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Association between mitral annulus calcification and subtypes of heart failure rehospitalization

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Abstract

Background: *Mitral annulus calcification (MAC) has been associated with cardiovascular diseases, including heart failure (HF); however, the associations between MAC and both the category and etiology of HF have not been fully elucidated. The aim of this study was to investigate the relationship between MAC and three types of HF rehospitalization: HF with preserved ejection fraction (HFpEF), HF with mid-range EF (HFmrEF), and HF with reduced EF (HFrEF).*

Methods: *We enrolled consecutive patients undergoing echocardiography, who were admitted to our hospital for clinically indicated congestive HF between April 2014 and March 2018. Cox proportional-hazards models were used after adjusting for age, gender, and hypertension.*

Results: *Of 353 patients, 40 (11.3%) had MAC. With a median follow-up of 2.8 years, 100 (28%) patients were rehospitalized for congestive HF (HFpEF 40%, HFmrEF 16%, HFrEF 44%, respectively). According to the Kaplan-Meier method, the estimated incidence of HFpEF rehospitalization in the MAC group was significantly greater than that in the non-MAC group ($p < 0.001$) whereas the incidences of HFmrEF and HFrEF rehospitalization were comparable between the groups ($p = 0.101$ and $p = 0.291$, respectively). In a multivariate analysis, MAC remained significantly associated with HFpEF rehospitalization (hazard ratio: 3.379; 95% confidence interval: 1.651–6.597). At initial HF hospitalization, E/e' was significantly higher in the MAC group (both septum and lateral, $p < 0.05$), suggesting a possible relationship between MAC and left ventricular diastolic function.*

Conclusions: *Mitral annulus calcification was associated with increased HFpEF rehospitalization and might be a cause of left ventricular diastolic dysfunction.* (Cardiol J 2023; 30, 2: 256–265)

Key words: mitral annulus calcification, heart failure, heart failure with preserved ejection fraction

Introduction

Mitral annulus calcification (MAC) is a chronic degenerative process in the fibrous support structure of the mitral valve [1–3]. MAC is often observed in elderly patients with atherosclerotic disease, and its prevalence increases with aging, multiple cardiovascular risk factors, and chronic kidney disease (CKD) [2–5]. MAC has been associated with increased cardiovascular disease (CVD) including congestive heart failure (HF), mitral valve disease, arrhythmias, stroke, and mortality [3, 6–11].

Heart failure commonly occurs as a result of several CVDs, leading to cardiovascular death. Recently, HF has been divided into three groups based on the left ventricular ejection fraction (LVEF): HF with preserved LVEF (HFpEF, LVEF ≥ 50%), HF

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with mid-range LVEF (HFmrEF, LVEF 40–49%), and HF with reduced LVEF (HFrEF, LVEF < 40%) [12]. Each HF phenotype is associated with different clinical outcome, characteristics, etiology, and required management. HFpEF patients are older, more often women, more likely to have hypertension, and less likely to have coronary artery disease (CAD), compared to HFrEF patients. HFmrEF patients show intermediate characteristics [13–15]. In addition, the incidence of HF rehospitalization in HFpEF patients is lower than that in HFrEF patients, and HFmrEF is intermediate between the other two groups. Therefore, it is considered that the HFmrEF phenotype represents a transitional status or overlap between HFpEF and HFrEF.

While previous studies have shown that MAC is a cause of HF, the association of MAC with the category and etiology of HF has not been fully elucidated. The aim of this study was to investigate the relationship between MAC and the three types of HF rehospitalization.

Methods

Subjects

This study is a retrospective observational cohort. We enrolled 456 consecutive patients undergoing transthoracic echocardiography (TTE), who were admitted to Fukuoka University Hospital for clinically indicated congestive HF between April 2014 and March 2018. The diagnosis of HF was made by the attending cardiologists in our hospital based on the criteria of the Framingham study [16]. We divided the patients into MAC and non-MAC groups at baseline. The primary endpoints were the incidence of HF rehospitalization and their subtypes (i.e. HFpEF, HFmrEF, and HFrEF) at the follow-up date. Secondary endpoints were myocardial infarction (MI), cardiovascular death, and all-cause death. TTE was performed twice: on admission for the initial HF and at rehospitalization due to HF, with a commercially available system (Vivid E9, GE Healthcare, Milwaukee, WI, USA; or EPIQ 7G, Philips Medical Systems, Andover, MA, USA). Selection to the MAC or non-MAC group was determined by TTE at the initial HF hospitalization, and subtypes of HF rehospitalization were divided into three groups according to TTE-derived LVEF at the HF rehospitalization. Cases of HF rehospitalization due to ischemic heart disease (IHD, n = 8), valvular heart disease (VHD, n = 58), or post valvular surgery (n = 37) were excluded. HF rehospitalization due to IHD was defined as CAD requiring revascularization on admission (i.e. acute coronary syndrome), and VHD was defined as moderate to severe aortic and/or mitral valve disease at each TTE. Ultimately, we included 353 patients and performed further analysis.

All data were retrospectively collected at the initial HF hospitalization and rehospitalization, and analyzed using the database of Fukuoka University Hospital. The study was performed according to the Declaration of Helsinki regarding investigations in humans and approved by the ethics committee of Fukuoka University Hospital (EC/IRB: U19-12-002). Informed consent was obtained in the form of an opt-out on a website.

MAC assessed by TTE

Mitral annulus calcification was defined as the presence of bright echo density located at the junction of the atrioventricular groove and posterior mitral leaflet on M-mode or two-dimensional imaging in parasternal or apical windows. The severity of MAC was defined as previously described [3, 17]: mild (focal, limited increasing echo density of the mitral annulus), moderate (marked echo density involving one-third to one-half of the mitral ring circumference), or severe (marked echo density involving more than one-half of the circumference of the mitral ring or with intrusion into the left ventricular [LV] inflow tract, or maximal MAC thickness measured from the anterior to the posterior edge at its greatest width > 4 mm) determined in a parasternal short-axis view at the level of the mitral annulus. In the present study, we identified the presence of MAC as MAC of greater than moderate severity (Fig. 1). The presence and severity of MAC were collected by 2 investigators who were blinded to clinical information about the subjects. Patients with MAC of greater than moderate severity by both investigators were considered to be the MAC group.

Statistical analysis

Values are expressed as mean ± standard deviation if the variable was normally distributed, or median (interquartile range) if not. The Shapiro-Wilk test was used to assess whether data were normally distributed or not. A two-tailed $p < 0.05$ was considered statistically significant. Patients were divided into two groups according to the presence of MAC. Groups were compared using Student's t-test or the Wilcoxon test for continuous values, and the chi-squared test was used for categorical data, as appropriate. Kaplan-Meier estimates were used to evaluate the association of MAC with HF rehospitalization, MI, cardio-

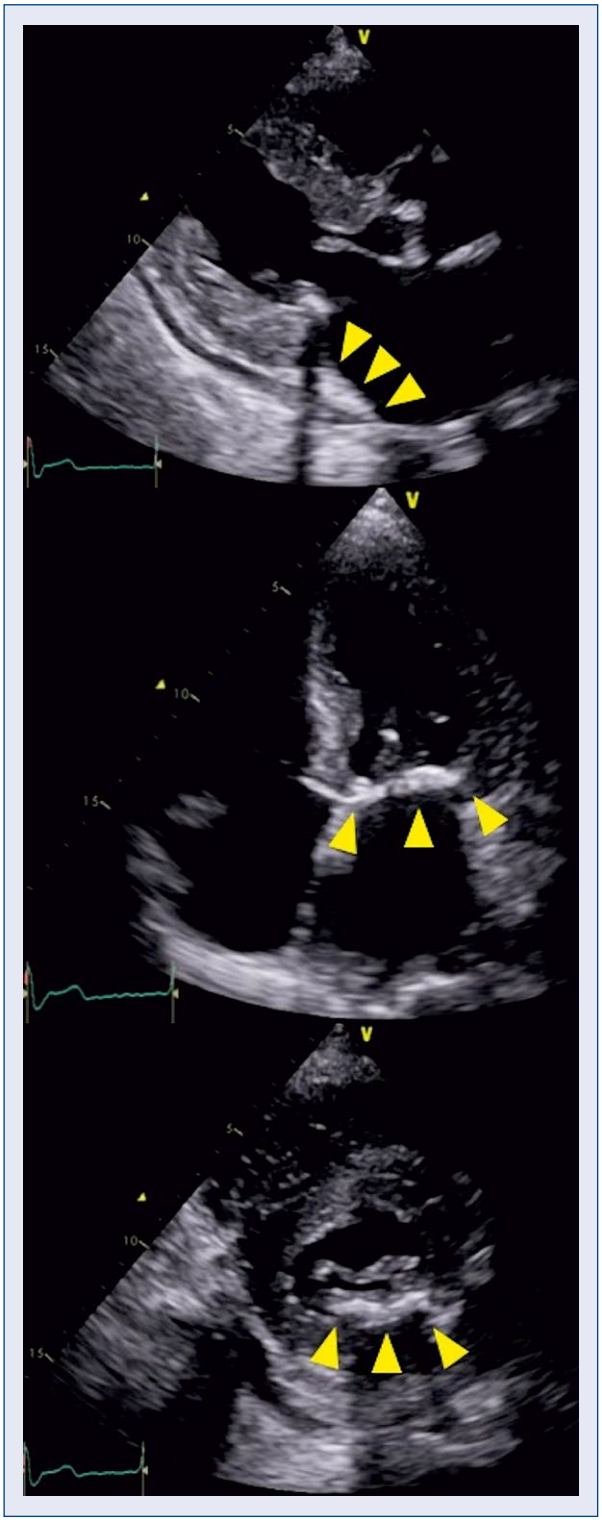

Figure 1. Representative case of mitral annulus calcification.

vascular death, and all-cause death. Above all, HF rehospitalization was studied according to the three subtypes defined by LVEF. Cox proportional hazards regression models were used to assess the relationship between baseline clinical characteristics, including MAC and HFpEF rehospitalization. In multivariate Cox proportional hazard regression analyses, MAC was adjusted for the following baseline variables by each model: model 1, adjusted for age, gender, and hypertension, which are traditional HFpEF risk factors [13–15]; models 2 and 3, adjusted for covariates that were significant in a univariate analysis. All statistical analyses were performed with JMP 12 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline characteristics

Of the 353 patients who met the inclusion criteria, 40 (11.3%) had MAC. The baseline clinical characteristics and echocardiographic measurements are shown in Table 1. At the baseline examination, patients with MAC were significantly older and had a lower frequency of smoking and a smaller body surface area (BSA) compared to those without MAC. There were no significant differences between groups with respect to gender, prevalence of hypertension and atrial fibrillation, or laboratory values, including B-type natriuretic peptide, creatinine, and hemoglobin.

Among TTE variables, LVEF, E-wave velocity (transmitral Doppler flow pattern; TMF), and E/e' septum and lateral (tissue Doppler image; TDI) were significantly higher in the MAC group. While the LV end-systolic dimension was significantly smaller and the LV end-diastolic dimension tended to be smaller in the MAC group, there were no significant differences in the indexed LV end--systolic dimension (LV end-systolic dimension/ /BSA), indexed LV end-diastolic dimension (LV end-diastolic dimension/BSA), left atrial (LA) diameter, LA volume index, A wave velocity (TMF), e' septum (TDI), or e' lateral (TDI) between the groups.

Outcomes

During a median follow-up of 2.8 years, there were 100 (28%) HF rehospitalizations, 4 (1%) MIs, 30 (9%) cardiovascular deaths, and 49 (14%) all-cause deaths. Of the 100 HF rehospitalizations, 40 were HFpEF, 16 were HFmrEF, and 44 were HFrEF. The incidence of HF rehospitalization, especially HFpEF rehospitalization, was significantly higher and cardiovascular death tended to be more prevalent in subjects with MAC than in those without MAC (Table 2).

Table 1. Baseline clinical characteristics and echocardiographic measurements.

	Non-MAC (n = 313)	MAC (n = 40)	P
Age [years]	75 (65–83)	82 (75–88)	< 0.001
Male	210 (67%)	21 (53%)	0.073
Hospital days	17 (12–22)	17 (10–22)	0.733
NYHA:			0.933
II	94 (30%)	13 (33%)	
III	93 (30%)	12 (30%)	
IV	126 (40%)	15 (37%)	
Ischemic heart disease	118 (38%)	18 (45%)	0.375
Smoking	176 (56%)	15 (38%)	0.025
Hypertension	199 (64%)	25 (63%)	0.894
Diabetes mellitus	133 (42%)	11 (28%)	0.063
Atrial fibrillation	127 (41%)	20 (50%)	0.258
Medication at discharge:			
ACE-I or ARB	229 (73%)	24 (60%)	0.091
Beta-blocker	237 (76%)	28 (70%)	0.439
Diuretics	271 (87%)	34 (85%)	0.786
Body mass index [kg/m^2]	23.0 (20.8–26.6)	21.6 (19.3–25.3)	0.054
Body surface area [m^2]	1.62 (1.49–1.77)	1.48 (1.35–1.67)	0.001
Laboratory data:			
BNP [pg/mL]	579 (327–1024)	701 (332–1105)	0.306
Creatinine [mg/dL]	1.11 (0.84–1.66)	1.17 (0.91–1.47)	0.961
Hemoglobin [g/dL]	12.2 ± 2.4	11.4 ± 2.2	0.069
TTE, baseline:			
LVEF [%]	40.2 (28.3–53.3)	52.4 (38.4–61.9)	0.002
LVDd [mm]	52.4 ± 9.7	49.2 ± 8.5	0.053
Indexed LVDd [mm/m^2]	32.2 ± 6.0	32.9 ± 6.2	0.523
LVDs [mm]	41.6 (33.2–49.7)	34.0 (29.3–42.5)	0.001
Indexed LVDs [mm/m^2]	25.7 (20.1–30.6)	22.6 (19.2–28.5)	0.101
LA diameter [mm]	43.9 (39.2–49.1)	45.7 (40.8–53.0)	0.166
LA volume index [mL/m^2]	44.9 (33.1–61.1)	51.6 (38.2–76.1)	0.189
E wave velocity (TMF) [cm/s]	72.1 (52.6–96.6)	80.9 (63.8–115.2)	0.019
A wave velocity (TMF) [cm/s]	67.1 (48.5–88.7)	69.9 (38.3–110.7)	0.635
e' septum (TDI) [cm/s]	4.7 (3.7–6.0)	4.4 (3.0–6.2)	0.551
e' lateral (TDI) [cm/s]	6.1 (4.5–8.4)	6.1 (4.6–7.5)	1.000
E/e' septum	15.4 (11.4–20.5)	20.5 (15.6–22.9)	0.017
E/e' lateral	11.8 (7.9–17.4)	14.9 (11.8–17.1)	0.039

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables or the number (percent) of patients for category variables. ACE-I — angiotensin converting enzyme inhibitor; ARB — angiotensin II receptor blocker; BNP — B-type natriuretic peptide; Indexed LVDd — LVDd/body surface area; Indexed LVDs — LVDs/body surface area; LA — left atrium; LVDd — left ventricular end-diastolic dimension; LVDs — left ventricular end-systolic dimension; LVEF — left ventricular ejection fraction; MAC — mitral annulus calcification; NYHA — New York Heart Association functional classification; TDI — tissue Doppler image; TMF — transmitral Doppler flow pattern; TTE — transthoracic echocardiography

Figure 2 shows Kaplan-Meier survival curves for HF rehospitalization. The incidence of HF rehospitalization in patients with MAC was significantly higher (log-rank, p = 0.004). The incidence of HFpEF rehospitalization was significantly higher and that of HFmrEF rehospitalization tended to be higher in patients with MAC (log-rank, p < 0.001; p = 0.101, respectively), whereas the incidence of HFrEF hospitalization tended to be lower in the MAC group (log-rank, p = 0.291). Figure 3

Table 2. Association with mitral annulus calcification (MAC) and clinical outcome.

	Non-MAC (n = 313)	MAC (n = 40)	P
All-cause death	41 (13%)	8 (20%)	0.256
Cardiovascular death	23 (7%)	7 (18%)	0.050
Myocardial infarction	4 (1%)	0 (0%)	0.325
Heart failure rehospitalization	80 (26%)	20 (50%)	0.002
Heart failure subtype:			0.008
HFpEF	27 (34%)	13 (65%)	
HFmrEF	12 (15%)	4 (20%)	
HFrEF	41 (51%)	3 (15%)	

HFpEF — heart failure with preserved ejection fraction; HFmrEF — heart failure with mid-range ejection fraction; HFrEF — heart failure with reduced ejection fraction

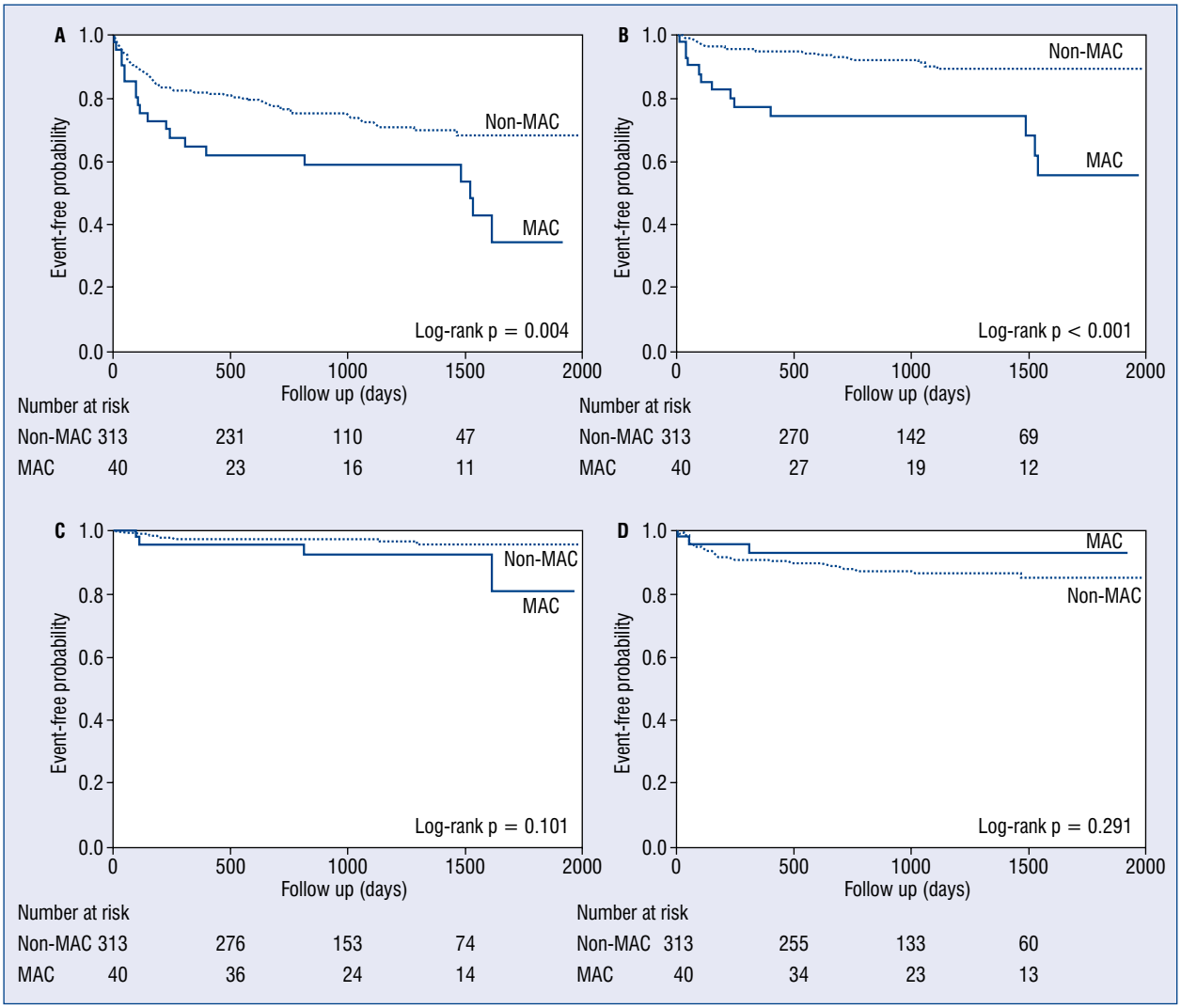

Figure 2. Kaplan-Meier estimates for the primary endpoint according to the presence or absence of mitral annulus calcification (MAC); **A.** Heart failure rehospitalization; **B.** Heart failure with preserved ejection fraction (HFpEF) rehospitalization; **C.** Heart failure with mid-range ejection fraction (HFmrEF) rehospitalization; **D.** Heart failure with reduced ejection fraction (HFrEF) rehospitalization.

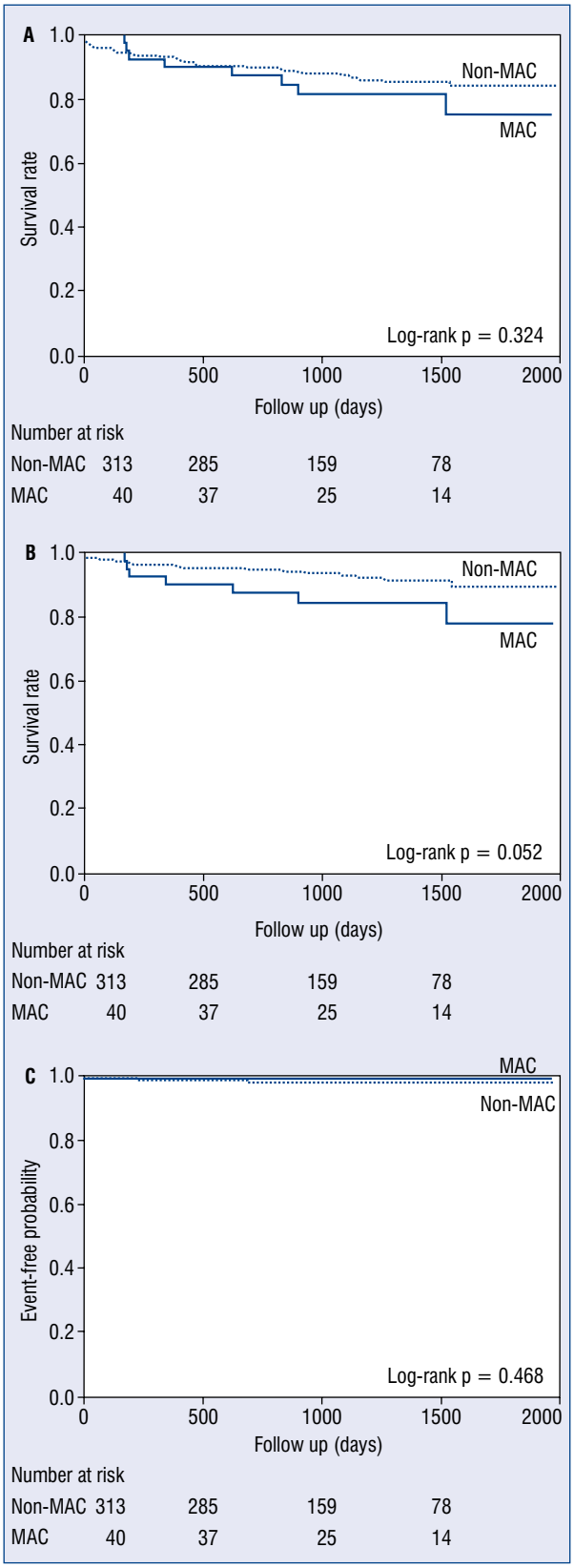

Figure 3. Kaplan-Meier estimates for secondary endpoints according to the presence or absence of mitral annulus calcification (MAC); **A.** All cause death; **B.** Cardiovascular death; **C.** Acute coronary syndrome.

shows Kaplan-Meier survival curves for MI, cardiovascular death, and all-cause death. Although the incidence of cardiovascular death tended to be higher in patients with MAC (log-rank, p = = 0.052), there were no significant differences in MI or all-cause death (log-rank, p = 0.468; p = 0.324, respectively).

A Cox proportional hazards regression to evaluate the association of MAC with HFpEF rehospitalization is shown in Table 3. Univariate regression demonstrated that age (hazard ratio [HR] 1.045; 95% confidence interval [CI] 1.016–1.078; p = 0.002), hemoglobin (HR 0.787; 95% CI 0.685–0.902; p = 0.001), LV end-diastolic dimension (HR 0.95; 95% CI 0.919–0.982; p = = 0.024), LV end-systolic dimension (HR 0.93; 95% CI 0.90–0.96; p < 0.001), and MAC (HR 4.016; 95% CI 2.005–7.643; p < 0.001) were significantly associated with HFpEF rehospitalization. Multivariate Cox proportional hazard regression was performed to identify the association between MAC and HFpEF rehospitalization using three models: model 1, adjusted for age, gender, and hypertension; model 2, adjusted for age, hemoglobin, and LV end-diastolic dimension; and model 3, adjusted for age, hemoglobin, and LV end-systolic dimension. In all models, MAC remained significantly associated with HFpEF rehospitalization (all p < 0.05).

Discussion

In the current study, MAC was associated with an increased incidence of HF rehospitalization, especially HFpEF rehospitalization. The multivariate analysis indicated that MAC might be a cause of HFpEF rehospitalization after adjusting for covariates.

Previous studies have reported that MAC is associated with CVD from various causes including HF [6–8], and our study had a similar outcome. While studies have shown that MAC is a cause of HF, the etiology and mechanism of HF due to MAC has not been fully elucidated. The present study suggests a possible mechanism. In this study, MAC was especially associated with HFpEF rehospitalization. HFpEF is increasing in prevalence and is associated with substantial morbidity and mortality; however, limited treatments are available [18]. Myocardial hypertrophy and fibrosis [19], impaired diastolic compliance and relaxation [20], and elevated intracardiac filling pressures due to renal failure, fluid retention, and exercise intolerance have been demonstrated to be complicatedly associated with the physiological mechanism of

Table 3. Univariate and multivariate relationships between heart failure with preserved ejection fraction rehospitalization and baseline clinical characteristics, transthoracic echocardiography (TTE) variables, and presence of mitral annulus calcification (MAC).

	Univariate analysis			Multivariate analysis								
				Model 1			Model 2			Model 3		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age	1.045	1.016–1.078	0.002	1.033	1.004–1.067	0.026	1.014	0.985–1.048	0.366	1.01	0.981–1.043	0.517
Female	1.137	0.586–2.132	0.696	0.987	0.499–1.885	0.968	–	–	–	–	–	–
Hospital days	0.997	0.963–1.026	0.861	–	–	–	–	–	–	–	–	–
NYHA	–	–	0.458	–	–	–	–	–	–	–	–	–
Ischemic heart disease	1.025	0.534–1.914	0.939	–	–	–	–	–	–	–	–	–
Smoking	0.607	0.319–1.131	0.116	–	–	–	–	–	–	–	–	–
Hypertension	1.827	0.925–3.937	0.084	1.764	0.885–3.831	0.11	–	–	–	–	–	–
Diabetes mellitus	1.196	0.634–2.227	0.575	–	–	–	–	–	–	–	–	–
Atrial fibrillation	1.241	0.662–2.313	0.496	–	–	–	–	–	–	–	–	–
Laboratory data:	–	–	–	–	–	–	–	–	–	–	–	–
BNP	0.999	0.999–1.0	0.057	–	–	–	–	–	–	–	–	–
Creatinine	1.458	0.043–16.602	0.806	–	–	–	–	–	–	–	–	–
Hemoglobin	0.787	0.685–0.902	0.001	–	–	–	0.839	0.722–0.974	0.021	0.871	0.75–1.01	0.067
TTE:	–	–	–	–	–	–	–	–	–	–	–	–
LVDd	0.95	0.919–0.982	0.024	–	–	–	0.967	0.932–1.003	0.072	–	–	–
LVDs	0.93	0.9–0.96	< 0.001	–	–	–	–	–	–	0.948	0.914–0.981	0.002
LA diameter	0.995	0.959–1.03	0.766	–	–	–	–	–	–	–	–	–
LA volume	0.993	0.979–1.004	0.264	–	–	–	–	–	–	–	–	–
LA volume index	0.991	0.969–1.009	0.362	–	–	–	–	–	–	–	–	–
e' septum	1.069	0.955–1.161	0.223	–	–	–	–	–	–	–	–	–
E' lateral	1.051	0.938–1.164	0.375	–	–	–	–	–	–	–	–	–
E/e' septum	0.986	0.943–1.021	0.461	–	–	–	–	–	–	–	–	–
E/e' lateral	0.99	0.937–1.031	0.667	–	–	–	–	–	–	–	–	–
MAC	4.016	2.005–7.643	< 0.001	3.379	1.651–6.597	0.001	3.02	1.473–5.914	0.003	2.677	1.299–5.275	0.009

BNP — B-type natriuretic peptide; CI — confidence interval; HR — hazard ratio; LA — left atrium; LVDd — left ventricular end-diastolic dimension; LVDs — left ventricular end-systolic dimension; Model 1 — adjusted for age, gender, and hypertension; Model 2 — adjusted for age, hemoglobin, and LVDd; Model 3 — adjusted for age, hemoglobin, and LVDs; NYHA — New York Heart Association functional classification

HFpEF. In our study, patients with MAC had a higher E/e' than those without MAC; moreover, they had a low e' (septum and lateral) and a high LA volume index, suggesting that MAC may cause LV diastolic dysfunction. Certainly, it is difficult to distinguish that an increase in E/e' occurs due to MAC or LV diastolic dysfunction. While previous studies have reported that patients with MAC had increased E velocities and decreased lateral e' because of decreased mitral orifice and restriction of posterior mitral leaflet excursion, little is known about the usefulness of septal e' in those with MAC [21, 22]. In this study, both septal and lateral e' were decreased. Our findings suggest that MAC might be a cause of HFpEF rehospitalization, along with older age, female sex, renal failure, anemia, hypertension, diabetes mellitus [15], and disturbed LV diastolic function. The mitral annulus is located at the junction between the LV and LA. MAC might disturb the diastolic function of not only the LV but also the LA [23], resulting in increased rehospitalization due to HFpEF.

Although MAC is known as a chronic calcification of the fibrous support structure of the mitral valve [1–3], the pathophysiological mechanism is not fully understood. Previously, the clinical causes of MAC were considered to be age-related calcification, atherosclerotic change, or CKD [2–5]. Regarding pathological findings, in specimens from patients with MAC, foam cells were observed on the ventricular surfaces of the posterior mitral leaflet, suggesting that MAC and atherosclerosis have a similar etiology [24]. On the other hand, the condition of mitral valve stress is increased in parallel with increased LV systolic pressure due to hypertension, aortic stenosis, and hypertrophic cardiomyopathy. The increased mitral valve stress contributes to increased mitral closing pressure, which accelerates degeneration of the mitral valve [25–27]. In addition, MAC was often observed in elderly females, and post-menopausal osteoporosis-related ectopic calcium has been demonstrated to be deposited in the mitral valve [28, 29]. Because HFpEF rehospitalization occurred in 65% of the MAC group, these patients had characteristics of both HFpEF and MAC. There were no significant differences in creatinine between the groups because there were few CKD patients in this study.

Patients with symptomatic mitral valve disease who were intolerant to optimal medical therapy required invasive treatment. MAC affects the outcomes and strategies of open surgery (e.g. conversion from mitral valve repair to replacement) [30, 31]. Furthermore, transcatheter edge-to-edge mitral valve repair using a MitraClip® (Abbott Vascular Inc., Santa Clara, CA, USA) is contraindicated in MAC [30]. Surgical treatment for mitral valve disease with MAC requires calcium debridement, and consequently contributes to fatal cardiac complications such as atrioventricular disruption, LV free wall rupture, and injury of the left circumflex artery. On the other hand, Thaden et al. [32] reported that MAC was an independent predictor of an increased transmitral mean pressure gradient after transcatheter edge-to-edge mitral valve repair. Neither treatment might be suitable for patients with MAC. Several studies using a transcatheter aortic valve replacement device or a transcatheter mitral valve replacement device have been reported [33, 34]. Although both treatments were feasible for patients who either were at high operative risk or were inoperable, they were still associated with significant cardiac adverse events, including all-cause death, cardiovascular death, and LV outflow tract obstruction. Procedural experience, device refinements, and optimal patient selection are needed.

Limitations of the study

Our study has several limitations that should be considered. First, our study was a retrospective analysis performed at a single tertiary referral center with a limited number of study patients, and there was a potential selection bias. Furthermore, while the prevalence of MAC (11.3%) was similar to that in previous studies, the variables in the multivariate analysis were limited because of the small sample size. Second, while we investigated the patient characteristics, including basal cardiomyopathy, comorbidities, society, medication at discharge, TTE findings, and biochemical data, we did not collect information on the triggers of acute decompensated HF such as afterload mismatch, infection, drug discontinuation, or medication at hospitalization. Third, because we divided patients with rehospitalization into three groups according to LVEF, we did not exclude cases of cardiomyopathy with preserved LVEF such as hypertrophic cardiomyopathy, restrictive cardiomyopathy, or amyloidosis. Thus, the rate of HFpEF rehospitalization might be affected by cardiomyopathy with preserved LVEF besides MAC. Fourth, in our study, MAC was identified using echocardiography. However, it has been suggested that cardiac computed tomography is more useful than echocardiography because of its relatively low specificity in distinguishing between calcification and dense collagen [6, 35]. Most of the patients

with MAC in the present study did not undergo cardiac computed tomography. Finally, the results of our study need further validation and evaluation in a larger prospective study.

Conclusions

In this study, MAC was associated with increased HFpEF rehospitalization. It was suggested that MAC might be a cause of LV diastolic dysfunction.

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