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ORIGINAL PAPER

Prognostic impact of regurgitant volume to left atrial volume ratio on ventricular functional mitral regurgitation

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Aims

In patients with ventricular functional mitral regurgitation (VFMR) undergoing transcatheter edge-to-edge repair (M-TEER), the prognostic significance of the ratio between mitral regurgitant volume and left atrial volume (LAV) remains unclear. This ratio may reflect the proportional or disproportionate burden of regurgitation on the left atrium. To address this gap, we aimed to investigate the association between the regurgitant volume (RVol)/LAV ratio and clinical outcomes in patients with VFMR, using data from a multicentre prospective registry.

Methods and results

We calculated the RVol/LAV ratio from baseline transthoracic echocardiograms. The median value of the RVol/LAV ratio was 0.40. A total of 1830 patients who underwent M-TEER were allocated into two groups: the low RVol/LAV (RVol/LAV ratio <0.40) and high RVol/LAV (RVol/LAV ratio ≥0.40) groups. The primary endpoint was heart failure hospitalization. Eight hundred eighty-eight and 942 patients were included into the low RVol/LAV ratio and high RVol/LAV ratio groups, respectively. The median follow-up period was 508 days. At 3 years after repair, 215 (37.6%) and 187 (32.1%) patients

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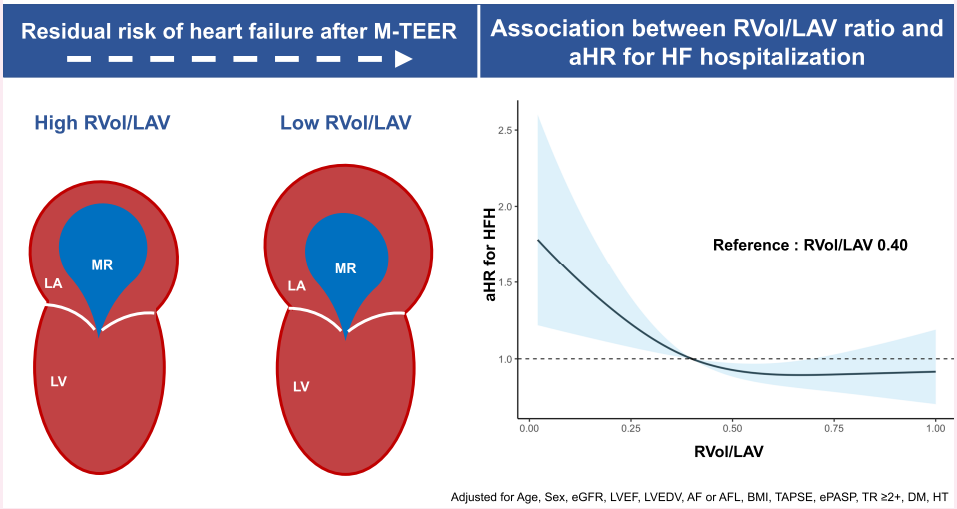
in the low RVol/LAV and high RVol/LAV groups, respectively, were hospitalized for heart failure. The patients in the low RVol/LAV group demonstrated a significantly higher risk of heart failure hospitalization than did those in the high RVol/LAV group (hazards ratio, 1.25; 95% confidence interval, 1.03–1.52; $P = 0.022$). Furthermore, using multivariable Cox regression analysis, the low RVol/LAV was an independent predictor of the primary endpoint.

Conclusion The RVol/LAV ratio might serve as a valuable metric for improving risk stratification in patients with VFMR.

Clinical trials OCEAN Mitral registry (UMIN ID: UMIN000023653)

Graphical Abstract



RVol/LAV ratio and risk of heart failure hospitalization in VFMR patients treated with M-TEER.

Keywords ventricular functional mitral regurgitation • transcatheter edge-to-edge repair • regurgitant volume • left atrial volume • regurgitant volume/left atrial volume ratio (RVol/LAV)

Introduction

The presence of ventricular functional mitral regurgitation (VFMR) indicates poor prognosis in patients with heart failure.[1,2] The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial demonstrated that mitral valve transcatheter edge-to-edge repair (M-TEER) using MitraClip significantly reduced composite events, including all-cause death and heart failure hospitalization (HFH).[3] However, the Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trial failed to establish the superiority of MitraClip plus guideline-directed medical therapy (GDMT) over GDMT alone.[4] Based on these different results of the two trials, many discussions have been conducted about left ventricular (LV) size and mitral regurgitation severity[5–7] leading to disproportionate and proportionate mitral regurgitation. Proportionate mitral regurgitation, where the LV is larger relative to the regurgitant volume (RVol), might be associated with less benefit from M-TEER.[8] Based on this concept, although several studies have attempted to validate it, the results have been inconsistent.[9–11]

Considering mitral regurgitation and the left atrium, mitral regurgitation directly impacts the left atrium, causing its enlargement.[12] Left atrial size is recognized as an indicator of disease severity and associated with poorer outcomes in patients with secondary mitral regurgitation.[13] However, in patients who underwent M-TEER, whether baseline left atrial size could be a predictor remains controversial.[14,15] Thus, a previous study investigated the relationship between left atrial volume (LAV) and RVol and outcomes in patients with VFMR who underwent M-TEER.[16] A low baseline RVol/LAV ratio predicted HFH in VFMR patients on GDMT alone. However, M-TEER reduced HFH and mortality regardless of the RVol/LAV ratio. In real-world practice, it remains unclear how the RVol/LAV ratio influences the prognosis of patients treated with M-TEER. The aim of this study was to investigate the relationship between the RVol/LAV ratio and prognosis in patients receiving M-TEER for VFMR.

Methods

Study population

The OCEAN (Optimized CathEter vAlvular iNtervention)-Mitral registry is an ongoing, physician-led, multicentre study evaluating M-TEER with MitraClip (Abbott Vascular) in patients with significant mitral regurgitation unresponsive to optimal medical therapy. From April 2018 to June 2023, 3764 symptomatic patients were prospectively enrolled across 21 centres in Japan. A multidisciplinary heart team assessed all patients, and M-TEER eligibility was determined based on current guidelines.[17] M-TEER was considered suitable for managing patients who remained symptomatic despite optimal medical therapy for heart failure. All patients underwent 2D transthoracic echocardiography before and after the procedure and intraprocedural transoesophageal

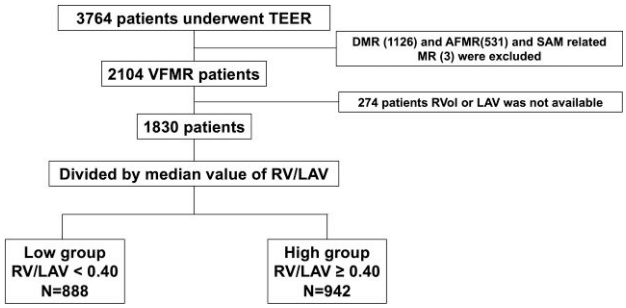


Figure 1 Patient flow diagram. Of 3764 patients undergoing TEER, 2104 had VFMR. After excluding 274 without RVol or LAV data, 1830 patients were analysed and divided by the median RVol/LAV (0.40) into low (<0.40, $n = 888$) and high (≥0.40, $n = 942$) groups.

echocardiography. An experienced echocardiographer performed all echocardiographic assessments. Mitral regurgitation severity was determined based on qualitative and quantitative criteria according to the American Society of Echocardiography and classified as 0+ (none), 1+ (mild), 2+ (moderate), 3+ (moderate to severe), and 4+ (severe).[18] RVol was measured using either the proximal isovelocity surface area (PISA) method or the volumetric method, depending on institutional practice and image quality. When the PISA method was applied, the effective regurgitant orifice area (EROA) was also calculated. LAV was determined using the biplane Simpson's method from apical four- and two-chamber views at ventricular end-systole.

We focused on analysing VFMR and excluded degenerative mitral regurgitation and atrial functional mitral regurgitation cases. Atrial functional mitral regurgitation (AFMR) was defined as secondary mitral regurgitation with dilated left atrium [LAV index ≥34 mL/m^2 or left atrial diameter ≥40/38 mm (male/female)] and normal LV function [LV ejection fraction (LVEF) ≥ 50%] and size [LV end-diastolic volume (LVEDV) <150 mL or LV end-diastolic diameter <55 mm).

This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000023653) and complied with the standards set by the International Committee of Medical Journal Editors. The Institutional Review Board of each participating institution approved the study protocol. The research was conducted in accordance with the Declaration of Helsinki and adhered to the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare of Japan.

Data collection and endpoint

Demographic data, medication history, blood tests, and electrocardiographic findings were collected at admission. Pre- and post-procedural transthoracic and transoesophageal echocardiographic data were recorded. Follow-up at 30 days and 1, 2, 3, and 5 years included phone interviews when in-person visits were missed to assess survival and clinical outcomes. The primary endpoint of the present study was HFH. The secondary endpoints included a composite of cardiovascular death and HFH. Although follow-up was available up to 5 years, all survival analyses and Kaplan–Meier curves were truncated at 3 years to ensure clarity and sufficient numbers at risk. Median follow-up time was calculated using the reverse Kaplan–Meier method.

Statistical analysis

Patients were divided into two groups based on the RVol/LAV ratio (<median vs. ≥median). Continuous variables are shown as mean ± standard deviation (SD) or median (Q1–Q3), and categorical variables as counts and percentages. Group differences were assessed using Student's *t*-test, Mann–Whitney *U* test, χ^2, or Fisher's exact test, as appropriate. Kaplan–Meier analysis with log-rank test evaluated event-free survival. Cox regression was used to assess the association between RVol/LAV and outcomes, including a multivariable model adjusted for clinically relevant confounders. RVol/LAV was also entered as a continuous variable to evaluate linear associations. A multivariable Cox proportional hazards model was fitted using a restricted cubic spline with four knots (df = 3) for RVol/LAV. For graphical clarity, outliers were excluded based on the 1.5 × interquartile range (IQR) rule. This exclusion was applied for display purposes only and not in the statistical modelling. Missing covariate data were handled using multiple imputation by chained equations under the assumption of missing at random. Twenty imputed datasets were generated, and results from the multivariable Cox proportional hazards models were combined using Rubin's rules.

A sensitivity analysis was performed among patients who met the COAPT criteria, using both the previously reported RVol/LAV cutoff value of 0.67[16] and the median RVol/LAV value in the present study. The COAPT criteria were as follows (LVEF ≥20%), LVEDV ≤70 mm, estimated pulmonary artery systolic pressure ≤70 mmHg, absence of moderate or severe right ventricular dysfunction, absence of severe tricuspid regurgitation, absence of haemodynamic instability.[19] Considering all analyses, a two-tailed *P*-value <0.05 was considered statistically significant. All analyses were performed using JMP Pro 17 software (SAS Institute Inc., Cary, NC, USA). Restricted cubic spline Cox regression models were constructed using RStudio (version 2024.09.0 + 375; RStudio, Inc., Boston, MA, USA) to enable flexible modelling and visualization.

Results

Patients flow

Out of 3764 patients, 1830 patients with RVol and LAV data were evaluated. Patients were categorized into two groups based on the baseline RVol/LAV ratio, using a median value of 0.40 (*Figure 1*). The high RVol/LAV ratio group was defined as those with a ratio of 0.40 or greater ($n = 942$), while the low RVol/LAV ratio group included those with a ratio below 0.40 ($n = 888$). The distribution of RVol/LAV is presented in *Figure 2*.

Baseline patients' characteristics

Table 1 summarizes the baseline characteristics of the study cohort, categorized according to the median baseline RVol/LAV ratio. Of all patients, the mean age was 75 years; 64% were male participants. Approximately 60% of patients had hypertension, 35% had diabetes mellitus, and 39% had ischaemic cardiomyopathy. The patients in the low RVol/LAV group were relatively younger, had a higher body mass index and comprised a higher proportion of male participants in comparison with the high RVol/LAV group. Additionally, there was a higher prevalence of atrial fibrillation or flutter and a lower prevalence of ischaemic cardiomyopathy in the low RVol/LAV group. Regarding medications, mineralocorticoid receptor antagonist usage and loop diuretic usage were significantly more frequent in the low RVol/LAV group.

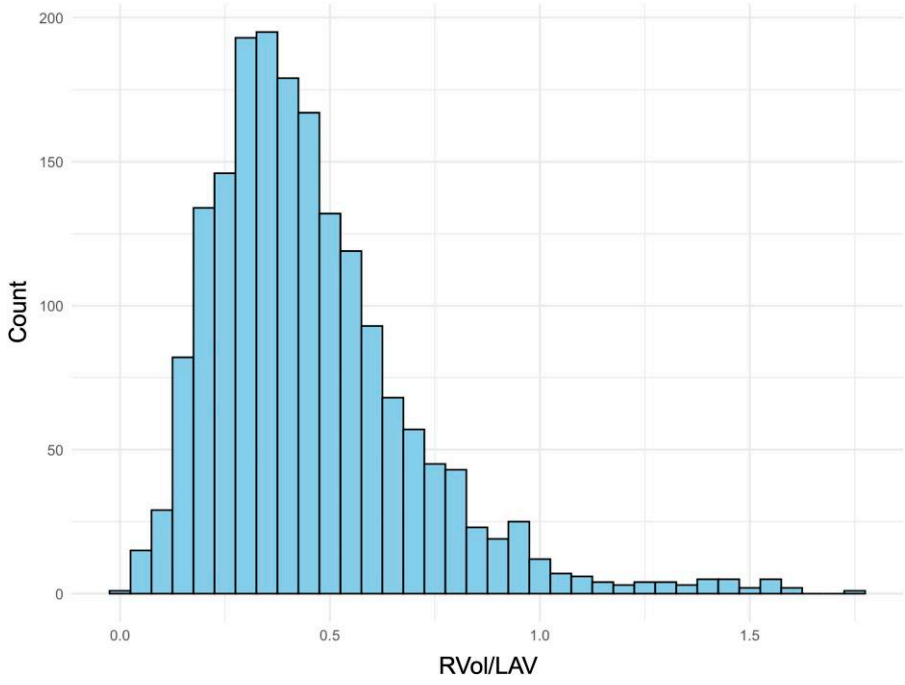


Figure 2 Distribution of RVol/LAV. Histogram showing the distribution of RVol/LAV ratio among the study population.

Table 2 presents baseline echocardiographic measurements in the study cohort. Significant differences were observed in several echocardiographic parameters between the two groups. The LVEF was slightly higher in the low RVol/LAV group compared with that in the high RVol/LAV group. The LAV index was substantially higher, and RVol was significantly lower in the low RVol/LAV group. Moderate or greater tricuspid regurgitation was more prevalent in the low RVol/LAV group. Following the procedure, post-procedural mitral regurgitation severity was comparable across the groups.

The association between baseline RVol/LAV and the primary endpoint

The median follow-up was 508 days (IQR 353–1045). The cumulative incidence of HFH at 1, 2, and 3 years was 15.7, 24.2, and 32.1% in the high RVol/LAV group, and 19.8, 29.9, and 37.6% in the low RVLAV group, respectively (*Table 3*). The patients in the low RVol/LAV group exhibited a significantly higher risk of HFH [hazard ratio, 1.25; 95% confidence interval (CI), 1.03–1.52; $P = 0.022$; *Figure 3A*] and the composite of cardiovascular death and HFH (hazard ratio, 1.21; 95% CI, 1.02–1.43; $P = 0.026$; *Figure 3B*) than did those in the high RVol/LAV group, but not with cardiovascular death alone (hazard ratio, 1.11; 95% CI, 0.88–1.39; $P = 0.385$; *Figure 3C*). Regarding HFH, results from the Fine–Gray competing risk analysis were consistent with those of the primary outcome (see Supplementary data online, *Figure S1*).

Prognostic predictors of heart failure hospitalization using Cox analysis

Table 4 lists the results of a multivariable Cox regression analysis for HFH, presenting the adjusted hazard ratio (aHR). Low RVol/LAV was found to be an independent prognostic predictor (aHR, 1.26; 95% CI, 1.03–1.54; $P = 0.027$). Other factors associated with HFH were age (aHR, 1.02; 95% CI, 1.01–1.03; $P < 0.001$), estimated glomerular filtration rate (eGFR) (aHR, 0.89; 95% CI, 0.84–0.94; $P < 0.001$), LVEDV (aHR, 1.02; 95% CI, 1.00–1.04; $P = 0.041$), and atrial fibrillation (AF) or atrial flutter (AFL) (aHR, 1.33; 95% CI, 1.07–1.65; $P = 0.009$). However, neither LAV nor RVol alone achieved statistical significance as a predictor of HFH (*Table 5*). Setting RVol/LAV = 0.40 as the reference, values below 0.40 were associated with an increased risk of heart failure events, particularly at the lowest RVol/LAV values. Estimates were adjusted for Age, Sex, eGFR, LVEF, LVEDV, AF or AFL, body mass index (BMI), tricuspid annular plane systolic excursion (TAPSE), estimated pulmonary artery systolic pressure (ePASP), tricuspid regurgitation (TR) ≥2+, diabetes mellitus (DM), and hypertension (HT) (*Figure 4*). When modelled as a linear term, each 0.1-unit increase in RVol/LAV ratio was associated with a lower risk of heart failure events (aHR, 0.95; 95% CI, 0.91–0.99; $P = 0.037$) (see Supplementary data online, *Table S1*).

A sensitivity analysis in patients who met the COAPT criteria

Among the patients in the current study, approximately one-third ($n = 657$) met the COAPT-like profile definition.[19] The baseline characteristics and echocardiographic parameters are summarized in Supplementary data online, *Tables S2* and *S3*. The clinical outcomes in patients stratified by the previously reported RVol/LAV cutoff of 0.67[16] were not significantly different for the primary endpoint (hazard ratio, 1.30; 95% CI, 0.83–2.04; $P = 0.252$), composite of HFH and cardiovascular death (hazard ratio, 1.18; 95% CI, 0.80–1.72; $P = 0.408$), and cardiovascular death alone (hazard ratio, 0.93; 95% CI, 0.55–1.56; $P = 0.781$) (see Supplementary data online, *Figure S2A–C*). When applying the RVol/LAV cutoff of 0.40 to patients with the COAPT-like profile definition, HFH was significantly higher in patients with RVol/LAV < 0.40 (hazard ratio, 1.47; 95% CI, 1.08–2.00; $P = 0.017$) (see Supplementary data online, *Figure S3A*). Regarding the composite of HFH and cardiovascular death (hazard ratio, 1.22; 95% CI, 0.93–1.56; $P = 0.138$), as well as cardiovascular death alone (hazard ratio, 1.01; 95% CI, 0.73–1.41; $P = 0.955$), there were no significant differences in these patients (see Supplementary data online, *Figure S3B* and *C*).

Table 1 Baseline characteristics according to the median baseline RVol/LAV ratio

	Total 1830	Low RVol/LAV ($n = 888$)	High RVol/LAV ($n = 942$)	*P*-value	Missing (%)
Age, years	75.7 ± 9.7	75.0 ± 9.5	76.3 ± 9.8	0.007	0 (0%)
Male (%)	1179 (64.4%)	612 (68.9%)	567 (60.2%)	<0.001	0 (0%)
BMI (kg/m^2)	21.3 ± 3.5	21.7 ± 3.6	20.9 ± 3.4	<0.001	1 (0.1%)
Hypertension (%)	1108 (60.5%)	544 (61.3%)	564 (59.9%)	0.544	0 (0%)
Diabetes (%)	635 (34.7%)	318 (35.8%)	317 (33.7%)	0.332	0 (0%)
Atrial fibrillation or flutter (%)	1061 (58.0%)	617 (69.5%)	444 (47.1%)	<0.001	0 (0%)
Prior PCI/CABG (%)	783 (42.8%)	337 (38.0%)	446 (47.3%)	<0.001	0 (0%)
ICM (%)	705 (38.5%)	305 (34.3%)	400 (42.5%)	<0.001	0 (0%)
Prior stroke (%)	208 (11.4%)	109 (12.3%)	99 (10.5%)	0.234	0 (0%)
COPD (%)	156 (8.5%)	73 (8.2%)	83 (8.8%)	0.651	0 (0%)
STS score for MVR	11.2 ± 8.7	11.0 ± 8.6	11.3 ± 8.7	0.419	107 (5.8%)
eGFR (mL/min/1.73 m^2)	37.2 ± 19.8	37.3 ± 19.1	37.0 ± 20.5	0.759	20 (1.1%)
BNP (pg/mL)	497 [245–957]	493 [242–930]	512 [248–1026]	0.208	475 (25.9%)
Pacemaker (%)	111 (6.1%)	52 (5.9%)	59 (6.3%)	0.715	0 (0%)
ICD (%)	141 (7.7%)	77 (8.7%)	64 (6.8%)	0.132	0 (0%)
CRTP/D (%)	309 (16.9%)	157 (17.7%)	152 (16.1%)	0.378	0 (0%)
NYHA functional class			0.187		
NYHA I (%)	29 (1.6%)	17 (1.9%)	12 (1.3%)		0 (0%)
NYHA II (%)	602 (32.9%)	276 (31.1%)	326 (34.6%)		0 (0%)
NYHA III (%)	886 (48.4%)	431 (48.5%)	455 (48.3%)		0 (0%)
NYHA IV (%)	313 (17.1%)	164 (18.5%)	149 (15.8%)		0 (0%)
Medication at baseline					
ACE-inhibitor/ARB (%)	991 (54.2%)	489 (55.1%)	502 (53.3%)	0.446	0 (0%)
Beta-blocker (%)	1520 (83.1%)	742 (83.6%)	778 (82.6%)	0.581	0 (0%)
MRA (%)	1113 (60.9%)	565 (63.7%)	548 (58.2%)	0.016	1 (0.1%)
SGLT2-inhibitor (%)	502 (27.4%)	249 (28.0%)	253 (26.9%)	0.571	0 (0%)
Loop diuretic (%)	1500 (82.0%)	753 (84.8%)	747 (79.3%)	0.002	0 (0%)
ARNI (%)	238 (13.0%)	114 (12.8%)	124 (13.2%)	0.815	3 (0.2%)

Values are presented as mean ± SD, number (percentage), or median (IQR), as appropriate.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRTP/D, cardiac resynchronization therapy pacemaker/defibrillator; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; ICM, ischaemic cardiomyopathy; MRA, mineralocorticoid receptor antagonist; MVR, mitral valve replacement; NYHA, New York Heart Association classification; PCI, percutaneous coronary intervention; RVol/LAV, regurgitant volume/left atrial volume ratio; SGLT2i, sodium–glucose cotransporter 2 inhibitor; STS, Society of Thoracic Surgeons.

Discussion

The findings of this study

The primary findings of the present study were: first, lower RVol/LAV ratio was an independent predictor of HFH in patients with VFMR who underwent M-TEER. Secondly, this ratio was more useful for predicting HFH than its individual components.

Left atrial enlargement and mitral regurgitation severity, relationship to M-TEER

Although mitral regurgitation itself contributes to LA enlargement, additional factors such as a longer history of atrial fibrillation, male sex, and higher BMI have been associated with more advanced LA remodelling and dysfunction.[12,20,21] In line with these observations, we found that patients in the low RVol/LAV group had larger LAVs, a higher prevalence of atrial fibrillation, and a greater proportion of men than those in the high group, suggesting more pronounced LA remodelling. Collectively, these findings indicate that LA disease—potentially reflecting atrial myopathy—may play a pivotal role in the low RVol/LAV group. Therefore, the prognostic implications of MR should not be interpreted solely on the basis of regurgitant burden, but rather considered in the broader context of concomitant atrial disease, which may represent an additional pathophysiological substrate influencing outcomes.

According to current guidelines, VFMR is characterized by restrictive leaflet motion due to tethering in the setting of LV systolic dysfunction (LVEF <50%), whereas AFMR is primarily driven by atrial enlargement leading to mitral annular dilatation, typically with no or only mild LV dilatation and preserved LVEF (≥50%).[22] However, in clinical practice, the two mechanisms frequently coexist. In a COAPT sub-study of patients with secondary MR and LV dysfunction, a history of AF was associated

Table 2 Echocardiographic measurements according to the median baseline RVol/LAV ratio

	Total 1830	Low RVol/LAV ($n = 888$)	High RVol/LAV ($n = 942$)	*P*-value	Missing (%)
Pre-procedural results					
LVEF (%)	33.2 ± 9.8	33.8 ± 10.0	32.7 ± 9.6	0.016	1 (0.1%)
LVESV (mL)	125.0 ± 61.1	124.4 ± 60.5	125.5 ± 61.7	0.694	53 (2.9%)
LVESVi (mL/m^2)	80.6 ± 37.7	78.4 ± 36.2	82.7 ± 38.9	0.015	54 (3.0%)
LVEDV (mL)	180.4 ± 71.0	180.7 ± 70.6	180.1 ± 71.3	0.862	63 (3.4%)
LVEDVi (mL/m^2)	116.5 ± 43.0	114.1 ± 41.6	118.8 ± 44.3	0.021	64 (3.5%)
LAV (mL)	128.6 ± 74.0	161.6 ± 89.1	97.5 ± 34.2	<0.001	0 (0%)
LAVi (mL/m^2)	83.2 ± 45.8	102.5 ± 55.2	64.9 ± 22.8	<0.001	1 (0.1%)
EROA (PISA) (cm^2)	0.34 ± 0.16	0.30 ± 0.14	0.38 ± 0.17	<0.001	123 (6.7%)
Regurgitant volume of MR (mL)	50.0 ± 22.2	41.3 ± 18.2	58.3 ± 22.4	<0.001	0 (0%)
E/e′ of septum	20.9 ± 9.2	19.9 ± 9.1	21.8 ± 9.2	<0.001	213 (11.6%)
TR ≥ moderate (%)	583 (31.9%)	332 (37.4%)	251 (26.6%)	<0.001	0 (0%)
TAPSE (mm)	15.6 ± 4.6	15.2 ± 4.6	15.9 ± 4.6	0.005	280 (15.3%)
Estimated PASP (mmHg)	40.5 ± 15.2	40.6 ± 15.0	40.4 ± 15.3	0.8340	308 (16.8%)
MR severity at rest				<0.001	1 (0.1%)
1+	38 (2.1%)	28 (3.2%)	10 (1.1%)		
2+	272 (14.9%)	147 (16.6%)	125 (13.3%)		
3+	507 (27.7%)	261 (29.4%)	246 (26.1%)		
4+	1012 (55.3%)	452 (50.9%)	560 (59.5%)		
Post-procedural results					
Number of clips implanted	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.4	0.002	0 (0%)
MR severity				0.592	6 (0.3%)
0+/1+	1564 (85.7%)	749 (84.7%)	815 (86.7%)		
2+	218 (12.0%)	114 (12.9%)	104 (11.1%)		
3+	20 (1.1%)	11 (1.2%)	9 (1.0%)		
4+	22 (1.2%)	10 (1.1%)	12 (1.3%)		

Values are mean ± SD or *n* (%).
E/e′, ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity; EROA, effective regurgitant orifice area; LAV, left atrial volume; LAVi, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; MR, mitral regurgitation; PISA, proximal iso velocity surface area; PASP, pulmonary artery systolic pressure; TR, tricuspid regurgitation; TAPSE, tricuspid annular plane systolic excursion.

Table 3 Clinical outcomes according to the median baseline RVol/LAV ratio

	Low RVol/LAV ($n = 888$)	High RVol/LAV ($n = 942$)	HR (95% CI)	*P*-value
Heart failure hospitalization				
1 year	151 (19.8%)	126 (15.7%)		
2 years	196 (29.9%)	166 (24.2%)		
3 years	215 (37.6%)	187 (32.1%)	1.25 (1.03–1.52)	0.022
CV death or heart failure hospitalization				
1 year	196 (24.6%)	165 (20.0%)		
2 years	249 (35.8%)	223 (31.6%)		
3 years	276 (45.8%)	251 (40.8%)	1.21 (1.02–1.43)	0.026
CV death				
1 year	78 (9.9%)	64 (7.9%)		
2 years	111 (17.0%)	105 (16.2%)		
3 years	130 (24.3%)	131 (25.1%)	1.11 (0.88–1.39)	0.385

CI, confidence interval; CV, cardiovascular; HR, hazards ratio.

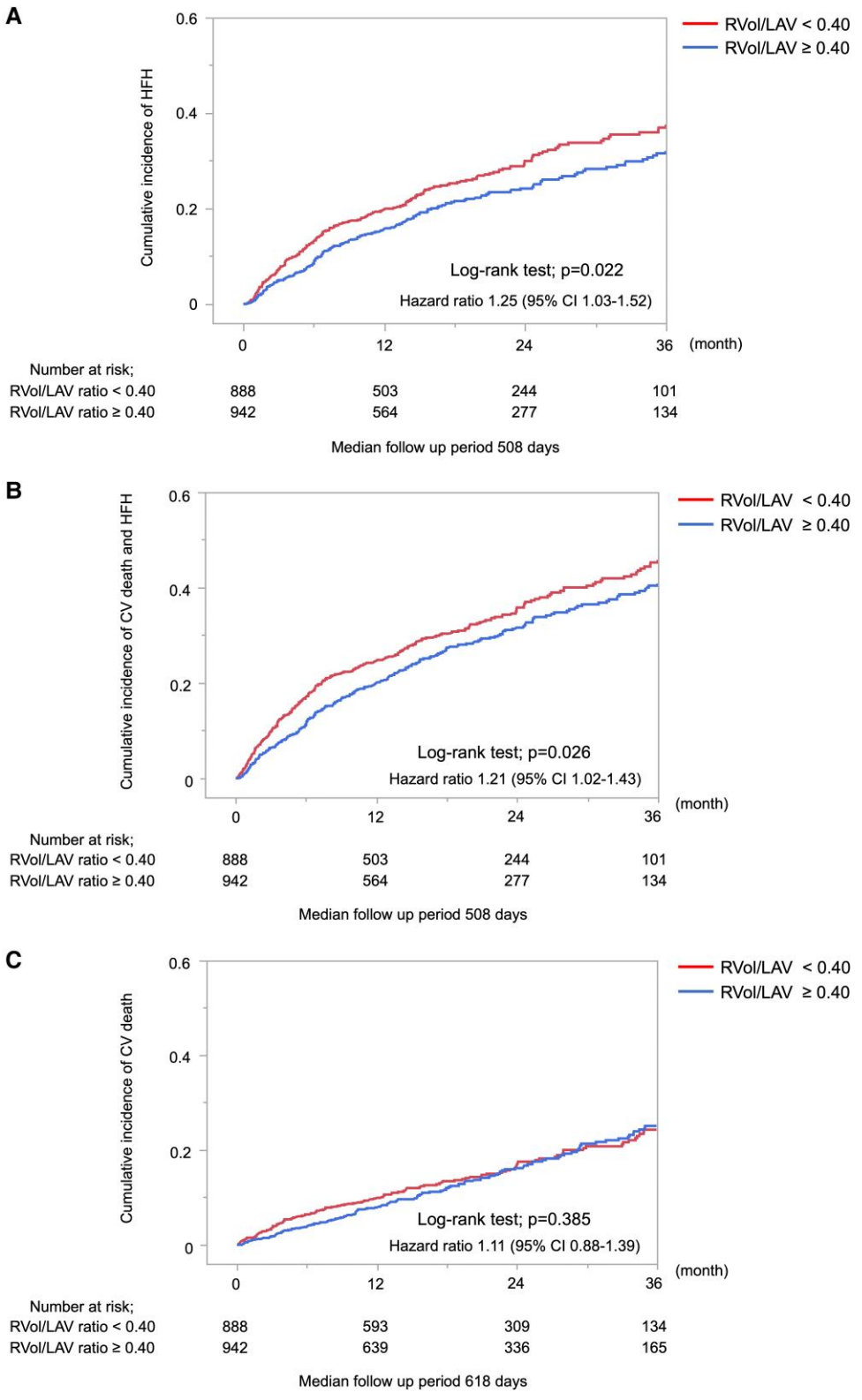


Figure 3 Kaplan–Meier curves for each event based on the median baseline RVol/LAV ratio. (*A*) The lower RVol/LAV ratio group had a significantly higher incidence of HFH. (*B*) Similarly, the incidence of the composite outcome of HFH and cardiovascular (CV) death was significantly higher in this group. (*C*) In contrast, there was no significant difference in CV death between the two groups. RVol/LAV, regurgitant volume/left atrial volume.

Table 4 Multivariable analysis for primary endpoints

	Adjusted HR	95% CI	*P*-value
Age[a]	1.02	1.01–1.03	<0.001
Male	0.96	0.77–1.19	0.696
eGFR[b]	0.89	0.84–0.94	<0.001
LVEF[a]	0.99	0.98–1.00	0.056
LVEDV[b]	1.02	1.00–1.04	0.041
AF or AFL	1.33	1.07–1.65	0.009
RVol/LAV <0.4 (vs. ≥0.4)	1.26	1.03–1.54	0.027
BMI[a]	0.98	0.95–1.01	0.173
TAPSE[a]	1.00	0.98–1.03	0.779
ePASP[b]	1.07	0.99–1.15	0.057
TR ≥2+	1.04	0.83–1.30	0.761
Diabetes mellitus	0.98	0.80–1.21	0.870
Hypertension	1.01	0.82–1.24	0.940

CI, confidence interval; HR, hazard ratio; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; AF, atrial fibrillation; AFL, atrial flutter; BMI, body mass index; TAPSE, tricuspid annular plane systolic excursion; ePASP, estimated pulmonary artery systolic pressure; TR, tricuspid regurgitation; RVol/LAV, regurgitant volume/left atrial volume.
[a]Per 1-unit increase.
[b]Per 10-unit increase.

Table 5 Multivariable analysis for primary endpoints

	Adjusted HR[a]	95% CI	*P*-value
RVol/LAV <0.4 (vs. ≥0.4)	1.26	1.03–1.54	0.027
LAV[b]	1.01	0.99–1.03	0.055
RVol[b]	0.97	0.92–1.01	0.139

LAV, left atrial vVolume; RVol, regurgitant volume; CI, confidence interval; HR, hazard ratio; DM, diabetes mellitus; HT, hypertension; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; AF, atrial fibrillation; AFL, atrial flutter; BMI, body mass index; TAPSE, tricuspid annular plane systolic excursion; ePASP, estimated pulmonary artery systolic pressure; TR, tricuspid regurgitation.
[a]Adjusted HR for age, sex, eGFR, LVEF, LVEDV, AF or AFL, BMI, TAPSE, ePASP, TR ≥2+, DM, and HT.
[b]Per 10-unit increase.

with atrial MR features, such as LA dilatation and annular enlargement, implying the presence of a mixed atrial–ventricular phenotype.[23] Patients with AF were more often male and experienced worse outcomes than those without AF. In our cohort, the low RVol/LAV group exhibited larger LAVs, higher LVEF, and greater prevalences of male and AF or AFL, findings that may represent mixed FMR. The profile observed in the low RVol/LAV group may reflect this bidirectional relationship and thereby contribute to disease progression.

The association between left atrial size and outcomes in VFMR patients undergoing M-TEER has been noted. Iliadis *et al.*[15] reported that while left atrial volume index (LAVi) >42 mL/m^2 was linked to higher mortality, this was not significant in multivariable analysis. Using subgroup analysis, enlarged LAV index was associated with a higher risk in cases of smaller EROA, emphasizing the importance of considering both left atrial size and mitral regurgitation severity. However, data on their relationship remains limited.

The relationship between RVol/LAV ratio and heart failure

The ventricular metric (RVol/LVEDV) has been widely used to evaluate proportionality in functional MR,[5] reflecting the balance between regurgitant volume and LV remodelling. In contrast, the atrial metric (RVol/LAV) indexes the regurgitant burden to LA size, thereby reflecting the contribution of LA remodelling and atrial disease burden, which is conceptually distinct from the ventricular ratio. RVol/LAV may be particularly relevant in patients with marked LA enlargement, where atrial disease plays a prominent role. In this context, RVol/LAV should not be viewed as a replacement for RVol/LVEDV but rather as a complementary index that incorporates the atrial component of remodelling. Recently, Coisne *et al.*[16] have reported that a low RVol/LAV ratio was an independent predictor of HFH in patients with VFMR treated with GDMT, when a cutoff value of 0.67, which was the median RVol/LAV in the COAPT trial, was applied in a sub-study of the COAPT trial. However, no significant difference in HFH was observed between the high and low RVol/LAV groups including patients treated with M-TEER. Given that M-TEER has been reported to improve left atrial size and function by reducing mitral regurgitation,[24–26] it is plausible that M-TEER attenuated the event rates in patients with a low RVol/LAV ratio. Accordingly, the optimal cutoff value of RVol/LAV in patients undergoing M-TEER may be lower than that in those treated with GDMT. In our study, the median RVol/LAV ratio was 0.40, which was lower than the previously reported threshold, and patients with RVol/LAV <0.40 showed a significantly increased risk of HFH (*Figure 3A*).

Several substantive differences with the COAPT trial likely explain the divergent findings. First, the median RVol/LAV ratio in our registry was substantially lower (0.40 vs. 0.67 in COAPT), which may indicate that our cohort included patients with larger left atrial relative to regurgitant volume. Secondly, we excluded atrial FMR, whereas the COAPT population included a broader spectrum of functional MR mechanisms. Thirdly, our cohort consisted exclusively of Japanese patients, and potential ethnic differences in atrial remodelling or treatment response may have influenced the results. Fourth, GDMT use was less intensive in our registry compared with the COAPT trial setting. Finally, study design differences are also critical: our registry included only patients undergoing M-TEER and is therefore susceptible to treatment-selection and collider bias, whereas randomization in COAPT substantially mitigated these issues. Taken together, these distinctions help explain why our findings diverged from those of the COAPT sub-analysis. When applying the COAPT-like profile definition[19] to our registry, we found that only one-third of patients fulfilled the criteria. In the sensitivity analysis, the COAPT-derived cutoff of 0.67 did not discriminate HFH risk, whereas in the overall cohort a lower cutoff of 0.40 consistently identified patients at higher risk, including those with a COAPT-like profile.

In clinical practice, a wide variety of patients are eligible for M-TEER; it is frequently performed not only in patients with COAPT-like profile, who are commonly referred to as responders but also in other patient groups. Our registry, which included a large number of M-TEER recipients with mitral regurgitation, reflects real-world clinical practice. Within this context, our finding of an association between low RVol/LAV and higher HFH risk may represent residual risk in VFMR patients after M-TEER. Such patients may warrant closer follow-up and comprehensive management strategies, including more intensive medical therapy and, when appropriate, advanced interventions such as LV assist device implantation or heart transplantation.

Nonetheless, the RVol/LAV ratio was not associated with cardiovascular mortality. This discrepancy between HFH and mortality outcomes may be explained by competing risks and the advanced disease stage of the study population. Patients with VFMR who underwent M-TEER were generally at high baseline risk, and competing

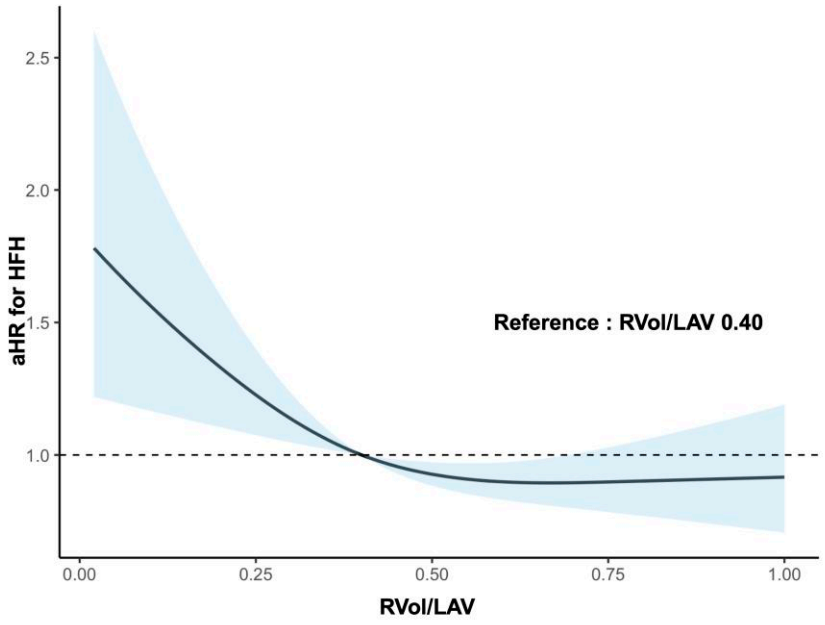


Figure 4 Adjusted hazard ratio of RVol/LAV ratio for HFH. Restricted cubic spline analysis showing the adjusted hazard ratio (aHR) for HFH according to RVol/LAV, with 0.40 set as the reference value. The solid line represents the estimated HR, and the shaded area indicates the 95% CI. The model was adjusted for age, sex, eGFR, LVEF, LVEDV, AF or AFL, BMI, TAPSE, ePASP, TR ≥2+, DM, and HT.

events—such as progressive ventricular dysfunction, arrhythmia, and non-cardiac comorbidities—may have attenuated the prognostic impact of MR-specific indices on CV mortality

Limitations

First, this was a retrospective observational study, and residual confounding may exist despite multivariable adjustment. Secondly, RVol was quantified using either the PISA method or a volumetric method according to each centre's routine practice. PISA provides rapid, jet-specific estimates, but in VFMR, it is vulnerable to non-hemispheric flow convergence, eccentric or multiple jets, and non-holosystolic regurgitation, which can lead to systematic under- or over-estimation. Conversely, the volumetric approach integrates regurgitation over the entire systole and may better reflect dynamic MR, yet it propagates error from pre-requisite measurements (LV volumes, left ventricular outflow tract (LVOT) area, and velocity–time integral (VTI)) and is affected by atrial fibrillation as well as concomitant aortic regurgitation or shunts. Many prior VFMR studies have primarily relied on PISA, despite its recognized limitations; however, neither technique can be considered definitive. In clinical practice, method selection is individualized by experienced echocardiographers; our registry reflects this real-world approach, which enhances generalizability but limits standardization. Consequently, mixed methodology and the absence of a core laboratory may have introduced non-differential measurement error and site-level heterogeneity, potentially attenuating observed associations. These factors should be considered when interpreting our results. Thirdly, our registry included only patients undergoing M-TEER and is therefore susceptible to treatment-selection and collider bias. Fourth, the cutoff value of 0.40 was data-derived and requires external validation, particularly given that a higher threshold of 0.67 has been reported by Coisne *et al.*[16] Finally, intervention decisions were made by each facility's heart team, and contemporary pharmacological therapy for secondary MR, including angiotensin receptor–neprilysin inhibitor (ARNI) and sodium–glucose cotransporter 2 inhibitors (SGLT2i), was underutilized due to the timing of patient enrolment.

Conclusion

A low RVol/LAV ratio at baseline was associated with a higher incidence of HFH in patients with VFMR who underwent M-TEER. Combining RVol and LAV might be more beneficial for risk stratification in patients with VFMR undergoing M-TEER.

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Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

The data that support the findings of this study are available within the article and its supplementary material.

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