusion of additional potentially relevant variables in multivariable Cox regression analysis.

	HR for additional variable		HR for AC score	
	Multivariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
+ History of paroxysmal AF	2.37 (0.96–5.88)	.063	1.44 (1.10–1.87)	.007
+ Tachy-brady syndrome	1.69 (0.78–3.68)	.183	1.43 (1.09–1.87)	.01
+ LVEF	0.95 (0.88–1.02)	.152	1.47 (1.14–1.89)	.003
+ Medial e′	0.73 (058–0.93)	.01	1.57 (1.21–2.05)	.001
+ Moderate or greater TR	2.17 (0.80–5.88)	.126	1.45 (1.12–1.88)	.005

Abbreviations: AF, atrial fibrillation; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation.

and Figure S2). Univariate analysis revealed that the AC score was associated with a risk of AF lasting ≥7 days (HR = 1.50; 95% CI = 1.17–1.93; $p = .002$) (Table S3). The multivariate analysis indicated that the association between the AC score and AF burden was not modified after introducing other relevant laboratory, clinical, and echocardiographic variables into the AC score (Table 7).

The receiver operating characteristic analysis showed that the C-statistic for 3-year cardiovascular events was 0.67 (95% CI, 0.56–0.79; $p = .008$) for the original HFA-PEFF score and 0.69 (95% CI, 0.57–0.81; $p = .005$) for the AC score (Figure 4A). For the 3-year risk of atrial fibrillation lasting ≥7 days, the *C*-statistic was 0.66 (95% CI, 0.55–0.77; $p = .008$) for the original HFA-PEFF score and 0.69 (95% CI, 0.59–0.79; $p = .002$) for the AC score (Figure 4B).

4 | DISCUSSION

To the best of our knowledge, this study is the first to report the prognostic value of the HFA-PEFF score in patients with SSS and preserved ejection fraction after pacemaker implantation. Our main finding was that patients with SSS complicated by HFpEF have a higher incidence of cardiovascular events and a greater AF burden after pacemaker implantation than those without HFpEF. Furthermore, multivariate analysis confirmed that HFA-PEFF and AC scores were independent risk factors for cardiovascular events and increased AF burden.

SSS commonly coexists with AF because these conditions are manifestations of AC.[2] Previous studies have reported that AF is associated with a high prevalence of HFpEF.[4] However, the diagnosis of HFpEF in the setting of AF or SSS is challenging because the symptoms, laboratory, and echocardiographic data overlap. Moreover, these studies used intermittent 12-lead electrocardiograms or Holter monitors to detect AF, which may have missed asymptomatic subclinical AF.

This study used the HFA-PEFF score to diagnose HFpEF.[7] The HFA-PEFF score includes functional, morphological, and biomarker components containing factors related to HFpEF and AF. The HFA of ESC recommends separate cutoffs for LAVI and BNP because LAVI was more enlarged and BNP levels were higher in patients with AF than in patients with SR.[12] Thus, with this cutoff value, the HFA-PEFF score can diagnose HFpEF with high accuracy even in patients with AF and AC.

In this study, 40% of the patients with SSS were diagnosed with HFpEF using the HFA-PEFF score. More than 50% of these patients experienced AF for at least 1 day over 3 years, and more than 30% had AF lasting ≥7 days. These results demonstrate a strong association between SSS, AF, and HFpEF.

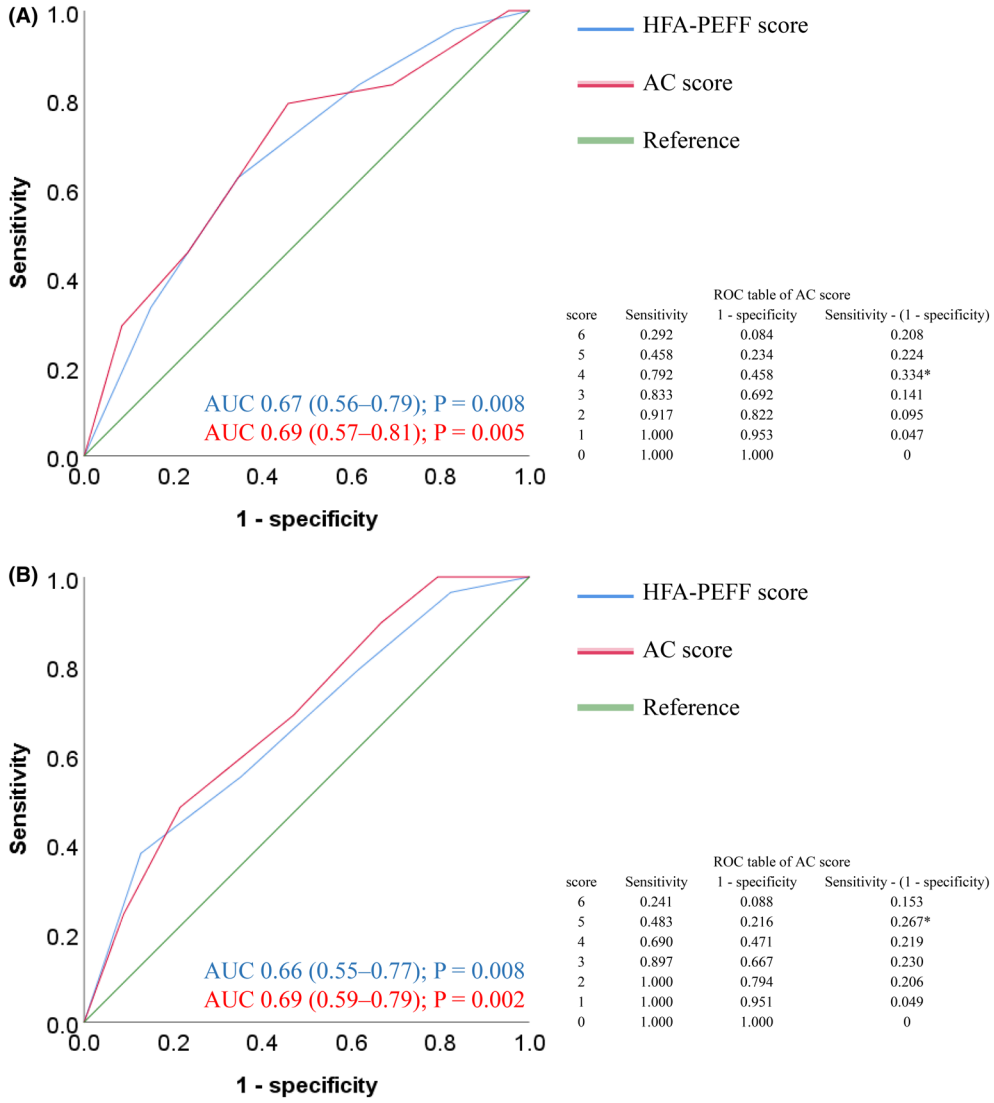

FIGURE 4 Receiver operating characteristic (ROC) curve. (A) The area under the curve (AUC) for predicting cardiovascular events within 3 years. (B) The AUC for predicting AF lasting ≥7 days within 3 years.

SSS is also associated with chronotropic incompetence, which is common in HFpEF.[13] A previous study reported that exercise intolerance and a limited chronotropic response in HFpEF were associated with functional, structural, and molecular remodeling of the sinoatrial node.[5] Rate-adaptive pacing complements heart rate responses in patients with cardiac pacing devices and chronotropic incompetence. However, improvements in exercise capacity vary across studies.[6,14] Previous studies have suggested that faster atrial pacing during exercise results in decreased exercise stroke volume due to increased intramyocellular calcium with a higher heart rate, impaired diastolic function, and inadequate time for relaxation with shorter diastolic periods as the heart rate increases.[15–17] The coexistence of AF prevents effective atrial pacing and leads to desynchrony between the atrium and ventricles, further exacerbating diastolic dysfunction. This mechanism may explain why, among patients with SSS and HFpEF, the incidences of cardiovascular events and AF remained high even after pacemaker implantation, highlighting the need for careful follow-up with remote monitoring.

A previous study described HFpEF and AF as 'vicious twins.'[4] However, this study revealed that these diseases are not merely 'vicious twins' but 'vicious triplets,' including SSS.

4.1 | Clinical implications

The HFA-PEFF score is a valuable index for stratifying risk among patients with SSS and preserved LVEF. However, this score includes numerous echocardiographic variables, which impede its use in daily practice despite the ESC guidelines recommending the HFA-PEFF score for diagnosing HFpEF. Therefore, we developed the AC score, which is a simplified version of the HFA-PEFF score. The parameters constituting the AC score, except for TRPG, were associated with

cardiovascular events or AF burden (Tables S2 and S3). Furthermore, the AC score was associated with cardiovascular events and AF burden to the same extent as the original HFA-PEFF score. Implementing the AC score may facilitate efficient follow-up care for patients with SSS after pacemaker implantation. Patients with an AC score <4, particularly those under remote monitoring, may require less frequent outpatient visits. In contrast, patients with an AC score ≥4 may need additional tests, such as cardiac magnetic resonance imaging, to exclude cardiomyopathies, such as cardiac amyloidosis or HCM. Additionally, patients with high AC scores may be suitable candidates for medications such as sodium-glucose cotransporter 2 inhibitors, angiotensin receptor–neprilysin inhibitors, oral anticoagulants, and mineralocorticoid receptor antagonists to manage HFpEF, prevent stroke, or address other cardiovascular events.

4.2 | Study limitations

This study has some limitations. First, this was a single-center observational study with a limited sample size, and patients with incomplete parameters were excluded. In this context, GLS data (a minor criterion in the functional domain of the HFA-PEFF score) were unavailable. Moreover, this study did not investigate the characteristics of the LA strain, right atrium, and right ventricle, which are associated with cardiovascular events and AF burden. Therefore, these findings may not be generalizable to all patients with SSS after pacemaker implantation. Second, the last two steps proposed by the HFA-PEFF score (Step 3 [Advanced workup using exercise testing] and Step 4 [Etiological workup]) were not considered. Third, we could not follow up on patients receiving postprocedural medications after pacemaker implantation. Fourth, the preprocedural prescription rates of sodium-glucose cotransporter 2 inhibitors, angiotensin receptor–neprilysin inhibitors, mineralocorticoid receptor antagonists, and loop diuretics were low. This study enrolled Japanese patients who underwent pacemaker implantation between 2019 and 2021. During this period, Japanese guidelines did not recommend sodium-glucose cotransporter 2 inhibitors or angiotensin receptor–neprilysin inhibitors for patients with HFpEF,[18,19] which likely contributed to the low prescription rates. Enhancing awareness of the usefulness of HFA-PEFF and AC scores and increasing prescription rates for these medications may improve outcomes.

4.3 | Conclusions

Patients diagnosed with HFpEF using the HFA-PEFF score have a higher incidence of cardiovascular events and a greater AF burden within 3 years after pacemaker implantation for SSS. The HFA-PEFF score may be useful for risk stratification in these patients.

ACKNOWLEDGMENTS

We are grateful to Midori Kawahara and Takako Yukiyoshi for their editorial assistance.

FUNDING INFORMATION

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by Kurashiki Central Hospital Medical Ethics Committee (No. 3688).

PATIENT CONSENT STATEMENT

All patients included in this study provided consent to participate.

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SUPPORTING INFORMATION

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

How to cite this article: Sumiyoshi H, Hayashi H, Yoshida K, Sakata A, Mizukami A, Minamino T, et al. The HFA-PEFF score and outcomes in patients with sick sinus syndrome and preserved ejection fraction after pacemaker implantation. J Arrhythmia. 2025;41:1–10. https://doi.org/10.1002/joa3.70088