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CLINICAL RESEARCH

Extracellular Volume in Primary Mitral Regurgitation

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ABSTRACT

OBJECTIVES This study used cardiovascular magnetic resonance (CMR) to evaluate whether elevated extracellular volume (ECV) was associated with mitral valve prolapse (MVP) or if elevated ECV was a consequence of remodeling independent of primary mitral regurgitation (MR) etiology.

BACKGROUND Replacement fibrosis in primary MR is more prevalent in MVP; however, data on ECV as a surrogate for diffuse interstitial fibrosis in primary MR are limited.

METHODS Patients with chronic primary MR underwent comprehensive CMR phenotyping and were stratified into an MVP cohort (>2 mm leaflet displacement on a 3-chamber cine CMR) and a non-MVP cohort. Factors associated with ECV and replacement fibrosis were assessed. The association of ECV and symptoms related to MR and clinical events (mitral surgery and cardiovascular death) was ascertained.

RESULTS A total of 424 patients with primary MR (229 with MVP and 195 non-MVP) were enrolled. Replacement fibrosis was more prevalent in the MVP cohort (34.1% vs. 6.7%; $p < 0.001$), with bi-leaflet MVP having the strongest association with replacement fibrosis (odds ratio: 10.5; $p < 0.001$). ECV increased with MR severity in a similar fashion for both MVP and non-MVP cohorts and was associated with MR severity but not MVP on multivariable analysis. Elevated ECV was independently associated with symptoms related to MR and clinical events.

CONCLUSIONS Although replacement fibrosis was more prevalent in MVP, diffuse interstitial fibrosis as inferred by ECV was associated with MR severity, regardless of primary MR etiology. ECV was independently associated with symptoms related to MR and clinical events. (DeBakey Cardiovascular Magnetic Resonance Study [DEBAKEY-CMR]; NCT04281823) (J Am Coll Cardiol Img 2020;■:■–■) © 2020 by the American College of Cardiology Foundation.

Primary mitral regurgitation (MR) is one of the most common valvular disorders. In patients with chronic primary MR, histopathologic studies indicate that myocardial fibrosis can develop with progressive stages of chronic volume overload (1–3). In a recent investigation of patients with primary MR that used cardiovascular magnetic resonance (CMR), we demonstrated that regional

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ABBREVIATIONS AND ACRONYMS

CMR = cardiovascular magnetic resonance

ECV = extracellular volume

EDV = end-diastolic volume

ESV = end-systolic volume

LGE = late gadolinium enhancement

LV = left ventricular

MOLLI = modified Look-Locker inversion recovery sequence

MR = mitral regurgitation

MVP = mitral valve prolapse

RV = right ventricular

myocardial fibrosis was more prevalent in mitral valve prolapse (MVP) compared with primary MR without MVP (4).

In addition to regional myocardial replacement fibrosis detectable with late gadolinium enhancement (LGE), CMR quantifies myocardial extracellular volume (ECV) by T1-mapping, based on the change in T1 times before and after administration of conventional extracellular gadolinium contrast (5). ECV has histological correlations with diffuse myocardial interstitial fibrosis in a number of medical conditions, including valvular heart disease (3,5). In addition, elevated ECV is associated with adverse cardiovascular outcomes in conditions such as aortic stenosis and heart failure (6,7).

Recent studies have suggested increased diffuse interstitial fibrosis in patients with primary MR; however, several knowledge gaps remain (2,8). Therefore, we designed our study, using ECV as a surrogate for diffuse interstitial fibrosis, to investigate if ECV in patients with primary MR is specifically associated with MVP, similar to replacement fibrosis, or if it is merely a manifestation of left ventricular (LV) remodeling from chronic volume overload, regardless of primary MR etiology. In addition, we examined the association of ECV and symptoms related to MR and clinical events.

METHODS

Consecutive patients who underwent contrast-enhanced CMR for assessment of chronic MR at the Houston Methodist Hospital (Houston, Texas) from January 2012 to June 2018 were enrolled into the DEBAKEY CMR Registry (DeBakey Cardiovascular Magnetic Resonance Study; NCT04281823), a prospective longitudinal registry designed to assess the usefulness of CMR in valvular heart disease. We excluded patients with any clinical history of the following confounding causes of myocardial fibrosis: 1) coronary artery disease; 2) cardiomyopathy; 3) infiltrative and/or inflammatory heart disease (e.g., amyloidosis, sarcoidosis, or myocarditis); 4) previous cardiac surgery; or 5) congenital heart disease. To avoid ambiguity regarding confounding etiologies of LV fibrosis, we excluded patients with the following CMR findings: 1) LV ejection fraction <50%; 2) coexisting valvular disease that was greater than mild in severity (except for tricuspid regurgitation that was secondary to MR; all primary tricuspid regurgitations related to structural leaflet abnormalities, such as endocarditis or carcinoid heart disease, were excluded); or 3) greater than mild concentric LV hypertrophy (LV wall thickness >1.3 cm and relative wall thickness >0.42). By their inherent nature, the preceding criteria also excluded patients with secondary MR, thus leaving only patients with primary MR in the study cohort. The patient enrollment process is summarized in **Figure 1**. The study was approved by the institutional review board at the Houston Methodist Research Institute, and patients gave written informed consent.

The primary MR study population was stratified further into MVP or non-MVP cohorts per criteria reported by Han et al. (9), which defined MVP as >2-mm displacement of any mitral valve scallops into the left atrium, as indicated on a 3-chamber view. The likely etiology of primary MR in the non-MVP cohort was deduced using all available medical history and diagnostic testing, including CMR findings.

CMR IMAGING PROTOCOL. CMR images were acquired using either 1.5- or 3.0-T clinical scanners (Siemens Avanto, Aera, or Verio; Siemens, Erlangen, Germany) with phased-array coil systems. Our CMR protocol was described in more detail in a previous publication (4). In brief, a standard examination consisted of a cine CMR for anatomic and functional assessment in a short-axis stack, as well as 2-, 3- and 4-chamber views using a steady-state, free-precession sequence. In addition, to evaluate the mechanism of MR, a high-resolution stack of small field-of-view cine CMR of the mitral valve was performed en-face, along with sequential 3-chamber views to cover all mitral scallops (10). Flow across the aortic valve was ascertained using phase-contrast imaging. Standard LGE-CMR identified replacement fibrosis using a magnitude and phase-sensitive segmented inversion-recovery sequence approximately 10 min after intravenous gadolinium contrast administration (gadopentetate dimeglumine or gadoterate meglumine, at a constant dose of 0.15 mmol/kg throughout the study). Short- and long-axis LGE images (2-, 3-, and 4-chamber) were acquired in identical orientations to the cine images. An electrocardiographically gated modified Look-Locker inversion recovery sequence (MOLLI) with motion correction was performed at a mid-LV short-axis level in a matching position for pre- and post-contrast administration (~15 to 20 min) (5). The pre-contrast MOLLI acquisition was performed using a 5(3)3 sampling scheme, and the post-contrast acquisition used a 4(1)3(1)2 sampling scheme.

CMR IMAGE ANALYSIS. The LV and right ventricular (RV) volumes were measured by planimetry of the endocardial borders on a stack of short-axis cine

images covering both ventricles from base to apex. Papillary muscles and trabeculae were excluded. LV end-diastolic volume (EDV), LV end-systolic volume (ESV), RVEDV, and RVESV were calculated by summation of these images. Mitral regurgitant volume was calculated as the difference between LV stroke volume and aortic forward stroke volume. The mitral regurgitant fraction was calculated as the ratio (percentage) of mitral regurgitant volume divided by LV stroke volume or mitral inflow stroke volume when aortic regurgitation was present (mitral inflow stroke volume = LV stroke volume-aortic regurgitant volume) (11). Volumetric assessment was performed by D.J.S., F.N., and E.Y.Y., and these results were kept separate and were not available during the LGE and ECV analyses.

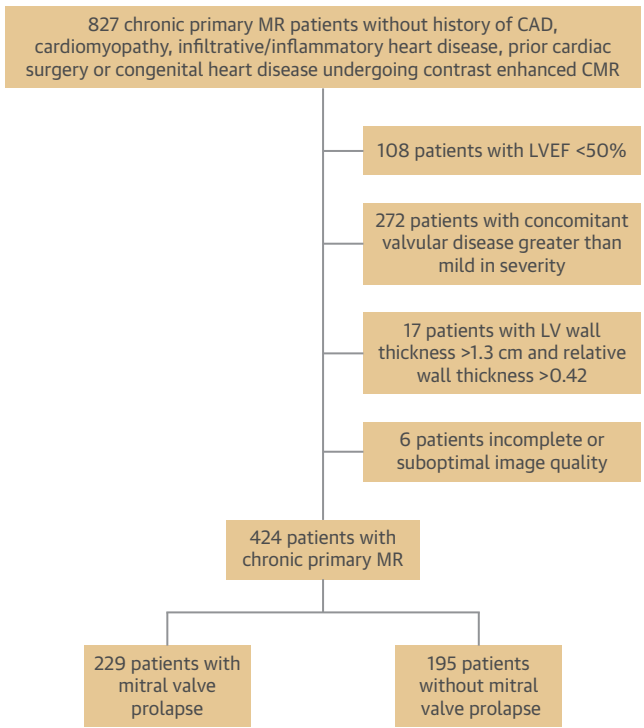
The presence and extent of replacement fibrosis, as demonstrated by LGE, was assessed in all LV segments according to the American College of Cardiology/American Heart Association 17-segment myocardial model by the consensus of 2 readers (D.K., D.J.S.) who were blinded to clinical history and imaging information. Replacement fibrosis was only considered present if it was identified on 2 contiguous or orthogonal slices and seen on both magnitude and phase-sensitive image reconstruction. A semi-quantitative method (Supplemental Appendix) was used to calculate the burden of replacement fibrosis as a percentage of the LV (4,12).

ECV analysis was performed separately from all volumetric quantitation by a single operator (D.K.) who was blinded to patient's clinical and imaging data at the time of analysis. Quantitative parametric images of myocardial T1 were generated with manual contouring to define a region of interest in the mid-LV septum at the same location for pre- and post-contrast. We excluded areas where LGE or artifacts were present in the septum; for this situation, the region of interest was placed in either the anteroseptum or inferoseptum where no LGE or artifact was evident. ECV was calculated using the following validated formula: ECV = [(ΔR1 myocardium)/(ΔR1 blood pool) × (1 - Hct)] (5). Hct refers to the hematocrit recorded on a venous blood sample obtained at the time of CMR and ΔR1 = 1/T1 post-contrast - 1/T1 pre-contrast.

SYMPTOMS AND CLINICAL EVENTS RELATED TO MR. Self-reported symptoms of dyspnea on exertion or declining exercise tolerance were obtained from patient interview at the CMR examination. To confirm the clinical significance of these self-reported symptoms, they were only considered related to MR if the patients were subsequently referred for mitral surgery due to their symptoms or experienced cardiovascular death within 90 days after CMR. In addition, patients were followed longitudinally for clinical events starting from the time of CMR imaging. The clinical events consisted of: 1) referral for mitral valve surgery; or 2) cardiovascular death (13). For this follow-up analysis, we excluded patients who underwent mitral valve surgery within 30 days after CMR to avoid the potential bias of a pre-designated CMR scan en-route to surgery (14). The decision for mitral valve surgery referral was made by treating physicians who were blinded to ECV data. The patients were censored from the analysis at the time of mitral valve surgery or death.

The outcome data collection started after all imaging analysis was completed and locked. Follow-up data were gathered from review of electronic medical records, structured telephone interviews with the patients, relatives, and/or their health care providers, and the Social Security Death Index database. The follow-up data were collected until January 2020. For ascertainment of clinical events, patient data were

FIGURE 1 Patient Selection Process



Patient selection process. CAD = coronary artery disease; CMR = cardiovascular magnetic resonance; LV = left ventricular; LVEF=left ventricular ejection fraction; MR = mitral regurgitation.

TABLE 1 Baseline Characteristics

	Total (N = 424)	Non-MVP (n = 195)	MVP (n = 229)	p Value
Clinical variables				
Age (yrs)	61.9 (51.7–70.7)	60.4 (47.1–69.8)	62.1 (52.7–72.1)	0.07
Male	204 (48.1)	74 (37.9)	130 (56.8)	**<0.001**
Body surface area (m^2)	1.9 (1.7–2.1)	1.9 (1.7–2.1)	1.9 (1.7–2.1)	0.99
History of heart failure	53 (12.5)	33 (16.9)	20 (8.7)	**0.01**
Diabetes	35 (8.3)	24 (12.3)	11 (4.8)	**0.01**
Hyperlipidemia	171 (40.3)	85 (43.6)	86 (37.6)	0.21
Hypertension	226 (53.3)	113 (57.9)	113 (49.3)	0.08
Current smoking	21 (5.0)	15 (7.7)	6 (2.6)	**0.02**
Systolic blood pressure (mm Hg)	131.5 ± 16.7	130.9 ± 16.4	132.0 ± 17.0	0.48
Diastolic blood pressure (mm Hg)	74.9 ± 11.4	75.0 ± 11.4	74.8 ± 11.5	0.88
Atrial fibrillation	45 (10.6)	17 (8.7)	28 (12.2)	0.24
CMR measures				
Left atrial volume index (ml/m^2)	61.3 (46.1–83.8)	51.0 (40.2–67.9)	73.3 (55.6–92.6)	**<0.001**
LV ejection fraction (%)	65.1 (60.1–71.0)	64.2 (60.0–72.0)	65.9 (60.3–71.0)	0.95
LV EDV index (ml/m^2)	86.6 (69.5–105.8)	76.8 (62.4–90.0)	95.5 (81.1–113.9)	**<0.001**
LV ESV index (ml/m^2)	29.9 (21.7–39.0)	26.8 (19.5–33.8)	33.0 (24.0–41.8)	**<0.001**
LV mass index (g/m^2)	63.3 (53.5–77.9)	60.0 (49.3–75.2)	66.7 (57.5–80.1)	**<0.001**
RV ejection fraction (%)	55.0 (50.0–60.3)	57.0 (51.4–61.8)	54.0 (49.0–59.0)	**<0.001**
RV EDV index (ml/m^2)	77.0 (63.3–93.9)	74.0 (59.4–87.7)	81.9 (68.3–98.4)	**<0.001**
RV ESV index (ml/m^2)	34.3 (26.5–45.1)	31.8 (23.9–40.3)	37.6 (28.8–47.6)	**<0.001**
Mitral regurgitant fraction (%)	30.0 (16.0–45.0)	18.0 (9.0–31.0)	41.0 (27.0–50.0)	**<0.001**
Mitral regurgitant volume (ml)	29.0 (13.0–53.5)	17.0 (8.0–28.0)	45.0 (28.0–65.0)	**<0.001**
Presence of LGE	91 (21.5)	13 (6.7)	78 (34.1)	**<0.001**
Extracellular volume (%)	26.4 ± 3.2	25.4 ± 3.0	27.2 ± 3.2	**<0.001**
Extracellular volume ≥30%	60 (14.2)	16 (8.2)	44 (19.2)	**0.001**
Other valvular regurgitation				
Mild aortic regurgitation	78 (18.4)	51 (26.2)	27 (11.8)	**<0.001**
Mild tricuspid regurgitation	148 (34.9)	67 (34.3)	81 (35.4)	0.908
Moderate tricuspid regurgitation	22 (5.2)	9 (4.6)	13 (5.7)	0.667
Severe tricuspid regurgitation	4 (0.9)	3 (1.5)	1 (0.4)	0.338

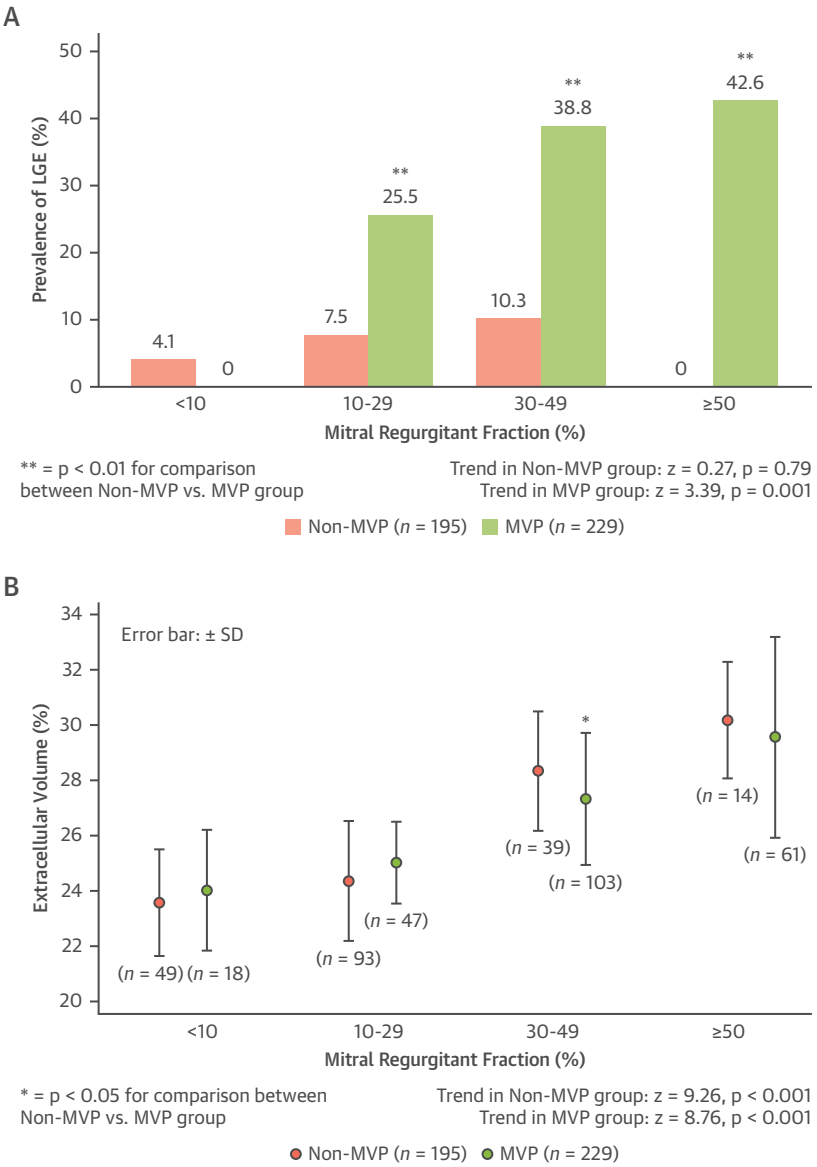
Values are n (%) for categorical variables, median (interquartile range) for continuous variables, or mean ± SD. **Bold** numbers indicate statistical significance.

CMR = cardiovascular magnetic resonance; EDV = end-diastolic volume; ESV = end-systolic volume; LGE = late gadolinium enhancement; LV = left ventricular; MVP = mitral valve prolapse; RV = right ventricular.

presented to an adjudication committee consisting of 2 board-certified cardiologists blinded to imaging data.

STATISTICAL ANALYSIS. Statistical analysis was performed by D.T.N. and E.A.G., who were not involved in the data collection process and were blinded to patient identifiers. Patient characteristics were reported as frequencies and proportions for categorical variables and as median and interquartile range or mean ± SD for continuous variables, when appropriate. Differences across groups were determined by chi-square or Fisher exact tests for categorical variables and the Kruskal-Wallis test or the unpaired Student's *t*-test for continuous variables as appropriate. ECV ≥30% was considered elevated based on our previous data in normal volunteers, which confirmed this was optimal by receiver-operating characteristic curve analysis (7,15). The univariable and multiple logistic regression analyses identified characteristics associated with replacement fibrosis. Simple and multiple linear regression analyses determined characteristics associated with ECV. Event-free survival for the composite events were depicted by Kaplan-Meier curves. Differences between MR severity and ECV subgroups were compared by the log-rank test. Cox regression modeling was conducted to determine the characteristics associated with having higher risk of composite events. Variable selection for the multiple logistic regression and multivariable Cox proportional hazard regression was conducted based on established clinically important variables and also using Stata's Lasso technique with the cross-validation selection option (16). Briefly, all variables used in the univariable analysis were assessed by the Lasso program, which suggested good models that included the

FIGURE 2 **Prevalence of Replacement Fibrosis and Mean Extracellular Volume in Patients With Primary Mitral Regurgitation**



Prevalence of replacement fibrosis as evidenced by **(A)** late gadolinium enhancement (LGE) and **(B)** mean extracellular volume (ECV) in patients with mitral valve prolapse (MVP) and non-MVP. Prevalence of replacement fibrosis in MVP was higher than non-MVP and increased with MR severity. ECV increased with severity of MR in relatively similar manner for MVP and non-MVP cohorts. MR = mitral regurgitation.

variables with the highest probability of being a risk factor. The likelihood ratio test further reduced model subsets. During the modeling process, the potential risk factors were discussed with senior clinicians with extensive clinical experience in the field to ensure the biologic plausibility of the selected covariates. To avoid over fitting, some variables that were significant in the univariate analysis but insignificant in multivariable modeling were not selected in the final model if their exclusion did not affect the diagnostic performance of the final model. The discrimination power of predictive models was assessed using the C-statistic. The good calibration of the model was determined by a nonsignificant Hosmer-Lemeshow's

TABLE 2 Clinical and CMR Characteristics Associated With Replacement Fibrosis

	Unadjusted		Adjusted	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Clinical variables				
Age (yrs)	1.02 (1.00–1.04)	**0.02**	–	–
Male	1.78 (1.11–2.85)	**0.02**	–	–
Body surface area (m^2)	1.36 (0.52–3.59)	0.53	–	–
History of heart failure	0.62 (0.28–1.36)	0.23	–	–
Diabetes	1.09 (0.48–2.49)	0.83	–	–
Hyperlipidemia	1.14 (0.71–1.83)	0.58	–	–
Hypertension	0.97 (0.61–1.55)	0.91	–	–
Current smoking	0.60 (0.17–2.07)	0.42	–	–
Systolic blood pressure (mm Hg)	1.01 (1.00–1.03)	**0.049**	–	–
Diastolic blood pressure (mm Hg)	0.99 (0.97–1.01)	0.52	–	–
Atrial fibrillation	1.99 (1.02–3.89)	**0.04**	–	–
CMR measures				
Left atrial volume index (ml/m^2)	1.01 (1.00–1.01)	0.06	–	–
LV ejection fraction (%)	0.96 (0.93–0.99)	**0.01**	0.85 (0.76–0.96)	**0.01**
LV EDV index (ml/m^2)	1.02 (1.01–1.02)	**<0.001**	–	–
LV ESV index (ml/m^2)	1.03 (1.01–1.05)	**<0.001**	–	–
LV mass index (g/m^2)	1.03 (1.02–1.04)	**<0.001**	1.03 (1.01–1.05)	**0.001**
RV ejection fraction (%)	0.97 (0.94–1.00)	**0.02**	–	–
RV EDV index (ml/m^2)	1.01 (1.00–1.02)	0.08	–	–
RV ESV index (ml/m^2)	1.02 (1.00–1.03)	**0.03**	–	–
Mitral regurgitant fraction (10% increment)	1.46 (1.26–1.68)	**<0.001**	–	–
Mitral regurgitant volume (ml)	1.02 (1.01–1.03)	**<0.001**	–	–
MVP	7.23 (3.87–13.52)	**<0.001**	–	…
Type of MVP				
Single-leaflet	6.42 (3.34–12.36)	**<0.001**	5.14 (2.42–10.90)	**<0.001**
Bi-leaflet	9.33 (4.46–19.53)	**<0.001**	10.51 (4.63–23.86)	**<0.001**
Extracellular volume fraction (%)	1.16 (1.08–1.25)	**<0.001**	–	–
Extracellular volume fraction ≥30%	1.88 (1.03–3.43)	**0.04**	–	–

C-statistic = 0.81 for multivariable model. Variables included in the multivariable model are age, systolic blood pressure, LV ejection fraction, LV EDV index, LV ESV index, LV mass index, mitral regurgitant fraction, MVP, and extracellular volume fraction. **Bold** numbers indicate statistical significance.

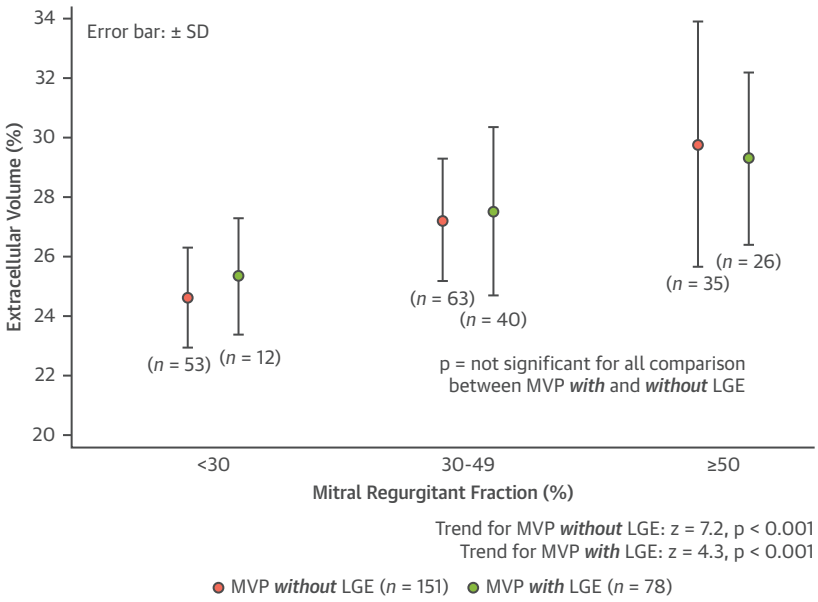
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

goodness-of-fit test. The best final model was selected based on the smallest Bayesian information criterion and largest C-statistic. All analyses were performed on Stata version 16.1 (StataCorp LLC, College Station, Texas). A p value of <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. Following the clinical history screening process, a total of 827 patients with chronic primary MR were enrolled. During the recruitment period, there were 681 patients who underwent mitral surgery at our institution. After excluding patients with imaging findings that could represent secondary MR or confounding etiologies for LV fibrosis, 424 patients remained and were included in the primary MR study cohort (Figure 1). The data on prevalence of replacement fibrosis from the first 181 patients in this present study and a pilot study in the asymptomatic MR subgroup (144 patients) was reported previously (4,15). The studies were performed with 1.5- and 3-T scanners in 148 (35%) patients and 276 (65%) patients, respectively. Baseline characteristics are summarized in Table 1. Of these patients, 48.1% were men with a median age of 61.9 years (interquartile range: 51.7 to 70.7 years). MVP was found in 229 (54.0%) patients, with posterior mitral leaflet prolapse being the most common condition (133 patients [31.4%]). Mild aortic regurgitation was found in 78 (18.4%) patients with a mean regurgitant volume of 9.0 ± 7.5 ml. The etiologies of MR in the non-MVP cohort included mitral calcification and/or thickening that resulted in restriction or malcoaption of leaflets (92 patients [21.7%]), rheumatic MR (15 patients [3.5%]), previous infective endocarditis (7

FIGURE 3 **Mean ECV in MVP**



Mean ECV in patients with MVP with and without replacement fibrosis as evidenced by LGE. ECV was similar among patients with MVP with or without LGE and increased with MR severity. Abbreviations as in Figures 1 and 2.

patients [1.7%]), suspected radiation-related or connective tissue disease (3 patients [0.7%]), and was indeterminate in 78 patients (18.4%).

Clinical characteristics and CMR findings of both cohorts are shown in Table 1. Diabetes and history of heart failure were more frequent in the non-MVP cohort. Patients with MVP had more severe MR and larger left atrial, LV, and RV volumes, and greater LV mass. LV ejection fraction was not different between the 2 cohorts.

REGIONAL REPLACEMENT FIBROSIS IN PRIMARY MR. Replacement fibrosis as evidenced by LGE was found in 91 (21.5%) patients and was more common in patients with MVP (34.1% vs. 6.7%; $p < 0.001$). The most common LGE pattern was mid-wall striae (46 patients [50.5]), followed by a patchy pattern (42 patients [46.2%]) and a subendocardial pattern (3 patients [3.3%]). The average replacement fibrosis burden was 1.9 ± 0.9% of the LV. In the MVP cohort, the most common location for replacement fibrosis was in the basal inferolateral wall (61 patients [26.6%]), followed by the basal inferior wall (15 patients [6.6%]), whereas the basal septum (9 patients [4.6%]) was the most common location in the non-MVP cohort.

The prevalence of replacement fibrosis increased with MR severity in the MVP cohort, whereas it was low and unrelated to MR severity in the non-MVP cohort (Figure 2A). On multivariable analysis, LV ejection fraction, LV mass index, and presence of MVP were associated with replacement fibrosis, with the highest odds ratio observed in bi-leaflet prolapse (Table 2). ECV was associated with replacement fibrosis on univariable analysis, but this relationship did not remain on multivariable modeling.

ECV IN PRIMARY MR. Intra- and interobserver variabilities for ECV measurement were tested in 50 studies and were performed at least 6 months after the initial analysis. These studies demonstrated excellent intra- and interobserver variability with intraclass correlation coefficients of 0.94 (95% confidence interval: 0.89 to 0.97) and 0.91 (95% confidence interval: 0.88 to 0.93), respectively. ECV in patients with primary MR with and without MVP increased with MR severity, regardless of MR etiologies (Figure 2B). Unlike replacement fibrosis, which was more prevalent in MVP, ECV was not significantly higher in patients with MVP (Figure 2B). Further stratification of patients with MVP based on the presence of LGE showed a similar trend, with relatively similar ECV among patients with MVP with or without LGE (Figure 3). On multivariable analysis, increasing age, female sex, lower systolic blood pressure, and increasing MR severity were

TABLE 3 Clinical and CMR Characteristics Associated With ECV

	Unadjusted		Adjusted	
	β Coef. (95% CI)	p Value	β Coef. (95% CI)	p Value
Clinical variables				
Age (yrs)	0.04 (0.02 to 0.06)	**<0.001**	0.03 (0.01 to 0.04)	**0.001**
Male	−0.67 (−1.28 to −0.05)	**0.03**	−0.90 (−1.37 to −0.44)	**<0.001**
Body surface area (m^2)	−1.36 (−2.64 to −0.07)	**0.04**	–	–
History of heart failure	1.76 (0.84 to 2.67)	**<0.001**	–	–
Diabetes	0.98 (−0.13 to 2.10)	0.08	–	–
Hyperlipidemia	0.03 (−0.60 to 0.66)	0.93	–	–
Hypertension	0.15 (−0.47 to 0.77)	0.64	–	–
Current smoking	0.10 (−1.32 to 1.52)	0.89	–	–
Systolic blood pressure (mm Hg)	−0.03 (−0.04 to −0.01)	**0.010**	−0.04 (−0.05 to −0.02)	**<0.001**
Diastolic blood pressure (mm Hg)	−0.02 (−0.04 to 0.01)	0.24	–	–
Atrial fibrillation	1.97 (0.99 to 2.96)	**<0.001**	–	–
CMR measures				
Left atrial volume index (ml/m^2)	0.03 (0.02 to 0.04)	**<0.001**	–	–
LV ejection fraction (%)	0.00 (−0.04 to 0.03)	0.83	–	–
LV EDV index (ml/m^2)	0.04 (0.03 to 0.05)	**<0.001**	–	–
LV ESV index (ml/m^2)	0.06 (0.04 to 0.08)	**<0.001**	–	–
LV mass index (g/m^2)	0.05 (0.03 to 0.06)	**<0.001**	–	–
RV ejection fraction (%)	−0.10 (−0.13 to −0.06)	**<0.001**	–	–
RV EDV index (ml/m^2)	0.02 (0.00 to 0.03)	**0.01**	–	–
RV ESV index (ml/m^2)	0.04 (0.03 to 0.06)	**<0.001**	–	–
Mitral regurgitant fraction (10% increment)	1.26 (1.14 to 1.39)	**<0.001**	1.19 (1.03 to 1.35)	**<0.001**
Mitral regurgitant volume (ml)	0.07 (0.06 to 0.07)	**<0.001**		
MVP	1.82 (1.22 to 2.41)	**<0.001**	–	–
Type of MVP				
Single-leaflet	1.91 (1.25 to 2.56)	**<0.001**	–	–
Bi-leaflet	1.62 (0.77 to 2.48)	**<0.001**	–	–
Presence of LGE	1.62 (0.88 to 2.35)	**<0.001**	–	–
Intercept	–	–	25.56 (23.63 to 27.49)	**<0.001**

F statistic = 49.98; $p < 0.001$; adjusted $R^2 = 0.54$ for multivariable model. Variables included in multivariable model are age, male sex, history of heart failure, systolic blood pressure, LV EDV index, LV mass index, mitral regurgitant fraction, MVP and presence of LGE. **Bold** numbers indicate statistical significance.

ECV = extracellular volume; other abbreviations as in Tables 1 and 2.

associated with increased ECV (Table 3), with the strongest correlation observed between severity of MR and ECV. MVP (either single- or bi-leaflet prolapse) and presence of replacement fibrosis were not independently associated with ECV on multivariable modeling.

SYMPTOMS AND CLINICAL EVENTS RELATED TO MR. The criteria for symptomatic MR were met in 89 patients. Of these, 88 were referred for mitral surgery and 1 experienced cardiovascular death within 90 days of CMR. The median time to mitral surgery was 21 days (interquartile range: 7 to 38 days). The average mitral regurgitant fraction in the symptomatic MR group was 51 ± 8.8%, and none of the patients with a mitral regurgitant fraction <30% was classified as having symptomatic MR. The mean ECV was higher in the symptomatic MR group (29.6 ± 2.9% vs. 25.5 ± 2.7%; $p < 0.001$) but with an overlapping range (Supplemental Figure 1). On multivariable analysis (Table 4), severity of MR, atrial fibrillation, LVEDV index, and ECV were independently associated with MR-related symptoms.

During the follow-up period (median follow-up: 2.6 years [interquartile range; 0.5 to 4.6 years]), 95 (22.4%) patients had clinical events. Of these, 82 underwent mitral repairs, 5 underwent mitral replacement, 3 were referred for surgery but declined, and 5 experienced cardiovascular death. The median time to clinical events was 5.6 months (interquartile range: 2.1 to 18.2 months). Male sex, severity of mitral regurgitation, and ECV were found to be associated with clinical events on multivariable analysis (Table 5). Kaplan-Meier curves for survival free of clinical events, stratified by severity of MR and ECV ≥30% as a threshold, are demonstrated in Figure 4. In patients with moderate or severe MR,

TABLE 4 Characteristics Associated With Symptoms Related to Mitral Regurgitation

	Unadjusted		Adjusted	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Clinical variables				
Age (yrs)	1.02 (1.00–1.03)	0.06	–	–
Male	1.20 (0.75–1.91)	0.45	–	–
Body surface area (m^2)	0.70 (0.26–1.89)	0.48	–	–
History of heart failure	1.26 (0.64–2.48)	0.50	–	–
Diabetes	0.76 (0.31–1.90)	0.56	–	–
Hyperlipidemia	0.89 (0.55–1.44)	0.65	–	–
Hypertension	0.87 (0.55–1.39)	0.56	–	–
Current smoking	0.61 (0.18–2.13)	0.44	–	–
Systolic blood pressure (mm Hg)	1.00 (0.98–1.01)	0.60	–	–
Diastolic blood pressure (mm Hg)	1.00 (0.98–1.02)	0.97	–	–
Atrial fibrillation	4.00 (2.11–7.60)	**<0.001**	4.21 (1.51–11.73)	**0.01**
CMR measures				
Left atrial volume index (per 20 ml/m^2)	2.07 (1.74–2.47)	**<0.001**	–	–
LV ejection fraction (%)	0.98 (0.95–1.00)	**0.10**	–	–
LV EDV index (per 20 ml/m^2)	2.24 (1.81–2.78)	**<0.001**	1.54 (1.03–2.29)	**0.04**
LV ESV index (per 20 ml/m^2)	3.42 (2.33–5.01)	**<0.001**	–	–
LV mass index (per 20 g/m^2)	1.94 (1.52–2.48)	**<0.001**	–	–
RV ejection fraction (%)	0.92 (0.89–0.94)	**<0.001**	–	–
RV EDV index (per 20 ml/m^2)	1.42 (1.17–1.72)	**<0.001**	–	–
RV ESV index (per 20 ml/m^2)	2.10 (1.56–2.82)	**<0.001**	–	–
Mitral regurgitant fraction (per 10% increment)	4.47 (3.21–6.24)	**<0.001**	3.53 (2.28–5.44)	**<0.001**
MVP	4.42 (2.52–7.74)	**<0.001**	–	–
Presence of LGE	2.45 (1.46–4.11)	**0.001**	–	–
ECV fraction (per 5% increment)	10.11 (6.01–17.02)	**<0.001**	2.17 (1.15–4.10)	**0.02**

Area under the curve = 0.93. Variables included in multivariable model are age, atrial fibrillation, left atrial volume index, LV EDV index, LV mass index, RV EDV index, mitral regurgitant fraction, presence of LGE, and ECV fraction. **Bold** numbers indicate statistical significance.

Abbreviations as in Tables 1 to 3.

those with elevated ECV demonstrated lower event-free survival.

DISCUSSION

REPLACEMENT FIBROSIS IN PRIMARY MR. The results of this study further support an association between regional replacement fibrosis and MVP. Despite adjustment for other factors, MVP, particularly bi-leaflet MVP, is the strongest covariate associated with replacement fibrosis. The most common location for replacement fibrosis is in segments adjacent to the posteromedial papillary muscle. Our data complemented previous CMR and autopsy studies that demonstrated a predilection for replacement fibrosis in this region (4,17). The regional pathophysiologies in MVP beyond volume overload–mediated LV remodeling, such as mechanical papillary muscle traction, mitral annular disjunction, and systolic curling, are likely responsible for the replacement fibrosis in this region (18,19).

ECV IN PRIMARY MR. Our data demonstrated that ECV was associated with severity of MR but not MVP or replacement fibrosis. With greater MR severity, patients with primary MR had increasing ECV, regardless of MR etiology. In the absence of an inflammatory or infiltrative process, as in our study population, an elevated ECV suggested an increase in the myocardial interstitial compartment, which was most likely due to diffuse interstitial fibrosis deposition. Bui et al. (8) reported a possible association between MVP and increased diffuse interstitial fibrosis. In their study, patients with MVP (most with 2+ MR) had a shorter post-contrast T1 time compared with a normal healthy control group without MR, which could imply a higher level of diffuse interstitial fibrosis in patients with MVP (8). However, that study did not include patients with primary MR without MVP as a control group, and therefore, the possibility that T1-time changes were a result of remodeling from MR could not be excluded (8). In our study, after adjusting for other covariates (especially MR severity), MVP was no longer a factor that was associated with elevated ECV. Chronic LV volume overload, a common consequence in all patients with MR, regardless of their MR etiology, was likely a more

TABLE 5 Characteristics Associated With Mitral Valve Surgery and Cardiovascular Death

	Unadjusted		Adjusted Model 1		Adjusted Model 2	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Clinical variables						
Age (yrs)	1.02 (1.00–1.03)	**0.02**	–	–	–	–
Male	1.93 (1.27–2.92)	**0.002**	2.30 (1.45–3.65)	**<0.001**	2.08 (1.31–3.29)	**0.002**
Body surface area (m^2)	2.73 (1.19–6.25)	**0.02**	–	–	–	–
History of heart failure	1.48 (0.86–2.54)	0.15	–	–	–	–
Diabetes	1.10 (0.55–2.20)	0.78	–	–	–	–
Hyperlipidemia	0.93 (0.62–1.40)	0.72	–	–	–	–
Hypertension	1.25 (0.83–1.88)	0.29	–	–	–	–
Current smoking	0.54 (0.17–1.69)	0.29	–	–	–	–
Systolic blood pressure (mm Hg)	1.01 (1.00–1.02)	**0.04**	–	–	–	–
Diastolic blood pressure (mm Hg)	1.01 (0.99–1.03)	0.29	–	–	–	–
Atrial fibrillation	1.62 (0.86–3.04)	0.13	–	–	–	–
CMR measures						
Left atrial volume index (per 20 ml/m^2)	1.11 (1.07–1.14)	**<0.001**	–	–	–	–
LV ejection fraction (%)	0.99 (0.97–1.02)	0.47	–	–	–	–
LV EDV index (per 20 ml/m^2)	1.98 (1.69–2.32)	**<0.001**	–	–	–	–
LV ESV index (per 20 ml/m^2)	2.55 (1.88–3.45)	**<0.001**	–	–	–	–
LV mass index (per 20 g/m^2)	1.75 (1.44–2.12)	**<0.001**	–	–	–	–
RV ejection fraction (%)	0.94 (0.92–0.97)	**<0.001**	–	–	–	–
RV EDV index (per 20 ml/m^2)	1.21 (1.03–1.42)	**0.02**	–	–	–	–
RV ESV index (per 20 ml/m^2)	1.56 (1.25–1.95)	**<0.001**	–	–	–	–
Mitral regurgitant fraction (per 10% increment)	2.70 (2.29–3.18)	**<0.001**	2.34 (1.88–2.91)	**<0.001**	2.54 (2.07–3.11)	**<0.001**
MVP	4.85 (2.93–8.02)	**<0.001**	–	–	–	–
Presence of LGE	2.02 (1.30–3.12)	**0.002**	–	–	–	–
ECV fraction (per 5% increment)	4.56 (3.40–6.10)	**<0.001**	1.90 (1.24–2.91)	**0.003**	–	–
ECV fraction ≥30%	6.71 (4.21–10.69)	**<0.001**	–	–	1.85 (1.06–3.24)	**0.03**

C-statistic = 0.88 for both adjusted models. Variables included in multivariable model 1 are age, male sex, systolic blood pressure, LV EDV index, LV mass index, mitral regurgitant fraction, presence of LGE, and ECV fraction (per 5%). For model 2, similar variables were included but ECV fraction (per 5% increment) was replaced with ECV ≥30% **Bold** numbers indicate statistical significance.

HR = hazard ratio; other abbreviations as in Tables 1 to 3.

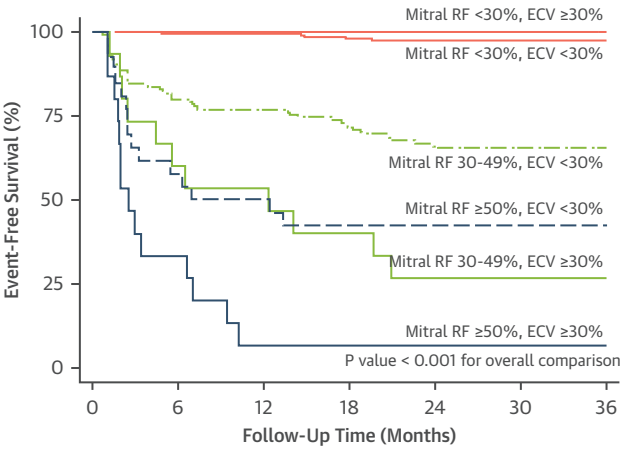
dominant pathophysiologic mechanism responsible for the development of diffuse interstitial fibrosis in patients with primary MR. The association of lower systolic blood pressure with elevated ECV was likely explained by the relationship between ECV and severity of MR. As the severity of MR increases, a significantly reduced aortic forward flow may result in lower systolic blood pressure. Similar findings of lower blood pressure in a more severe MR cohort was also found in a previous CMR study in patients with primary MR by Myerson et al. (14).

The level of LV remodeling and diffuse interstitial fibrosis development as a response to volume overload is variable among individuals with primary MR as seen by an overlapping ECV range among groups in our study. Some patients manifested increased diffuse interstitial fibrosis, as inferred by elevated ECV, at moderate degrees of MR, whereas others had normal levels of diffuse interstitial fibrosis despite severe MR. Comorbidities such as hypertension or diabetes were associated with diffuse interstitial fibrosis in previous studies and might contribute to increased diffuse interstitial fibrosis burden, independent of MR (5). In part, the difference in degree of diffuse interstitial fibrosis could explain the variation of symptom development in patients with MR, despite having similar MR severity.

We did not find an association of ECV and LV volumes, which are traditional parameters related to MR severity, on multivariable analysis. As interstitial fibrosis develops, it could be that the LV becomes stiff and less compliant. This might attenuate the adaptive reserve of the LV that maintains forward stroke volume by increasing LV size. The inverse relation between ECV expansion, a surrogate for diffuse interstitial fibrosis, and LV size was also observed in the CMR study from the MESA (Multi-Ethnic Study of Atherosclerosis) study (20).

POTENTIAL CLINICAL APPLICATION. Previous data suggested a link between replacement fibrosis and ventricular arrhythmia in patients with MVP (4,17–19). Bi-leaflet prolapse was considered a high-risk

FIGURE 4 **Kaplan-Meier Curves for Survival Free of Clinical Events**



Number at Risk							
Mitral RF <30%, ECV <30%	205	201	199	194	168	149	132
Mitral RF <30%, ECV ≥30%	2	2	2	2	2	2	2
Mitral RF 30-49%, ECV <30%	122	82	77	71	61	57	49
Mitral RF 30-49%, ECV ≥30%	20	9	8	6	4	3	3
Mitral RF ≥50%, ECV <30%	37	15	13	11	10	9	6
Mitral RF ≥50%, ECV ≥30%	38	5	1	1	1	1	1

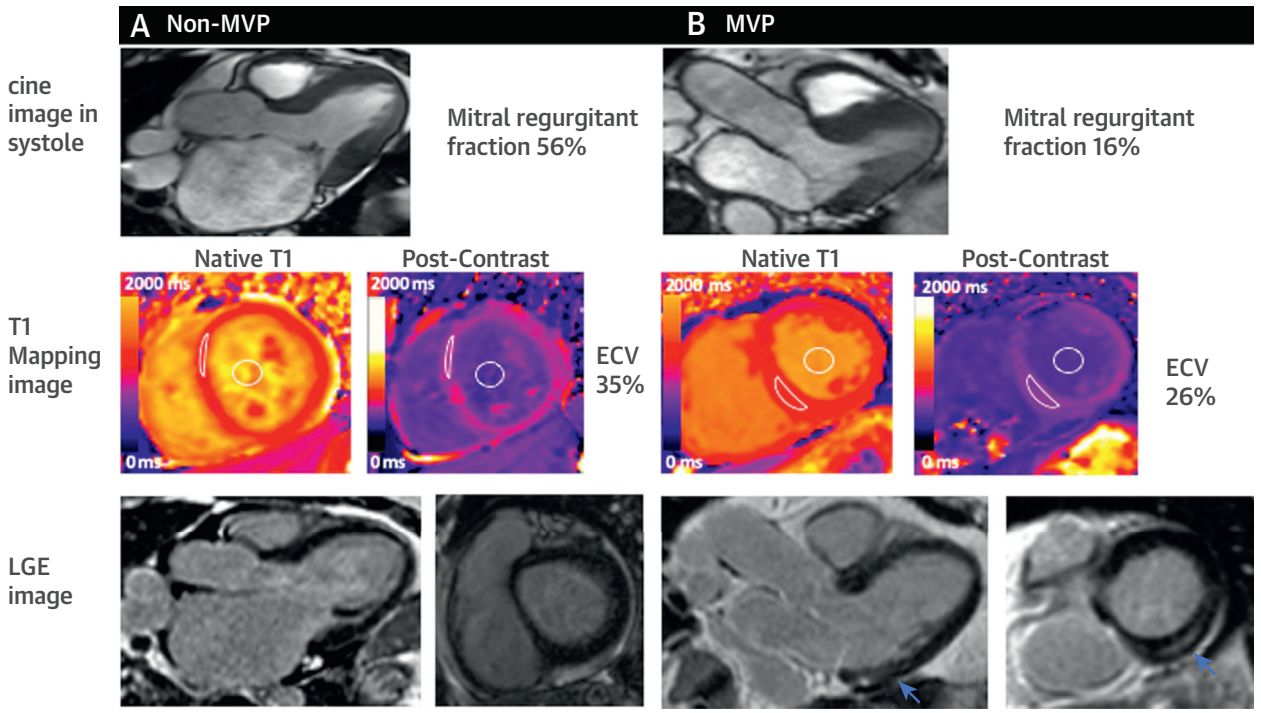
Kaplan-Meier curves for survival free of clinical events (mitral surgery and cardiovascular death), stratified by the mitral regurgitant fraction (RF) and elevated ECV. In patients with moderate or severe MR, those with elevated ECV (≥30%) demonstrated lower event-free survival. Other abbreviations as in **Figures 1 and 2**.

feature for development of malignant arrhythmia in patients with MVP (19). Our data demonstrated the strongest association of replacement fibrosis in patients with bi-leaflet prolapse and further supported the concept of local myocardial injury due to unique pathophysiologies in MVP. This process typically results in a small fibrotic burden in segments adjacent to the posteromedial papillary muscle that could be a substrate for malignant arrhythmia and sudden cardiac death (4, 17–19). Future studies should evaluate replacement fibrosis and arrhythmic risk stratification in patients with MVP.

Our data demonstrated an association of ECV and MR severity, regardless of primary MR etiology. ECV was associated with symptoms related to MR, and clinical events included mitral surgery and cardiovascular death. Diffuse interstitial fibrosis, as inferred by ECV, likely represents a global "end-product" of LV remodeling from MR and other concomitant LV insults that might be more closely associated with symptoms and clinical events related to MR (**Figure 5 and Central Illustration**). The degree of diffuse fibrosis in the LV might modulate how patients tolerate MR, and this could potentially contribute to earlier occurrence of MR symptoms. In our study, symptomatic patients with MR had higher ECV at comparable levels of MR severity than asymptomatic patients (Supplemental Figure 1). To complement our data, Edwards et al. (2) demonstrated reductions in exercise time and peak oxygen consumption during follow-up in patients with chronic, asymptomatic moderate, or severe degenerative MR with increased diffuse interstitial fibrosis.

Symptoms related to MR are considered a definitive indication for mitral surgery. However, once they have occurred, the prognosis of patients becomes less favorable because operative mortality is higher and post-operative survival is lower, even with normal LV size and systolic function (21). Imaging biomarkers that can detect subclinical changes before symptoms or development of LV systolic dysfunction and/or dilatation may have an essential role in the management of patient with MR. In a previous CMR study in asymptomatic patients with primary MR by Myerson et al. (14), incorporating LVEDV in addition to regurgitant volume did not provide incremental separation of the event-free survival analysis curves beyond regurgitant volume alone. In our study, an elevated ECV (≥30%) could potentially serve as an imaging biomarker that identified patients who were likely to

FIGURE 5 Example of Cine, T1-Mapping, and LGE Images of Patients in the Study

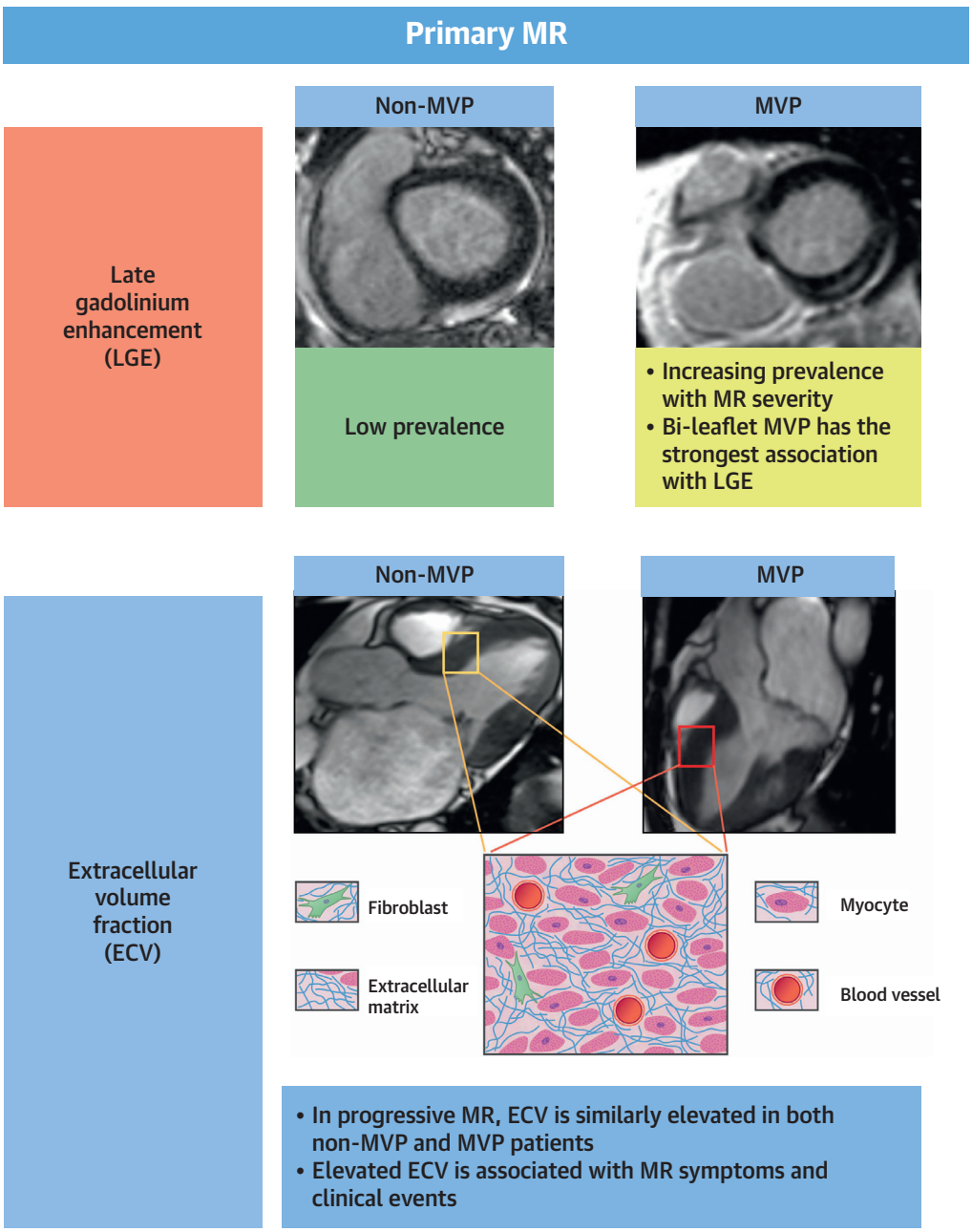


(A) A patient with non-MVP is a 43-year-old women with severe MR from rheumatic mitral disease who had dyspnea on exertion. ECV is elevated at 35%, whereas no LGE was detected. **(B)** Patient with MVP is a 72-year-old man with mild posterior MVP, mild MR, and symptomatic premature ventricular complexes. ECV was 26% but a small LGE was identified in the basal inferolateral wall **(arrows)**. Abbreviations as in Figures 1 and 2.

develop future indications for mitral surgery. Our pilot subgroup analysis in the asymptomatic MR cohort also demonstrated similar results (15). Future randomized multicenter studies with a larger study population will be required to confirm our findings and to evaluate potential benefits and clinical usefulness of ECV in patients with primary MR, particularly for risk stratification and selection of patients for mitral surgery.

STUDY LIMITATIONS. Despite a stringent study design, the patients enrolled in our study did not routinely undergo specific testing to rule out other possible causes of myocardial fibrosis (i.e., coronary angiography). However, clinical history and available testing results were thoroughly evaluated to minimize confounders. Although reported in previous publications, our study was not specifically designed to evaluate papillary muscle LGE (9). In our experience, the routine standard LGE technique might be suboptimal for assessment of papillary LGE due to the high signal intensity of the blood cavity adjacent to the papillary muscle that interferes with identification of small papillary muscle LGE. In a study by Han et al. (9), only 50% of patients who had papillary muscle LGE, identified by high-resolution, 3-dimensional LGE, were detected by standard LGE-CMR. For optimal identification, we believe high-resolution, dark-blood LGE-CMR is required, and this technique was not available at the time of this study. Magnetic field strength is known to affect myocardial T1 time; however, ECV measurements that require both pre-and post-contrast T1 time for calculations, are similar at 1.5 and 3 T and was chosen over native or post-contrast T1 time for our study (5). Although measuring ECV in the mid-septum is a recommended approach for global LV assessment, the regional variation in LV architecture, particularly in patients with MVP, may yield different ECV values if quantified from the entire LV, certainly if including segments with LGE (5). We made every effort to minimize the bias of LGE and ECV assessment by blinding the observers to clinical history, outcomes, and volumetric data. However, it remains a possibility that certain inherent features evident on the CMR images might have resulted in a nonpreventable bias of the observers. The region of interest for

CENTRAL ILLUSTRATION **Late Gadolinium Enhancement and Extracellular Volume in Primary Mitral Regurgitation**



Kitkungvan, D. et al. J Am Coll Cardiol Img. 2020;■(■):■–■.

Replacement fibrosis as demonstrated by late gadolinium enhancement (LGE) is more prevalent in patients with mitral valve prolapse (MVP) and increases with mitral regurgitation (MR) severity, with the strongest association seen in bi-leaflet MVP. Replacement fibrosis is uncommon in patients with non-MVP, regardless of severity of MR. Diffuse interstitial fibrosis as inferred by extracellular volume (ECV) increases with MR severity in a similar fashion for both patients with MVP and non-MVP. Elevated ECV is independently associated with MR-related symptoms and clinical events (mitral surgery and cardiovascular death).

T1-mapping was manually contoured to avoid artifacts and LGE that might have resulted in variation; however, this is unlikely to have significant impact on our ECV measurement because only small number of patients had LGE in the septum. Despite using a flow loop for a periodic quality control of flow measurement at our institution, the accuracy of flow measurements with different scanners and magnetic field strengths might still vary. However, our internal validation process for MR severity quantitation using multiple data points, including aortic flow, pulmonary flow, and LV and RV stroke volume as secondary cross-checks, should effectively reduce this variation. Valvular patients are frequently referred to CMR as a second-line test, and, as such, a referral bias might have affected the prevalence of disease, comorbidities, and rate of adverse clinical events in the patients in this study. We realized that symptoms related to MR reporting by the patients were subjective; objective measurement of symptoms such as exercise stress testing was not performed in our study. However, the addition of other criteria, including surgical referral, should minimize this limitation and allow us to include patients with clinically relevant MR-related symptoms for further analysis. Furthermore, the fact that the treating physicians were blinded to ECV data helped mitigate post-test referral bias.

CONCLUSIONS

Although replacement fibrosis is more prevalent in MVP, with the strongest association with bi-leaflet MVP, increased diffuse interstitial fibrosis as inferred by ECV was associated with severity of primary MR, independent of MR etiologies. Elevated ECV was independently associated with symptoms related to MR and clinical events.

AUTHOR DISCLOSURES

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Although replacement fibrosis is prevalent in MVP, with the strongest association in bi-leaflet MVP, diffuse interstitial fibrosis as inferred by increased ECV is associated with MR severity, regardless of primary MR etiology. Elevated ECV is associated with symptoms related to MR and clinical events.

TRANSLATIONAL OUTLOOK: Future studies are needed to evaluate and to confirm the clinical significance of replacement fibrosis and ECV expansion in primary MR and their role in patient risk stratification and management.

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KEY WORDS cardiovascular magnetic resonance, extracellular volume, mitral valve prolapse, myocardial fibrosis, primary mitral regurgitation

APPENDIX For an expanded Methods section and the supplemental figure, please see the online version of the paper.