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## Original Article

## Differences in clinical and echocardiographic features and outcomes between atrial functional mitral regurgitation patients with and without posterior mitral leaflet bending

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## ABSTRACT

**Background:** Posterior mitral leaflet (PML) bending is a cause of atrial functional mitral regurgitation (AFMR). We aimed to investigate differences in clinical and echocardiographic features and outcomes between AFMR patients with and without PML bending.

**Methods:** We retrospectively examined 118 AFMR patients with atrial fibrillation (AF), mild or greater MR without degenerative mitral valve changes, and left ventricular ejection fraction  $\geq 50\%$ . Patients were classified by the presence of PML bending: PML bending ( $n=24$ ) and no PML bending ( $n=94$ ). PML bending was defined as PML-to-anterior mitral leaflet angle ratio  $\geq 3.1$  calculated using receiver operating characteristics analysis for eccentric MR jet toward left atrial posterior wall. The study endpoint was a composite of cardiac death, admission for heart failure, and mitral valve surgery.

**Results:** Overall, a total of 88 patients (75%) had mild MR. There were no between-group differences in clinical and echocardiographic characteristics including AF duration and cardiac cavities size except for the length of inward bending of the left ventricular posterobasal wall and the mitral annular area. The 36-month event-free survival for the composite endpoint was significantly lower in the PML bending group (63% vs. 78%; Log-rank  $p=0.047$ ). In multivariate analysis, PML bending was also associated with the composite outcome.

**Conclusions:** AFMR patients with PML bending may have worse outcomes than those without PML bending despite similar clinical features.

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## Introduction

Classically, ischemic mitral regurgitation (MR) was considered representative of a secondary MR [1,2]. The basic mechanism of ischemic MR is leaflet tethering caused by papillary muscle displacement that results from left ventricle (LV) remodeling or dilatation [3,4].

Atrial functional mitral regurgitation (AFMR) is a recently recognized type of secondary MR [1]. Annular dilation owing to prominent left atrium (LA) dilatation caused by conditions such as long-standing atrial fibrillation (AF) is considered one underlying mechanism. However, annular dilation alone might not be sufficient to cause significant MR [5–7]. Thus, previous echocardiographic studies have proposed

several additional mechanisms, such as posterior mitral leaflet (PML) bending [8,9], insufficient leaflet remodeling to mitral valve (MV) annulus dilatation [10–12], flattened saddle shape [8,9,11,13], and reduced annular contractility [9,13]. In particular, PML bending has attracted attention because of the distinctive morphology of the MV complex, characterized by flattened anterior mitral leaflet (AML) and tethered PML resulting in eccentric MR jet toward the LA posterior wall (Fig. 1) [14,15]. However, no specific quantitative echocardiographic parameter of the MV complex indicates PML bending. In addition, little is known about the clinical and prognostic impact of PML bending in patients with AFMR.

Accordingly, the aims of this study are as follows: 1) to seek using two-dimensional echocardiography the morphological analysis to determine the presence of PML bending; 2) to compare clinical and echocardiographic characteristics and clinical outcomes between AFMR patients with and without PML bending. Our findings may help decide the effective therapeutic strategy for AFMR.

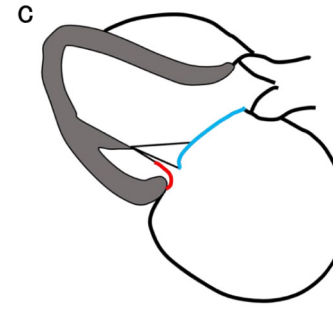
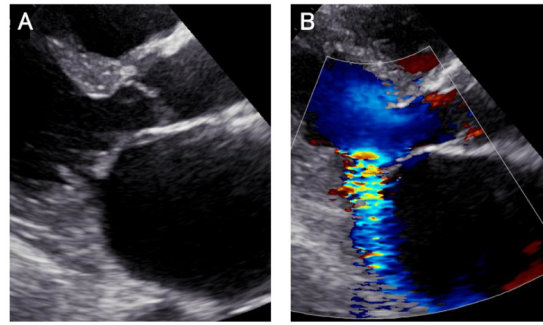
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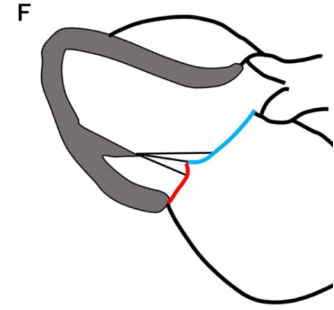
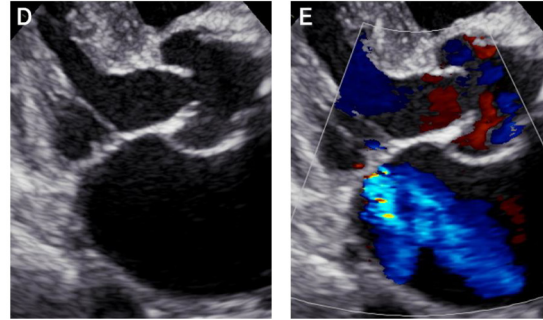
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AFMR with PML bending



AFMR without PML bending



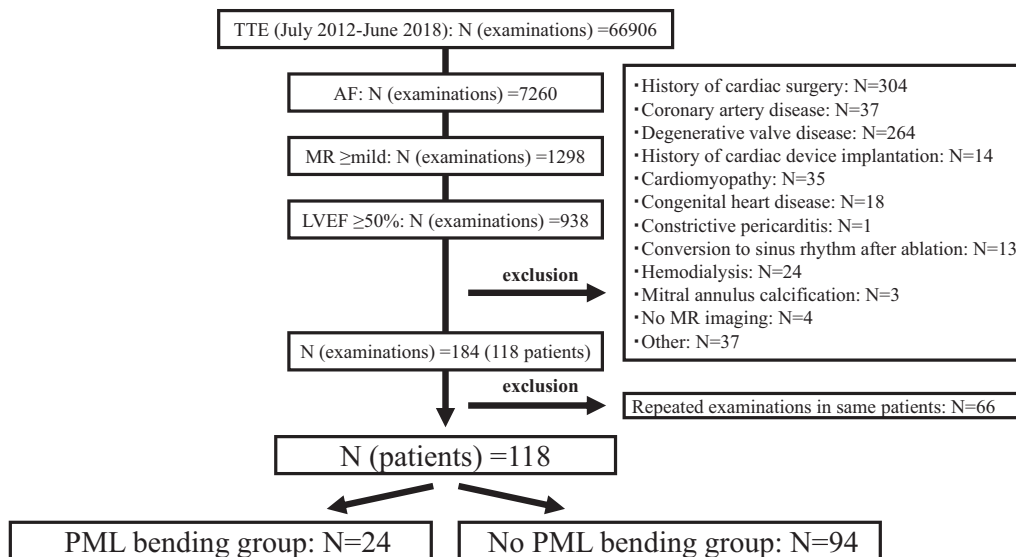
**Fig. 1.** Echocardiographic characteristics of atrial functional mitral regurgitation in patients with and without posterior mitral leaflet bending. Atrial functional mitral regurgitation (AFMR) with posterior mitral leaflet (PML) bending is characterized by posterior dominant mitral leaflet tethering with restricted motion that leads to sliding of the anterior mitral leaflet up toward the base of the PML (A and C). This creates an eccentric, posteriorly directed regurgitation jet (B). In contrast, AFMR without PML bending is characterized by good mobility of both leaflets (D and F) and leaflet closure in the mitral annular plane with limited coaptation that leads to a centrally directed regurgitation jet (E).

**Methods**

*Study population and data collection*

We retrospectively reviewed 66,906 transthoracic echocardiography (TTE) examinations performed at Tenri Hospital between July 2012 and June 2018. Patients with a documented AF at the time of examination who had mild or greater MR without degenerative MV changes, LV ejection fraction (LVEF)  $\geq 50\%$  were eligible for study inclusion. Exclusion criteria included the following: history of cardiac surgery or cardiac device implantation, degenerative valve disease, coronary

artery disease, cardiomyopathy, congenital heart disease, constrictive pericarditis, severe mitral annulus calcification, end-stage renal disease, and inadequate echocardiographic imaging. Patients who converted to sinus rhythm after catheter ablation were also excluded. Finally, a total of 118 patients were included for analysis. Clinical, electrocardiographic, and echocardiographic data were collected from the medical records and the echocardiographic laboratory database. Duration of AF was estimated from the electrocardiographic or clinical data. A study flow chart is shown in Fig. 2. Patients were grouped according to the presence of PML bending. The study was conducted in accordance with the principles of the Declaration of Helsinki. Institutional ethics



**Fig. 2.** Study flow chart. AF, atrial fibrillation; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TTE, transthoracic echocardiography; PML, posterior mitral leaflet.

committee approval was obtained (approval number: 1158). The requirement for written informed consent was waived because of the retrospective nature of the study.

#### TTE examination

Standard two-dimensional and Doppler TTE was performed by experienced sonographers using commercially available ultrasound machines (Vivid 7 and Vivid E9, GE Healthcare, Horten, Norway; or Artida and Aplio 400, Canon Healthcare, Otawara, Japan). All measurements were performed according to current guidelines [16]. LV dilatation was defined as LV end-diastolic diameter  $\geq 55$  mm [10]. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF were measured in the apical 2- and 4-chamber views using the biplane modified Simpson's method. LV mass was calculated using a validated formula: LV mass =  $0.8 \times [1.04 (2 \times \text{LV posterior wall thickness} + \text{LV end-diastolic dimension})^3 - (\text{LV end-diastolic dimension})^3] + 0.6$ . LA volume at end-systole was measured in the apical 2- and 4-chamber views using the area-length method. LV volume, LV mass, and LA volume were indexed by body surface area. The length of inward bending of the LV posterobasal wall was measured from the basal end of LV to LA posterior wall contacting the pericardium at early-diastole, as shown in Fig. 3 [17]. The E wave velocity was measured using pulse Doppler of the mitral inflow from the apical 4-chamber view, and e' as the average of the septal and lateral mitral annulus diastolic velocities using tissue Doppler imaging. Estimated right ventricular systolic pressure was obtained by adding the estimated right atrial pressure based on the inferior vena cava dimension and respiratory change to  $[(\text{tricuspid regurgitant velocity})^2 \times 4]$ . End-systolic tricuspid valve annulus length was obtained in the apical 4-chamber view. MR and tricuspid regurgitation (TR) severity was determined by expert cardiologists whose decisions were based on assessment of the regurgitant jet area, effective regurgitant orifice area using the Proximal Isovelocity Surface Area method, vena contracta width, and systolic flow reversal in the pulmonary vein or hepatic vein. TR color jet area was measured in the apical 4-chamber view at mid-systole.

#### Analysis of mitral valve morphology

The angle between the mitral annular plane and the line connecting the base and tip of the AML and PML were measured in the parasternal

long-axis view or the apical 3-chamber view at mid-systole (Fig. 3). PML-to-AML angle ratio was calculated as the PML angle divided by AML angle. AML and PML lengths were measured in the parasternal long-axis view or apical 3-chamber view at mid-diastole. The end-diastolic mitral annular area was obtained from its dimensions in the apical 3-chamber view and intercommissural view using an ellipsoid assumption: anteroposterior diameter  $\times$  intercommissural diameter  $\times$  0.785. Annular sphericity index was calculated as the anteroposterior diameter divided by the intercommissural diameter.

#### Definition of PML bending

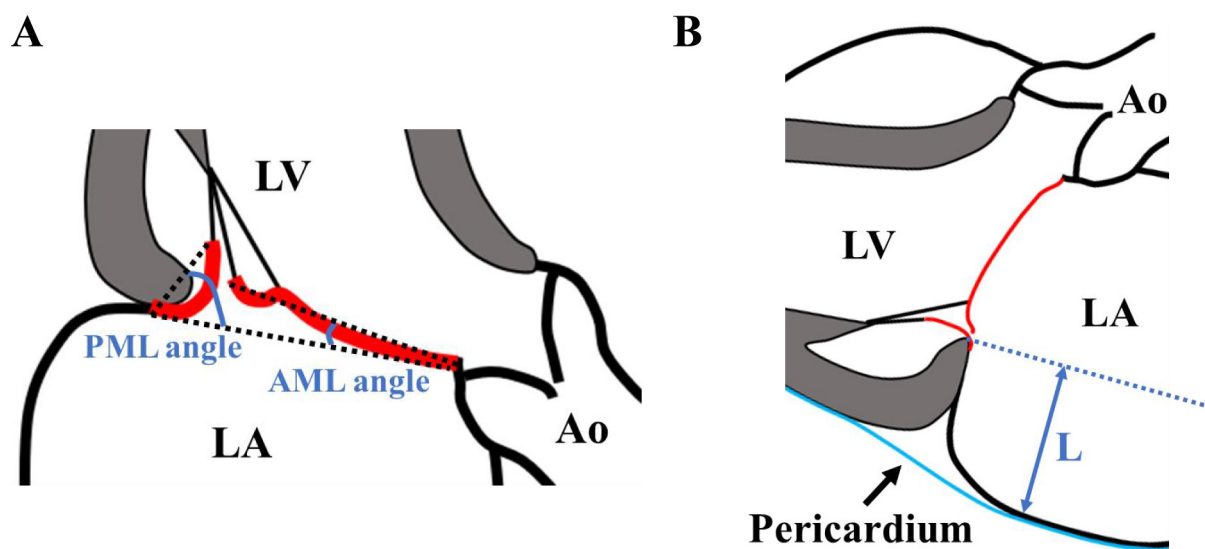
Using receiver operating characteristics (ROC) analysis for eccentric MR jet toward the LA posterior wall, we compared the area under the curve (AUC) values among AML angle, PML angle, and PML-to-AML angle ratio. These indexes were selected because the previous studies showed the predictive importance of leaflet angle on the MR jet direction. We chose the best index with the highest AUC value and used its best cut-off value of the maximum sum of sensitivity and specificity for the definition of PML bending.

#### Clinical outcomes

The study endpoint was a composite of cardiac death, admission for heart failure (HF), and open MV surgery. Cardiac death included sudden death with an unknown cause. Admission for HF was defined as unplanned hospitalization due to worsening HF symptoms and physical findings requiring hospitalization, diagnosed based on the Framingham criteria by an experienced cardiologist [18].

#### Statistical analysis

Categorical variables are expressed as numbers with percentage and were compared using the chi-square test or Fisher's exact test. Continuous variables are expressed as means with standard deviation or medians with interquartile range (IQR) and were compared using the Student's *t*-test or Wilcoxon rank sum test as appropriate. The Kolmogorov–Smirnov test was used to examine whether the data were normally distributed. Cumulative incidence of the study endpoint was estimated using the Kaplan–Meier method and compared using the log-rank test. We also performed a multivariate Cox regression analysis



**Fig. 3.** Measurement of leaflet tethering angles and the length of inward bending of the LV posterobasal wall. (A) Anterior mitral leaflet and posterior mitral leaflet angles were defined as the angle between the mitral annular plane and the line connecting the base and the tip of the corresponding leaflet at mid-systole. (B) The length of inward bending of the LV posterobasal wall (*L*) was measured from the basal end of the LV posterobasal wall to the LA posterior wall contacting the pericardium at early diastole. AML, anterior mitral leaflet; Ao, aorta; LA, left atrial; LV, left ventricle; PML, posterior mitral leaflet.

to assess whether PML bending is an independent predictor of the composite endpoint by adjusting for age, LV mass index, estimated right ventricular systolic pressure, moderate or greater MR, moderate or greater TR, and LA volume index, which are known prognostic predictors of AF or HF with preserved LVEF [19–21]. In the multivariate analysis, we determined the number of variables based on five events per predictor variable [22]. Consequently, seven predictor variables were included. When the number of events is small, including so many predictor variables does not follow a widely used “ten events per variable” rule. A simulation study, however, found this rule to be unduly strict [22]. All tests were two-tailed. Values of  $p < 0.05$  were considered significant. Statistical analyses were performed using R software (The R Foundation for Statistical Computing, Vienna, Austria) with its graphical user interface (EZR version 1.38; Saitama Medical Center, Jichi Medical University, Saitama, Japan) [23].

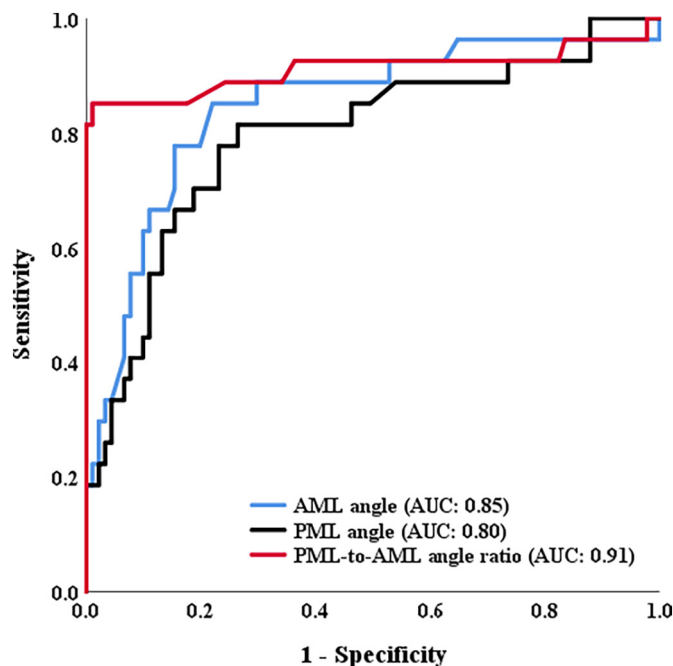
**Results**

*Definition of PML bending*

Fig. 4 shows the ROC curves of AML angle, PML angle, and PML-to-AML angle ratio for eccentric MR jet toward the LA posterior wall. Of these indexes, PML-to-AML angle ratio had the highest AUC value of 0.91. The best cut-off value of the angle ratio was 3.1, which yielded sensitivity and specificity of 85 % and 99 %, respectively. Hence, we defined PML bending as PML-to-AML angle ratio  $\geq 3.1$ .

*Patient and clinical characteristics*

Among the 118 study patients (mean age,  $78 \pm 9$  years; 52 % female), the PML bending group comprised 24 patients and the no PML bending group comprised 94. Patient characteristics did not significantly differ between the groups (Table 1). Overall, AF duration was longer than 1 year in approximately two-thirds of patients and 10 years or longer in approximately one-fourth; it did not significantly differ between the groups.



**Fig. 4.** Receiver operating characteristic curve of AML angle, PML angle, and PML-to-AML angle ratio for eccentric jet toward LA posterior wall. PML-to-AML angle ratio had the highest AUC value. AML, anterior mitral leaflet; AUC, area under the curve; LA, left atrium; PML, posterior mitral leaflet.

**Table 1**  
Clinical characteristics and echocardiographic data.

	PML bending (n=24)	No PML bending (n=94)	p-value
<b>Clinical characteristics</b>			
Age, years	76 ± 13	79 ± 8	0.13
Female sex	10 (42)	51 (54)	0.38
BSA, m <sup>2</sup>	1.5 ± 0.2	1.5 ± 0.2	0.54
NYHA class $\geq$ II	7 (29)	32 (34)	0.83
Prior HF hospitalization	9 (38)	31 (33)	0.86
Hypertension	18 (75)	68 (72)	1.0
Diabetes mellitus	3 (13)	17 (18)	0.73
Dyslipidemia	7 (29)	17 (18)	0.36
ACE-I/ARB	13 (54)	47 (50)	0.89
$\beta$ -blocker	14 (58)	41 (44)	0.29
MRA	3 (13)	19 (20)	0.57
Digitalis	6 (25)	13 (14)	0.31
Diuretics	17 (71)	59 (63)	0.62
Systolic blood pressure, mm Hg	127 (111–143)	130 (112–150)	0.24
Diastolic blood pressure, mm Hg	68 (59–74)	73 (64–83)	0.069
Heart rate, bpm	67 (57–82)	77 (64–90)	0.076
Hemoglobin, g/dL	12 ± 1.8	12 ± 1.9	0.82
eGFR, mL/min/1.73	58 ± 22	57 ± 28	0.86
BNP, pg/mL	292 (129–417)	235 (134–456)	0.79
<b>Atrial fibrillation</b>			
Paroxysmal	1 (4)	5 (5)	1.0
Duration			0.76
<1 year	3 (13)	8 (9)	
$\geq$ at least 1 year	4 (17)	25 (27)	
$\geq$ at least 5 years	5 (21)	14 (15)	
$\geq$ 10 years	7 (29)	23 (25)	
Unknown	5 (21)	24 (26)	
<b>Echocardiographic measurements</b>			
LVEF, %	62 ± 7	63 ± 7	0.60
LVEDD, mm	47 ± 6	47 ± 6	0.87
LVESD, mm	31 ± 5	31 ± 6	0.57
LVEDV index, mL/m <sup>2</sup>	56 ± 19	51 ± 16	0.26
LVESV index, mL/m <sup>2</sup>	21 ± 9	19 ± 7	0.27
LV dilatation	4 (17)	12 (13)	0.74
LV mass index, g/m <sup>2</sup>	116 ± 30	113 ± 29	0.67
E-wave, cm/s	116 ± 24	110 ± 26	0.30
DcT, ms	165 ± 46	179 ± 56	0.28
E/E' (average) ratio	15 ± 6.8	13 ± 4.6	0.12
Estimated RVSP, mmHg	37 ± 15	36 ± 11	0.68
LA diameter, mm	51 ± 9	50 ± 9	0.80
LA volume, mL	147 ± 54	137 ± 66	0.49
LA volume index, mL/m <sup>2</sup>	99 ± 34	90 ± 44	0.38
Length of inward bending of LV posterobasal wall, mm	16 ± 6	11 ± 3	<0.001
RA area, cm <sup>2</sup>	28 ± 15	27 ± 10	0.50
<b>Mitral valve</b>			
MR			0.43
Mild	16 (66.7)	72 (76.6)	
$\geq$ Moderate	8 (33.3)	22 (23.4)	
Eccentric jet	23 (95.8)	4 (4.3)	<0.001
AML angle, degrees	8 ± 4	17 ± 6	<0.001
PML angle, degrees	48 ± 11	29 ± 12	<0.001
PML-to-AML angle ratio	7.7 ± 3.9	1.8 ± 0.5	<0.001
AML length, mm	27 ± 4	24 ± 4	0.002
PML length, mm	15 ± 4	14 ± 4	0.47
Annulus area, cm <sup>2</sup>	11.6 ± 2.3	9.6 ± 2.3	<0.001
Sphericity index	0.93 ± 0.09	0.93 ± 0.14	0.96
<b>Tricuspid valve</b>			
TR			0.81
$\leq$ Mild	17 (70.8)	62 (66)	
$\geq$ Moderate	7 (29.2)	32 (34)	
Jet area, cm <sup>2</sup>	9.2 ± 5.4	9.0 ± 7.4	0.93
Annulus dimension, mm	35 ± 7	35 ± 6	0.94

Data shown are means ± standard deviation, medians (interquartile range), or numbers (%). ACE-I, angiotensin-converting enzyme inhibitor; AML, anterior mitral leaflet; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; BSA, body surface area; DcT, deceleration time; eGFR, estimated glomerular filtration rate; HF, heart failure; LA, left atrial; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PML, posterior mitral leaflet; RA, right atrial; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.

**Table 2**  
Clinical events.

	PML bending (n=24)	No PML bending (n=94)	p-value
Composite of events	10 (42)	25 (27)	0.21
Any event			
Cardiac death	3 (13)	9 (10)	0.71
Admission for HF	7 (29)	19 (20)	0.50
Mitral valve surgery	3 (13)	3 (3)	0.10
Replacement	3 (13)	2 (2)	
Repair	0	1 (1)	

Data shown are numbers (%).  
HF, heart failure; PML, posterior mitral leaflet.

**Echocardiographic data**

TTE measurements are presented in Table 1. In the overall cohort, the majority of patients were normal LV size, but 16 patients (14 %) had LV dilatation. There were no significant differences in LV size and function between the groups. LA was dilated in both groups and its size was not significantly different between the groups ( $99 \pm 34$  mL/m<sup>2</sup> vs.  $90 \pm 44$  mL/m<sup>2</sup>;  $p = 0.38$ ). Overall, a total of 88 patients (75 %) had mild MR. MR severity was similar in the groups. Based on the definition of PML bending, the prevalence of eccentric jet was higher in the PML bending group. The length of inward bending of the LV posterobasal wall was significantly greater ( $16 \pm 6$  mm vs.  $11 \pm 3$  mm,  $p < 0.001$ ), MV annulus area was significantly greater ( $11.6 \pm 2.3$  cm<sup>2</sup> vs.  $9.6 \pm 2.3$  cm<sup>2</sup>,  $p < 0.001$ ), PML angle was significantly greater ( $48 \pm 11^\circ$  vs.  $29 \pm 12^\circ$ ,  $p < 0.001$ ), and AML angle was significantly smaller ( $8 \pm 4^\circ$  vs.  $17 \pm 6^\circ$ ,  $p < 0.001$ ) in the PML bending group. Consequently, PML-to-AML angle ratio was significantly higher in the PML bending group ( $7.7 \pm 3.9$  vs.  $1.8 \pm 0.5$ ,  $p < 0.001$ ). TR severity and tricuspid valve annulus length were similar between the groups.

**Clinical outcomes**

Table 2 shows clinical events observed over a median follow-up of 29 months (IQR, 7.3–44). All the rates of cardiac death, admission for HF, and MV surgery tended to be higher in the PML bending group. All the patients who underwent MV surgery had worsening HF symptoms due to significant MR. The composite endpoint occurred in 10 (42 %) patients with PML bending and 25 (27 %) patients with no PML bending. In Kaplan-Meier analysis, the 36-month event-free survival for the composite endpoint was significantly higher in no PML bending group

(63 % vs. 78 %;  $p = 0.047$ ; Fig. 5). In a multivariate Cox proportional hazards model that adjusted for age, LV mass index, estimated right ventricular systolic pressure, moderate or greater MR, moderate or greater TR, and LA volume index, PML bending was independently associated with higher risk of composite endpoint event (adjusted hazard ratio 2.4; 95 % confidence interval, 1.1–5.3;  $p = 0.025$ ) (Table 3).

**Discussion**

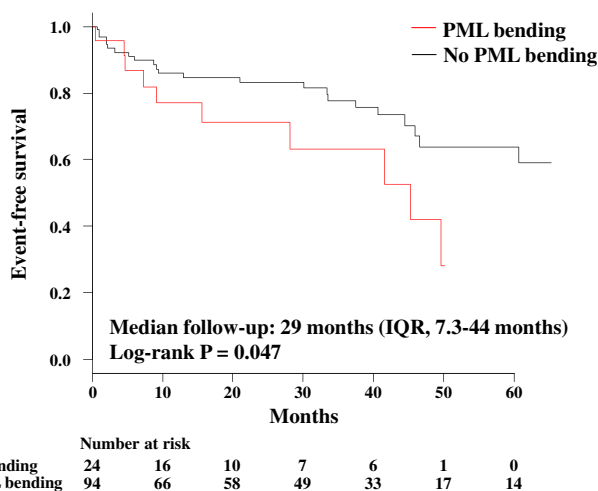
We identified differences in echocardiographic features and clinical outcomes between AFMR patients with and without PML bending characterized by MV morphology. The results of this study were summarized as follows: 1) PML bending was defined using PML-to-AML angle ratio  $\geq 3.1$ ; 2) AFMR patients with and without PML bending were similar with respect to numerous relevant clinical and echocardiographic characteristics such as AF duration and cardiac cavities size, but the length of inward bending of the left ventricular posterobasal wall was longer and mitral annular area was larger in the PML bending group; 3) PML bending may be a predictor of worse outcome.

*The definition of PML bending*

The underlying cause of PML bending is inward bending of the basal LV posterior wall, which occurs because of extreme enlargement of the posterior wall of the LA [17]. The PML is consequently tethered and restricted in motion, while the AML is not and the leaflet closes in systole at the level of the mitral annulus. As a result, relative anterior leaflet prolapse and an eccentric MR jet toward the LA posterior wall occur. Thus, it was conceivable that the eccentric MR jet with high PML-to-AML angle ratio had greater discriminative ability of the PML bending. There are two studies that support our finding. Ito et al. used AML–PML angle difference to represent posteriorly dominant leaflet tethering and showed that the difference was significantly larger in patients with AFMR than in those without AFMR [8]. Machino-Ohtsuka et al. demonstrated that PML tethering angle was the most influential independent predictor of AFMR severity and reported that PML angle was almost three times larger than AML angle in patients with AFMR [9]. However, these studies did not specifically examine leaflet angle ratio. In an echocardiographic study of patients with ventricular functional MR, the posterior to anterior leaflet tethering angle ratio was greater in patients with posteriorly dominant tethering of both leaflets than in patients with apical tethering of both leaflets ( $3.19 \pm 0.88$  vs.  $1.95 \pm 0.46$ ) [14]. Therefore, the definition of PML bending using an angle ratio of 3.1 in our study was reasonable. Further studies using three-dimensional transesophageal echocardiography or multi-detector computed tomography data are needed to confirm our findings.

*Comparison with previous studies in clinical features and outcomes*

The sequential relationship between LA enlargement, mitral annular dilatation, and MR in AF patients remains controversial [24]. Nevertheless, multiple studies have reported that LA enlargement causes mitral annular dilation following MR. Accordingly, catheter ablation is performed in AF patients with functional MR to decrease LA and mitral annulus size [7,25]. In two previous studies that reported PML bending as the main cause of AFMR, mean LA volume index was quite large in patients with significant MR ( $128 \pm 105$  mL/m<sup>2</sup> and  $95 \pm 41$  mL/m<sup>2</sup>, respectively) [8,9]. In contrast, two other studies that reported insufficient mitral leaflet adaptation was the main cause had relatively small LA volume index (median 69.7 mL/m<sup>2</sup> and mean  $50.5 \pm 19.5$  mL/m<sup>2</sup>, respectively) [10,11]. According to these findings, we suspected that AFMR patients with PML bending had a larger LA volume than those without PML bending. Another retrospective cohort study of 39 patients with moderate to severe or severe AFMR reported that patients with a posteriorly directed MR jet had a tendency of large LA (140 mL [IQR 104.5 to 208.5], posterior jet vs. 94 mL [IQR 78.2 to 149.3], central jet;  $p = 0.089$ ) and increased



**Fig. 5.** Kaplan–Meier event-free survival curves for the composite endpoint (cardiac death, admission for heart failure, or mitral valve surgery) in atrial functional mitral regurgitation patients with and without posterior mitral leaflet (PML) bending.

**Table 3**  
Univariate and multivariate analysis of composite endpoint events.

	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Age (per 5-year increase)	1.2 (0.97–1.5)	0.084	1.1 (0.93–1.4)	0.20
LV mass index (per 10-g/m <sup>2</sup> increase)	1.07 (0.95–1.2)	0.27	1.01 (0.89–1.2)	0.83
Estimated RVSP (per 5-mmHg increase)	1.2 (1.01–1.3)	0.031	1.1 (0.96–1.3)	0.19
≥Moderate MR	2.02 (1.02–4.0)	0.044	1.4 (0.63–3.0)	0.43
≥Moderate TR	1.2 (0.61–2.4)	0.58	1.05 (0.51–2.2)	0.89
LA volume index (per 10-mL/m <sup>2</sup> increase)	1.09 (1.03–1.2)	0.007	1.07 (0.99–1.2)	0.07
PML bending	2.1 (0.99–4.5)	0.052	2.4 (1.1–5.3)	0.025

CI, confidence interval; HR, hazard ratio; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; PML, posterior mitral leaflet; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.

mortality ( $p=0.070$ ) as well as a larger effective regurgitant orifice area ( $p=0.015$ ) compared with those with a central MR jet [26]. Thus, we expected that PML bending was a sign of more advanced stage of AFMR. The current study, however, revealed no significant difference in LA volume between AFMR patients with and without PML bending. Given that there are no significant causal relationships between PML bending and LA size, the occurrence of PML bending needs other factors in addition to LA dilatation. The inward bending of the LV posterobasal wall is considered one of the important causes of the hamstringing of the posterior leaflet, and our result also identified the association between the inward bending of LV posterobasal wall and the PML bending. Furthermore, we found that one-fifth of mild AFMR had PML bending, suggesting that PML bending occurred at an earlier stage of MR than previously thought. Of note, >40 % of patients with mild or moderate MR and PML bending achieved the endpoints over a median follow-up of only 29 months. Based on these findings, the cause of worse outcome in patients with PML bending may be not only the severity of MR but also the MV morphology or the background responsible for the PML bending. Further studies are required to elucidate the cause of worse outcome in patients with PML bending.

#### Surgical or percutaneous mitral valve intervention

The number of studies reporting treatment for AFMR is limited. However, several therapeutic options can be considered: medical therapy for heart failure, catheter ablation for AF, and MV repair via open surgery or a transcatheter procedure [1,20,27]. The latest treatment guidelines note a potential benefit for surgical intervention in patients with severe AFMR but not ventricular functional MR [1]. Takahashi et al. reported acceptable short-term morbidity and mortality in 10 patients with AFMR who underwent ring annuloplasty [28]. Transcatheter repair is not mentioned in the current guidelines [1,2]. However, select high-risk patients and those with contraindications for surgical MV repair or replacement may be candidates for a transcatheter procedure. Nagaura et al. reported successful transcatheter repair using the MitraClip (Abbott Vascular, Santa Clara, CA, USA) in 87 AFMR patients who did not have significant PML tethering [29]. Although surgical and transcatheter treatment of AFMR has demonstrated short-term success, outcome evidence according to AFMR phenotype remains limited. Our results showed an association of PML bending with worse outcomes, which suggests that understanding the mechanisms underlying AFMR is important for treatment decision-making and timing of intervention.

#### Limitations

This study has several limitations. First, it was retrospective and conducted in a single center; therefore, the sample size was relatively small. Second, MV morphology was analyzed using two-dimensional TTE imaging. In contrast to several previous studies that used three-dimensional transesophageal echocardiography [9–11], we could not evaluate the total mitral leaflet area-to-annular area ratio, which

represents mitral leaflet adaptation. Because insufficient leaflet adaptation is considered a cause of AFMR, incremental prognostic value of this parameter should be evaluated in future studies. Third, MR severity was not related to prognosis in patients with AFMR in this study, which was different from previous studies. We thought this was because limited data on MR severity were available from routine examination reports. MR severity was tried to be determined by comprehensive assessment based on several measurements. However, MR severity was mainly determined using the color jet area method in clinical practice, which is known for resulting in underestimation of the MR severity of the eccentric jet compared with the central jet. As a result, MR severity in patients with PML bending might be underestimated, because patients with PML bending usually had wall jet of the MR. This might explain why, in this study, the PML bending group met more clinical events than no PML bending group, and MR severity was not an independent prognostic factor in the multivariate analysis despite previous studies showing a prognostic factor of cardiac events. Special attention needs to be paid to evaluating MR severity for AFMR patients with PML bending.

#### Conclusions

Although AFMR patients with and without PML bending did not differ in clinical characteristics including AF duration and cardiac cavities size, patients with PML bending might have worse outcomes than those without PML bending.

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#### Declaration of competing interest

The authors declare no conflicts of interest associated with this manuscript.

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