Original Article

Comparison of cardiovascular magnetic resonance features and clinical consequences in patients with left ventricular non-compaction with and without mitral regurgitation—a multi-institutional study of the retrospective cohort study

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Background: Mitral regurgitation (MR) is common in patients with ischemic or idiopathic cardiomyopathies and may be associated with a poor prognosis; however, the impact of different degrees of MR on cardiovascular magnetic resonance images, left ventricular features, and clinical outcomes of left ventricular noncompaction are unknown. We aimed to investigate and compare cardiovascular magnetic resonance characteristics and clinical consequences in patients with left ventricular non-compaction (LVNC) with and without MR.

Methods: A cohort of 75 patients with left ventricular noncompaction were retrospectively studied from three institutions; all had undergone cardiovascular magnetic resonance examination with subsequent clinical follow-up. MR was evaluated by echocardiography. Left ventricular myocardial strains including global radial, circumferential, and longitudinal peak strains and left ventricular geometric and functional parameters, including left ventricular ejection fraction, end-diastolic volume, end-systolic volume, left ventricular mass, left ventricular sphericity index, longitudinal shorten, and late gadolinium enhancement (LGE) were measured and compared among groups. The primary endpoint was a composite of heart transplantation, implantable cardioverter–defibrillator insertion, and cardiac death.

Results: Compared with the no MR group, the MR groups showed significant deterioration in left ventricular myocardial strains (all $P<0.05$), and impaired left ventricular geometry and function, including lower left ventricular ejection fraction and greater left ventricular end-systolic volume and left ventricular mass ($P<0.05$). In the subgroup of moderate–severe MR, patients showed more impaired cardiovascular magnetic resonance features, including left ventricular sphericity index, left ventricular end-diastolic volume, and longitudinal shorten ($P<0.05$). In this subgroup, Kaplan-Meier analysis showed a significant difference in clinical outcomes (log-rank $\chi^2=4.516$, $P=0.034$; log-rank $\chi^2=4.419$, $P=0.036$, respectively). Additionally, multivariate analyses showed a 6.5-fold higher [hazard ratio, 6.5 (95% CI, 1.015–41.881)] risk of cardiac death with LGE in the moderate–severe MR cohort.

Conclusions: In patients with left ventricular noncompaction, MR induced more maladaptive left ventricular remodeling. The incidence of adverse outcomes may be related to the degree of MR. In moderate-severe MR patients, coexisting of LGE may have an additive deleterious effect on clinical outcomes.

Keywords: Left ventricular non-compaction (LVNC); mitral regurgitation (MR); outcome; late gadolinium enhancement (LGE); cardiovascular magnetic resonance

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Introduction

Left ventricular non-compaction (LVNC) is rare cardiomyopathy characterized by prominent trabeculation of the left ventricle (LV) and deep intertrabecular recesses (1,2). The highly heterogeneous clinical manifestations and outcomes of LVNC include disabling congestive heart failure (HF), malignant arrhythmias, and sudden cardiac death (3). Although the method of diagnosing LVNC is mainly focused on the thickness of noncompacted to compacted myocardial layers ratio measured at the end-diastole, other features may also be useful for risk stratifications.

Secondary mitral regurgitation (MR) is seen in severe LV dysfunction and LV dilatation without organic mitral valve disease (4), which is common in patients with LVNC (5). Significant MR may worsen cardiac hemodynamics and exacerbate symptoms, with adverse outcomes (6). Studies of ischemic cardiomyopathy showed that HF, adverse cardiac prognoses, and cardiac mortality are more likely in MR patients (7,8). MR may be a leading factor for the progression of cardiomyopathy (9,10). However, MR effects on LV function and clinical outcomes in patients with LVNC have not been clarified.

This study was performed to evaluate: (I) cardiac geometry and function in LVNC patients with MR, (II) the impact of the mitral valve (MV) on major adverse cardiac events (MACE) in patients with LVNC, and (III) cardiovascular magnetic resonance (CMR) indicators that may be associated with outcomes in LVNC patients with MR. We present the following article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-769/rc).

Methods

Study design

This retrospective observational cohort study was undertaken in three tertiary-care referral centers in China, which has an established clinical database of patients referred for CMR and echocardiography imaging. This study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013) and was approved by Clinical Trials and Biomedical Ethics Committee of West China Hospital (K2019059); West China Second University Hospital, Sichuan University (No. 756/2019) and Peking Union Medical College Hospital (ZS-1790). All patients provided written informed consent prior to participation.

Participants

We retrospectively screened a total of 12,469 patients who underwent both CMR and echocardiography from Peking Union Medical College Hospital, West China Hospital and West China Second University Hospital, respectively, from January 2013 and December 2020, and extracted consecutive patients who had CMR reports that included descriptions of "noncompaction", "hypertrabeculation" or "cardiomyopathy" (*Figure 1*).

The inclusion criteria were based on LVNC diagnostic criteria, and Petersen's CMR and clinical criteria, including: (a) a distinct two-layered myocardium with prominent trabeculation; (b) intertrabecular recesses communicating with the LV cavity; (c) end-diastolic ratio of noncompacted/compacted (NC/C) myocardium >2.3:1 in ≥1 of any LV

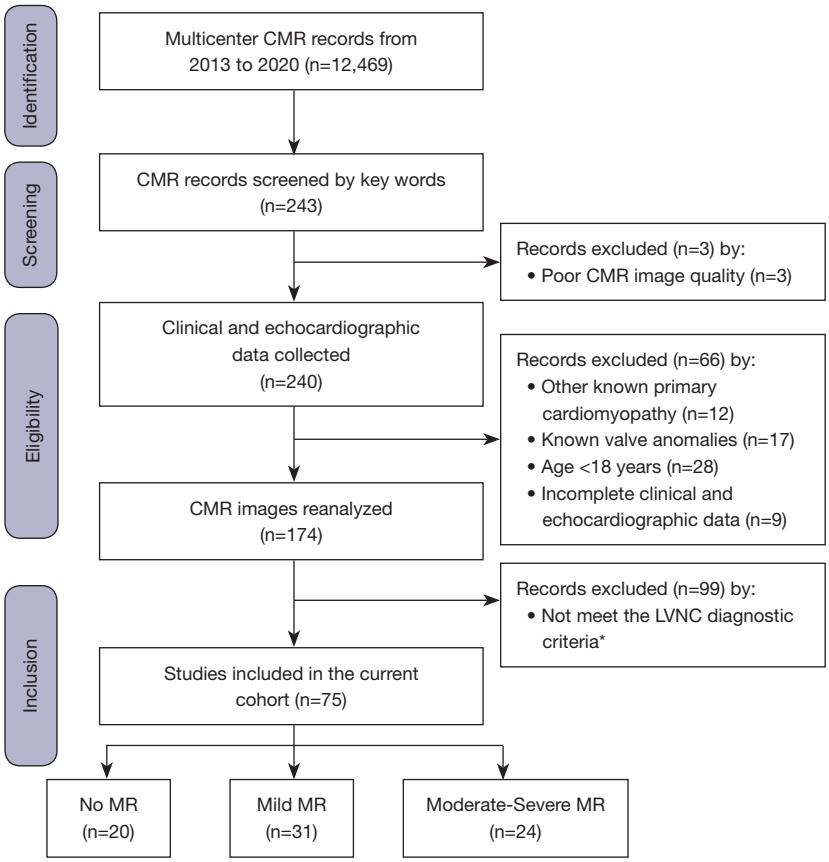

Figure 1 Flow diagram of the study patients. *, this part of patients can only be diagnosed as hypertrabeculation. CMR, cardiac magnetic resonance; MR, mitral regurgitation.

segments on CMR images; (d) absence of other known primary cardiomyopathy states (including congenital heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, cardiac amyloidosis, or sarcoidosis); and (e) no known valve anomalies(11); (f) adults (≥18 years), with any LVEF (*Figure 2A,2B*). The exclusion criteria were incomplete clinical data (n=9) and poor CMR image quality (n=3). The clinical, CMR and echocardiographic data of each center were collected by two experienced doctors and were anonymized before analysis.

CMR image acquisition

All examinations in the three centers were performed using a 3.0 T magnetic resonance scanner (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany). Dedicated cardiac software, respiratory gating technology, and electrocardiogram triggering were used with a standardized CMR scanning protocol in accordance with international guidelines (12). The balanced steady-state free-precession sequence cine (repetition time: 39.34 ms, echo time: 1.22 ms, flip angle: 40°, slice thickness: 8 mm, the field of view: 250×300 mm, and matrix size: 208×139) was performed in vertical and horizontal long-axis and short-axis orientations (including two-, three-, and four-chamber images). The scanning ranges of the short axis were acquired to slice the entire LV and right ventricle from the base to apex, with 8–12 continuous cine images acquired, for LV volume, mass, and functional assessment. Late gadolinium enhancement (LGE) images were obtained using a breath-hold inversion-recovery sequence (repetition time/echo time: 750 ms/1.18 ms, flip angle: 40°, slice thickness: 8 mm, the field of view: 400×270 mm, and matrix size: 256×148) 15 minutes after an intravenous bolus of 0.2 mL/kg gadobenate dimeglumine (0.5 mmol/mL; MultiHance, Bracco, Milan, Italy) was administered (*Figure 2C-2E*).

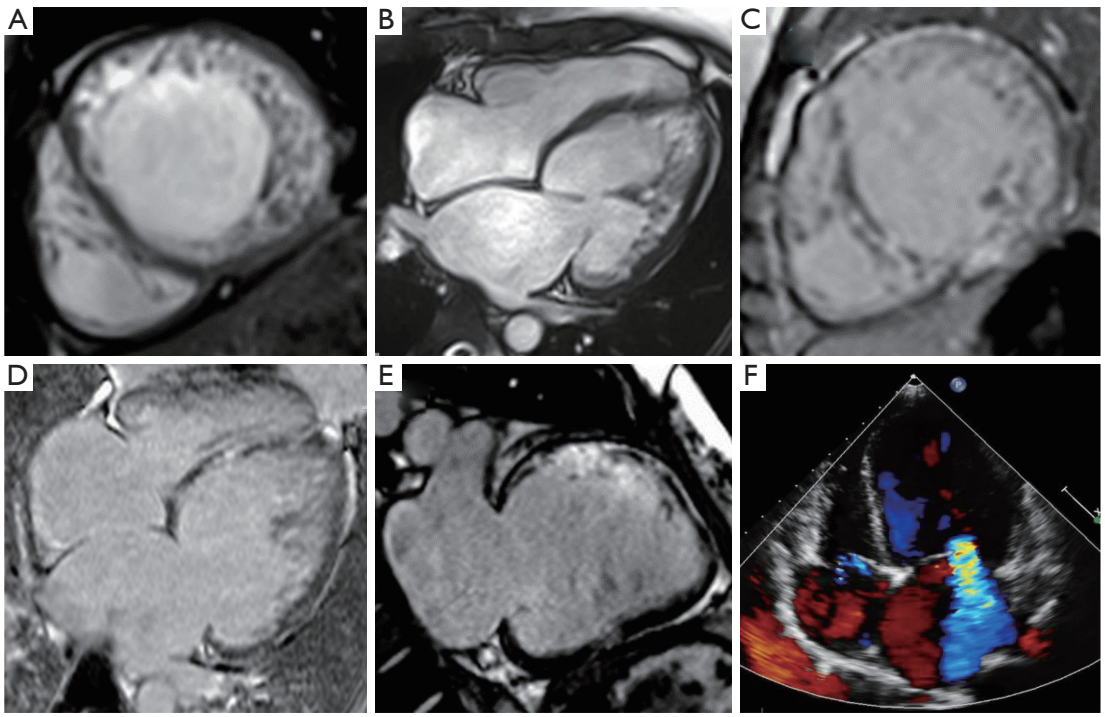

Figure 2 Typical images of a 43-year-old woman with LVNC. (A,B) The steady-state free-precession cine sequence in short-axis and long-axis views showing an obvious noncompacted myocardial layer in the mid-apical portions of the left ventricle. (C-E) Late gadolinium enhancement images in short-axis and long-axis orientations. (F) Echocardiography showing severe mitral regurgitation. LVNC, left ventricular non-compaction.

Echocardiographic acquisition and analysis

All echocardiographic examinations were performed and analyzed by experienced investigators according to the latest international recommendations on the quantification of cardiac chambers (13) and evaluation of MV regurgitation (14), using a commercial ultrasonic instrument (E9, GE Medical Systems, Milwaukee, WI, USA). MR severity was prospectively quantified by color flow jet area and classified as mild (<4 cm^2 or <20% of left atrium area), moderate (4–10 cm^2 or 20%–40% of LA area), or severe (>10 cm^2 or >40% of LA). In addition, left atrial (LA), ventricular size, swirling jet, or reversal of flow in pulmonary veins should be considered when the diagnosed with severe MR (*Figure 2F*).

CMR analysis

All CMR images were analyzed using a commercially available cardiac workstation (cvi42, v. 5.10.2; Circle Cardiovascular Imaging, Calgary, Canada) in the West China Second Hospital of Sichuan University by two experienced radiologists who were blinded to the clinical information. Disagreements, if any, were resolved by consensus including a third expert. For participants with multiple CMR examinations, an initial examination was performed for the primary analysis.

From short- and long-axis cine images, LV geometric and functional parameters were analyzed. The papillary muscles were excluded from compacted LV myocardium (15). The LV geometric parameters included the end-diastole NC/C ratio, LV longitudinal shorten (L-shorten), and LV sphericity index (LVSI). The LVSI was calculated as end-diastolic volume (EDV)/[(end diastolic long-axis diameter 3×π)/6] (21). For each segment without compaction, the end-diastole NC/C ratio was quantitatively calculated from the short-axis views, and the maximum ratio was used for analysis after excluding the apical NC/C ratio (segment 17). LV mass was calculated only in LV compact mass (excluding NC). LA antero-posterior diameter (APD) and transverse diameters (TD) were measured by the vertical distance from the farthest point of the posterior wall

of the LA to the atrial septum on the three-chamber cine image at the LA end-diastolic phase. Left atrial transverse diameters (LATD) was measured on the four-chamber cine image, which should be measured perpendicular to the LA length. The cardiac function parameters included LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), left-ventricle ejection fraction (LVEF), and stroke volume. Strains, including the LV global longitudinal peak strain (GLPS), circumferential (GCPS), and radial peak strain (GRPS), were analyzed based on manual tracking of the endocardial and epicardial region at end-diastole in the short- and long-axis slices in the tissue-tracking module. LGE was visually assessed on short-axis image in compact layers. The long-axis images were used to confirm the presence of LGE.

Follow-up

All patients were followed up by clinical visits or telephonic interviews by experienced cardiologists who were blinded to the imaging data. The primary endpoint was a composite of cardiovascular death, heart transplantation, and implantable cardioverter–defibrillator insertion. Follow-up duration was determined from the data of the first CMR examination to the occurrence of an endpoint event.

Statistical analysis

Continuous variables were tested for normality using the Shapiro-Wilk test and are expressed as mean ± SD using unpaired *t*-tests or one-way analysis of variance. Categorical variables are presented as frequencies (percentages) using chi-square tests or Fisher's exact tests. The survival curve, generated by the Kaplan-Meier analysis and tested by the log-rank test, was used to compare the cumulative incidence of the endpoint based on the presence of MR.

All analyses were performed using SPSS version 23 (IBM, Armonk, New York, USA). A two-tailed P value <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 75 patients [46 (61%) men] were included in this study; the mean age of the participants was 44.5± 14.6 years and the incidence of MR was 57 (74%). A total of 26.7% patients had no MR, but with a possibly decreased LVEF (35%) in this group. Patients had similar age, sex, BMI, family history, and comorbidities (hypertension and diabetes; P>0.05). New York Heart Association (NYHA) class ≥ III (n=31, 40.3%) was common in all participants, and patients with moderate–severe MR had a poor NYHA grade (P<0.05). Higher prescription rates of guideline-recommended HF therapies were seen in the moderate–severe MR group. Clinical and demographic characteristics of the patients are summarized in *Table 1*.

Echocardiographic results

Table 2 reports LVEF and MR grading derived from each center's analysis; 55 (73.3%) patients with LVNC had MR [mild, moderate, and severe MR in 31 (41.3%), 20 (26.7%), and 4 (5.3%) participants, respectively].

Findings of CMR imaging

Detailed CMR characteristics are listed in *Table 3*. The mean LVEF was 30.9%±16.6%. The LVEF and LVESV (both P<0.05) differed significantly from no MR group, through mild MR, to moderate–severe MR groups. Compared with the no MR group, the LAAPD, LATD EDV, LVSI, and L-shorten changed significantly in the moderate–severe MR groups (all P<0.05) but were preserved in the mild MR group. The LV-GRPS, GCPS, and GLPS (all P<0.05) declined significantly from no MR group, through mild MR, to moderate–severe MR groups. Sixteen patients with LVNC (21.3%) had LV-LGE. Patients in the MR cohort had a significantly higher incidence of LGE than in the no MR cohort (P<0.05; *Table 3*).

Association between MR grating and composite cardiac events

The average follow-up duration was 54.1±25.7 months. Nineteen patients developed MACE during follow-up (13 cardiac deaths, 1 heart transplantation, and 5 implantable cardioverter–defibrillator insertion), resulting in a 25.3% incidence of the primary endpoint in the study cohort. In the moderate–severe MR, no MR, and mild MR groups, MACE occurred in 10 (41.7%), 3 (15.0%), and 6 (19.4%) patients, respectively. Compared with no MR and mild MR cohort, the moderate–severe MR cohorts showed significant differences in MACE by Kaplan-Meier analysis (log-rank χ^2=4.516, P=0.034; log-rank χ^2=4.419, P=0.036, respectively) (*Figure 3*).

Table 1 Baseline characteristics of the study population and of patients with and without MR

Variable	All patients (n=75)	Patients without MR (n=20)	Patients with mild MR (n=31)	Patients with moderate-severe MR (n=24)
Clinical characteristics				
Age, yrs	44.5±14.6	42.4±14.9	42.8±15.0	48.5±13.8
Male; n (%)	46 (61.3)	12 (60.0)	22 (71.0)	12 (50.0)
BMI (kg/m^2)	24.8±14.6	22.7±3.0	26.9±22.2	23.8±4.6
Diabetes, n (%)	15 (20.0)	4 (20.0)	5 (16.0)	6 (25.0)
Hypertension, n (%)	13 (17.3)	7 (35.0)	2 (6.0)	4 (16.7)
Family history of CVD, n (%)	13 (17.3)	3 (15.0)	5 (16.0)	5 (21.0)
Smoking, n (%)	21 (28.0)	2 (10.0)	13 (42.0)*	6 (25.0)*
HR (beats/min)	76.8±19.4	74.1±17.1	76.8±19.9	79.1±21.2
NYHA functional class	2.1±1.1	1.5±1.1	2.1±1.2	2.6±0.8*
0, n (%)	7 (9.3)	3 (15.0)	3 (9.7)	1 (4.2)
I, n (%)	14 (18.7)	8 (40.0)	5 (16.1)	1 (4.2)
II, n (%)	23 (30.7)	6 (30.0)	11 (35.5)	6 (25.0)
III, n (%)	24 (32.0)	2 (10.0)	7 (22.6)	15 (6.3)
IV, n (%)	7 (9.3)	4 (20.0)	5 (16.1)	1 (4.2)
> III, n (%)	31 (41.3)	6 (30.0)	12 (41.4)	16 (61.5)*
Medical therapy				
Beta-blocker, n (%)	56 (74.7)	12 (60.0)	22 (71.0)	22 (91.7)*
ACE inhibitors, n (%)	29 (45.3)	8 (40.0)	11 (35.5)	15 (62.5)*
ARB, n (%)	19 (25.3)	5 (25.0)	7 (22.6)	7 (29.2)
Diuretic, n (%)	54 (72.0)	12 (60.0)	20 (64.5)	22 (91.7)*
Duration of follow-up, months	54.1±25.7	57.2±26.0	57.6±25.0	46.9±25.9

*, P<0.05 versus MR– cohort. MR, mitral regurgitation; BMI, body mass index; CVD, cardiovascular disease; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Table 2 Echocardiographic analysis

Variable	All patients (n=75)
LVEF	32.8±15.8
Mitral regurgitation	
Normal, n (%)	20 (26.7)
Mild MR, n (%)	31 (41.3)
Moderate MR, n (%)	20 (26.7)
Severe MR, n (%)	4 (5.3)

LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

Association between myocardial fibrosis and cardiac death in patients with moderate–severe MR

In the moderate–severe MR cohort, six (25.0%) and seven (29.2%) patients presented with LGE and experienced cardiac death, respectively. The survival rates were 88.2% (15/17) and 28.5% (2/7) in patients with and without LGE, respectively, indicating a statistically significant difference between the LGE+ and LGE– cohorts for cardiac death in the moderate–severe MR group (*Figure 4*). Multivariate analysis (*Table 4*) revealed that LGE was associated with

Table 3 Cardiovascular magnetic resonance characteristics for patients with and without MR

Variable	All patients (N=75)	No MR (n=20)	Mild MR (n=31)	Moderate-severe MR (n=24)
LV geometry and function				
LVEF (%)	30.9±16.6	45.1±17.6	27.4±15.2*	23.6±9.1*
LVEDV (mL)	243.2±94.1	191.5±69.3	245.3±93.0	283.4±96.1*
LVESV (mL)	177.2±94.5	112.5±73.1	184.8±91.4*	221.4±89.0*
LVmass (g)[φ]	120.8±43.0	95.2±24.1	125.3±37.8*	136.4±52.6*
LVSI	0.73±0.23	0.65±0.16	0.74±0.21	0.79±0.28*
L-shorten	0.34±0.11	0.37±0.70	0.35±0.11	0.30±0.11*
Maximum NC/C	3.54±0.92	3.62±1.23	3.52±0.86	3.50±0.88
LAAPD (mm)	37.45±10.46	31.45±6.00	34.37±9.99	46.26±8.30*
LATD (mm)	45.66±11.90	40.10±8.08	41.75±11.90	54.54±9.22*
Myocardial strain				
GPRS (%)	12.6±9.5	20.3±11.4	11.0±8.0*	8.1±4.6*
GPCS (%)	−9.4±4.8	−13.2±4.8	−8.4±4.2*	−7.3±3.7*
GPLS (%)	−6.4±4.1	−9.4±3.6	−6.1±3.5*	−4.3±3.9*
LGE[ψ]	18 (24.0)	2 (10.0)	9 (29.0)*	7 (29.17)*

[φ], LV mass was calculated only about LV compact mass (excluding NC); [ψ], LGE was diagnosed only in compact layers (excluding NC); *, P<0.05 versus MR− cohort. MR, mitral regurgitation; LV, left ventricular; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; SI, sphericity index; L-shorten, longitudinal shorten; NC/C, non-compacted-to-compacted; LA, left atrial; APD, antero-posterior diameter; TD, transverse diameter; GPRS, global peak radial strain, GPCS, global peak circumferential strain, GPLS global peak longitudinal strain; LGE, late gadolinium enhancement.

cardiac death [hazards ratio, 6.5 (95% CI, 1.015–41.881)].

Discussion

This multicenter cohort study investigated the role of MR in the cardiac features and clinical outcomes of patients with LVNC and found that: (I) MR was associated with maladaptive LV remodeling: as the degree of MR increased, LV remodeling became more severe, and LV function worsened; (II) the moderate–severe MR cohort exhibited a higher incidence of MACE, than the no MR or mild MR cohorts; and (III) in the moderate–severe MR cohorts, coexisting LGE further deteriorated the clinical outcomes. These observations indicate the deleterious effect of MR on myocardial function and adverse outcomes in patients with LVNC. Coexisting LGE in LVNC patients with moderate-severe MR further deteriorates clinical outcomes. Therefore, when MR is detected in patients with LVNC on routine echocardiography, CMR may be necessary for further risk stratification.

Characteristics of hemodynamic changes in MR

MR is the most common valve disease and is divided into primary and secondary forms. Primary MR, which refers to morphological and structural abnormalities of the valve and its appendages, was excluded from our study. Secondary MR occurs when normal or near-normal mitral leaflets cannot be adequately coapted because of LV dysfunction, mitral annular dilation, or both (16). Although valvular regurgitation can now be detected by CMR, echocardiography remains the first-line method for the assessment of valvular heart disease, and is most commonly used for easily accessible examination in routine clinical assessment (14,17). Our study showed that 73.3% of patients with LVNC had MR: 41.3%, 26.7%, and 5.3% had mild, moderate, and severe MR, respectively, on echocardiography.

The results showed that, with MR aggravation among the three groups, the LV volume would increase (EDV and ESV increased significantly) and more severe adverse

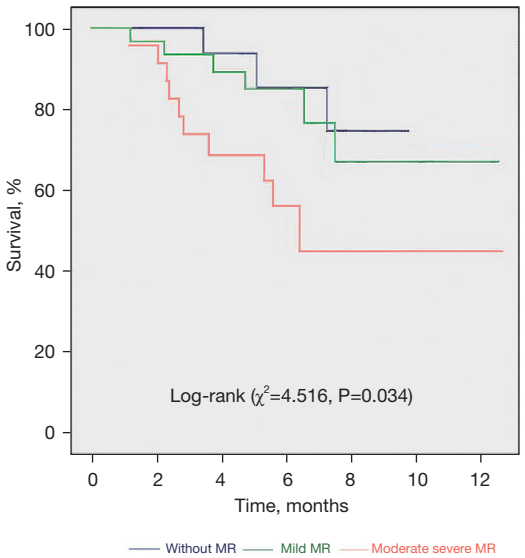

Figure 3 Major adverse events and MR in patients with LVNC. Kaplan-Meier curve showing worse clinical outcomes in patients with moderate–severe MR, compared with no MR and mild MR cohorts (χ^2=4.516, P=0.034; χ^2=4.419, P=0.036, respectively). LVNC, left ventricular non-compaction; MR, mitral regurgitation.

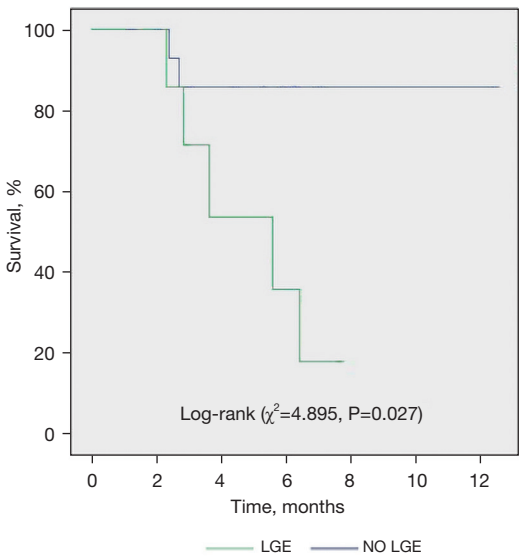

Figure 4 Cardiac death and LGE in patients with LVNC combined with moderate–severe MR. Kaplan-Meier analysis showing a significant difference in cardiac death between LGE+ and LGE– cohorts in moderate–severe MR group. LVNC, left ventricular non-compaction; LGE, late gadolinium enhancement; MR, mitral regurgitation.

remodeling (L-shorten and LVSI significantly differed) was evident. In contrast, whereas the LV wall thickened (LV mass increased significantly) to maintain the LVEF, with resultant further enlargement of the MV ring and MV exacerbation, and eventual enlargement of the LV and LA, which subsequently increased LV mass, pulmonary congestion, and cardiac dysfunction (LVEF decreased significantly).

Effect of MR on LV morphology and function in LVNC

CMR enables comprehensive assessment of myocardial deformation and the entire LV function and can accurately identify trabeculae due to its higher spatial resolution (11,18). Due to its higher spatial resolution and field of view, CMR shows increasing diagnostic potential in evaluating LV remodeling and dysfunction in patients with LVNC (11,18). MR is related to LV remodeling and poor prognosis, and MV repair induces LV reverse remodeling in dilated cardiomyopathy and in other idiopathic cardiomyopathies (19,20). Dreisbach *et al.* demonstrated impaired stain in patients with LVNC and that GCPS had independent and incremental diagnostic value (21). However, few studies have evaluated the MR impact on LV deformation and remodeling in patients with LVNC. In our study, GRPS, GCPS, and GLPS were significantly impaired in participants with MR than those without MR. GPLS, which represents the longitudinal contractile function, is impaired earlier and more severely in most progressive cardiomyopathies, as seen in our participants. MR, which is associated with hemodynamic overload, increases vulnerability to the involvement of the subendocardial myocardial layer, which is the main component of LVNC lesions. MR may have negative effects on LV global multilayer radial and circumferential strain in LVNC; thus, MR may aggravate left heart compliance, as represented by more severe impairment of the global strain. In our subgroups, the degree of MR was not significantly associated with the degree of strain impairment, although global strain tended to decrease in patients with moderate–severe MR. Another interesting indicator was LVSI, which can be obtained from the cine images without requiring any extra contrast agent and sequence. A previous study (22) showed that LVSI is useful to reflect LV structural remodeling and the severity of nonischemic dilated cardiomyopathy. In our study, SI significantly increased in the moderate-severe MR group, indicating that the LV became rounder and blunter. The abovementioned results suggest that MR, regardless of the degree, is closely related

Table 4 Cardiac mortality by univariable and multivariable analyses in LVNC patients with moderate-severe MR

Variable	Unadjusted HR [95% CI]	P value	Adjusted HR [95% CI]	P value
Clinical characteristics				
Age	1.111 [1.013–1.219]	0.026	1.148 [1.012–1.302]	0.032
Male sex	2.144 [0.404–11.384]	0.370		
BMI	0.914 [0.756–1.104]	0.350		
NYHA ≥ III	1.389 [0.269–7.180]	0.695		
Hypertension				
Diabetes mellitus	2.862 [0.636–12.884]	0.171		
Heart rate (per 10 bpm)	0.990 [0.956–1.024]	0.559		
Family history of CAD	1.193 [0.230–6.179]	0.834		
Smoking	1.731 [0.309–9.692]	0.533		
CMR parameters				
LVEF	1.020 [0.935–1.113]	0.652	1.003 [0.916–1.098]	0.947
EDV	0.995 [0.987–1.004]	0.305		
ESV	0.995 [0.985–1.005]	0.300		
LVmass	0.992 [0.975–1.009]	0.337		
LVSI	0.250 [0.090–6.751]	0.410		
L-shorten	0.007 [0.000–4.846]	0.137		
GPRS (%)	0.911 [0.758–1.095]	0.321		
GPCS (%)	0.967 [0.779–1.200]	0.760		
GPLS (%)	0.919 [0.736–1.146]	0.453		
LGE presence	5.265 [1.018–27.240]	0.048	6.520 [1.015–41.881]	0.048

LVNC, left ventricular non-compaction; MR, mitral regurgitation; BMI, body mass index; NYHA, New York Heart Association; CVD, cardiovascular disease; CMR, cardiovascular magnetic resonance; CAD, coronary artery disease; LV, left ventricular; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; SI, sphericity index; L-shorten, longitudinal shorten; NC/C, non-compacted-to-compacted; GPRS global peak radial strain, GPCS, global peak circumferential strain, GPLS global peak longitudinal strain; LGE, late gadolinium enhancement.

to changes in LV compliance and morphology, and the resultant reduction in LV function.

MR aggravated clinical outcome in LVNC

MR, especially moderate–severe MR, may significantly affect myocardial morphology, compliance, and function and affect the prognosis of patients with LVNC. Thus, evaluating the MR impact on the prognosis of patients with LVNC is needed. A recent meta-analysis showed that even mild MR correlated with adverse outcomes in patients with ischemic or idiopathic cardiomyopathy (6). In our moderate–severe MR cohort, the incidence of MACE was significantly higher than that in MR or mild MR patients. In the moderate–severe MR cohort, Kaplan-Meier analysis showed a significant difference in adverse outcomes of cardiovascular death, heart transplantation, and implantable cardioverter–defibrillator insertion at the end of follow-up, compared with the no MR (P=0.034) and mild MR (P=0.036) cohorts. The mild MR and no MR patients showed no significant difference in survival, free of MACE (P=0.648). This suggests that the degree of MR is associated with MACE, possibly because mild MR has less impact on cardiac hemodynamics and, therefore, on cardiac function and outcome. These results demonstrated that LVNC patients with moderate–severe MR might have a higher

incidence of MACE and a worse prognosis; thus, more attention should be paid to these patients clinically.

In the multivariate analysis, after adjusting for age, sex, and LVEF, the presence of moderate–severe MR did not significantly correlate with worse outcomes in patients with LVNC (P>0.05), which was similar to the results of previous studies (6,23,24). This could be because moderate–severe MR can be considered an intrinsic consequence of LV dysfunction and maladaptive LV remodeling rather than an independent event. Patients with pathological LVEF or NYHA ≥ III, which are two parameters that are more commonly used in clinical settings to assess LV function, did not show a significantly higher incidence of MACE during follow-up. Thus, moderate–severe MR may be a more sensitive and reliable indicator than conventional noninvasive risk-stratifiers, such as pathological LVEF and NYHA; however, moderate–severe MR is not an independent predictor of MACE in patients with LVNC. Detection of moderate–severe MR in patients with LVNC on routine echocardiography necessitates the identification of a stronger predictor in this group for further risk stratification.

Combined effect of LGE and moderate–severe MR on mortality

Given the significantly higher incidence of MACE in LVNC patients with moderate–severe MR, it is necessary to identify possible indicators to predict the prognosis of these high-risk patients. As a robust predictor of MACE, LGE has been reported in many studies (25-27) and may be caused by myocardial microcirculation dysfunction and decreased coronary flow reserve in patients with LVNC (28,29). In addition, myocardial fibrosis may be associated with adverse remodeling, which may cause severe HF. Another possible reason is that LGE is often associated with malignant arrhythmias, leading to an adverse prognosis (25,30). In our series of patients with LVNC, there was no incremental association between the MR grade and the frequency of LGE+. However, in the moderate–severe MR group, LGE was associated with mortality after adjusting for age and LVEF, possibly due to the superimposed effect of LGE and moderate–severe MR. LV myocardial fibrosis, revealed by LGE, is an advanced step of LV remodeling. The LGE assessed by CMR may be the result of a series of pathological mechanisms such as coronary microcirculation, inflammation, edema, and fiber hyperplasia. While the adverse cardiac remodeling can be aggravated by moderate–severe MR, which can lead to focal cardiomyocyte necrosis due to increased metabolic demands and impaired microcirculatory function, this may result in cardiovascular dysfunction and, eventually, cardiac death. Since both fibrosis and moderate-severe MR are related to the occurrence and development of myocardial maladaptive remodeling, they may have a combined effect on worse outcome. LGE was potentially an independent predictor of cardiac death in the moderate–severe MR group and can improve risk stratification in LVNC.

Limitations

Our study has several limitations. First, this was a multicenter retrospective study, with inherent design-related limitations. Data collection and processing must be performed carefully. To avoid bias, researchers were blinded when clinical, CMR, and ultrasound data were collected. Second, the population of patients in the cohort was relatively small owing to the rare nature of the disease. Third, as all these three centers are tertiary-care referral centers, potential selection and referral biases among our groups were possible, which may limit the extrapolation of conclusions. Finally, indices of diastolic dysfunction and pulmonary pressure would be needed for a more accurate diagnosis of severe MR, which, however, could not be obtained and reassessed from every patient when we retrospectively collected echocardiographic data. Thus, there may be some deviation in the diagnosis of severe MR. In our study, moderate and severe MR were combined into a moderate-severe MR group to research and analysis, which may have reduced MR diagnostic deviation to some extent. To further ascertain the MR effect on MACE in patients with LVNC, larger prospective studies with longer follow-up periods are required.

Conclusions

MR is frequent in LVNC with LV dysfunction. More severe MR induced more maladaptive LV remodeling. The incidence of adverse outcomes may be related to the degree of MR. In patients with moderate-severe MR, coexisting LGE may have an additional deleterious effect on clinical outcomes. Clinically, when MR is detected by routine echocardiography in patients with LVNC, LGE by CMR may be necessary for further risk stratification.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-21-769/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Clinical Trials and Biomedical Ethics Committee of West China Hospital (K2019059); West China Second University Hospital, Sichuan University (No. 756/2019) and Peking Union Medical College Hospital (ZS-1790). All patients provided written informed consent prior to participation.

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