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ORIGINAL PAPER

Association of secondary mitral regurgitation and right ventricular dysfunction among patients with non-ischaemic cardiomyopathy

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Aims The association between secondary mitral regurgitation (MR) and right ventricular (RV) dysfunction in heart failure patients with non-ischaemic cardiomyopathy (NICM) is unclear. Hence, our objective was to study the association between secondary MR and the occurrence of RV dysfunction among patients with NICM using cardiac magnetic resonance (CMR).

Methods and results Patients with NICM were enrolled in a prospective observational registry between 2008 and 2019. CMR was used to quantify MR severity along with RV function. The RV dysfunction was defined as RV ejection fraction <45%. The outcome of the study was a composite event of all-cause death, heart transplantation, or left ventricular assist device implantation at follow-up. In the study cohort of 241 patients, RV dysfunction (RVEF < 45%) was present in 148 (61%). In comparison with patients without RV dysfunction, those with RV dysfunction had higher median MR volume {23 mL [interquartile range (IQR) 16–-31 mL] vs. 18 mL (IQR 12–25 mL), $P = 0.002$} and MR fraction [33% (IQR 25–43%) vs. 22% (IQR 15–29%), $P < 0.001$]. Furthermore, secondary MR was independently associated with RV dysfunction: MR volume ≥ 24 mL (OR 3.21, 95% CI 1.26–8.15, $P = 0.01$) and MR fraction ≥ 30% (OR 5.46, 95% CI 2.23–13.35, $P = 0.002$). Increasing RVEF (every 1% increase) was independently associated with lower risk of adverse events (HR 0.98; 95% CI 0.95, 1.00; $P = 0.047$).

Conclusion In patients with NICM, the severity of secondary MR is associated with an increased prevalence of RV dysfunction. The RV dysfunction is not only associated with the severity of LV dysfunction but also with the severity of secondary MR.

Clinical Trial Registration https://clinicaltrials.gov/ct2/show/NCT04281823.

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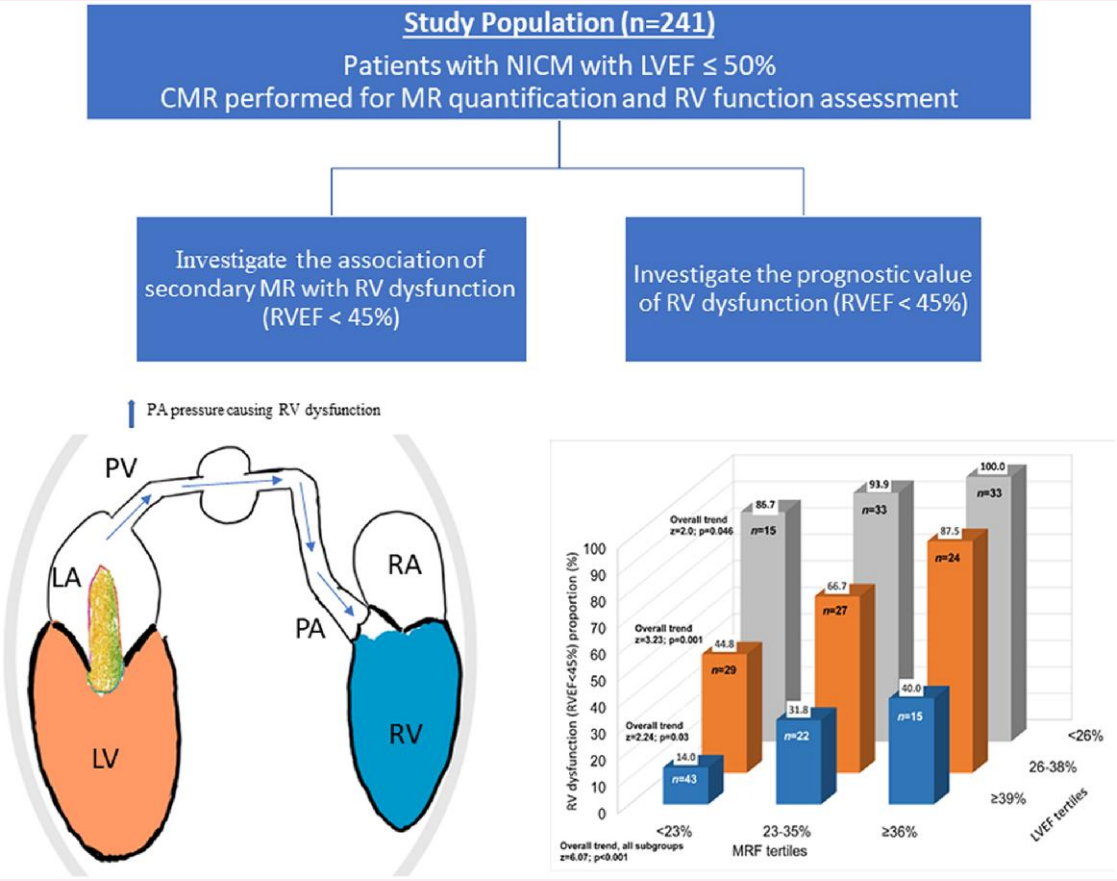
Graphical Abstract



This study addresses a critical evidence gap in the understanding of the implications of secondary mitral regurgitation (MR). In the current study, we demonstrate that secondary MR has an impact on right ventricular (RV) systolic function among patients with non-ischemic cardiomyopathy (NICM), even at lower amount than suggested thresholds for severe grades. This should be kept in mind while considering these patients for device therapy. Not all RV dysfunction in NICM is solely related to the advanced cardiomyopathy process.

Keywords secondary mitral regurgitation • heart failure • right ventricular dysfunction

Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) is frequently associated with right ventricular dysfunction (RVD), and the presence of RVD has an incremental prognostic significance in these patients beyond left ventricular (LV) ejection fraction (EF).[1–4] HF patients may have increased pulmonary artery pressure due to an increase in LV filling pressure from associated diastolic dysfunction and remodelling of the pulmonary vascular bed from neurohumoral mechanism associated with advancing HF.[5,6] The right ventricle (RV) is also very sensitive to increased afterload, and chronic pressure overload consequently results in progressive decline in RV systolic function.[7]

The aetiology of the underlying cardiomyopathy in HF also plays a considerable role in the involvement of the RV. Patients with non-ischaemic cardiomyopathy (NICM) are more likely to have RVD, but it is assumed that it may be due to the same molecular mechanisms driving the LV dysfunction in these patients.[8–10]

Often, HFrEF patients also have secondary mitral regurgitation (MR), which theoretically exacerbates RV afterload resulting in further RVD. Nonetheless, studies demonstrating a direct association between secondary MR and RVD are limited. Thus far, one study demonstrated that the degree of MR in ischaemic cardiomyopathy (ICM) patients is associated with the presence of RVD.[11] Since RVD is more frequently observed among patients with NICM,[8,10] it becomes even more unclear if secondary MR has any impact on the RVD in patients with NICM.

Besides being the gold standard for the assessment of RV function, cardiovascular magnetic resonance (CMR) imaging provides the ability to quantify the severity of secondary MR. The objective of the current study is to investigate the implications of secondary MR on RV function in patients with NICM where both RV function and MR severity are assessed by CMR.

Methods

Study population

Consecutive patients with reduced LVEF ≤ 50% undergoing contrast CMR between May 2008 and April 2019 for assessment of LV scar and

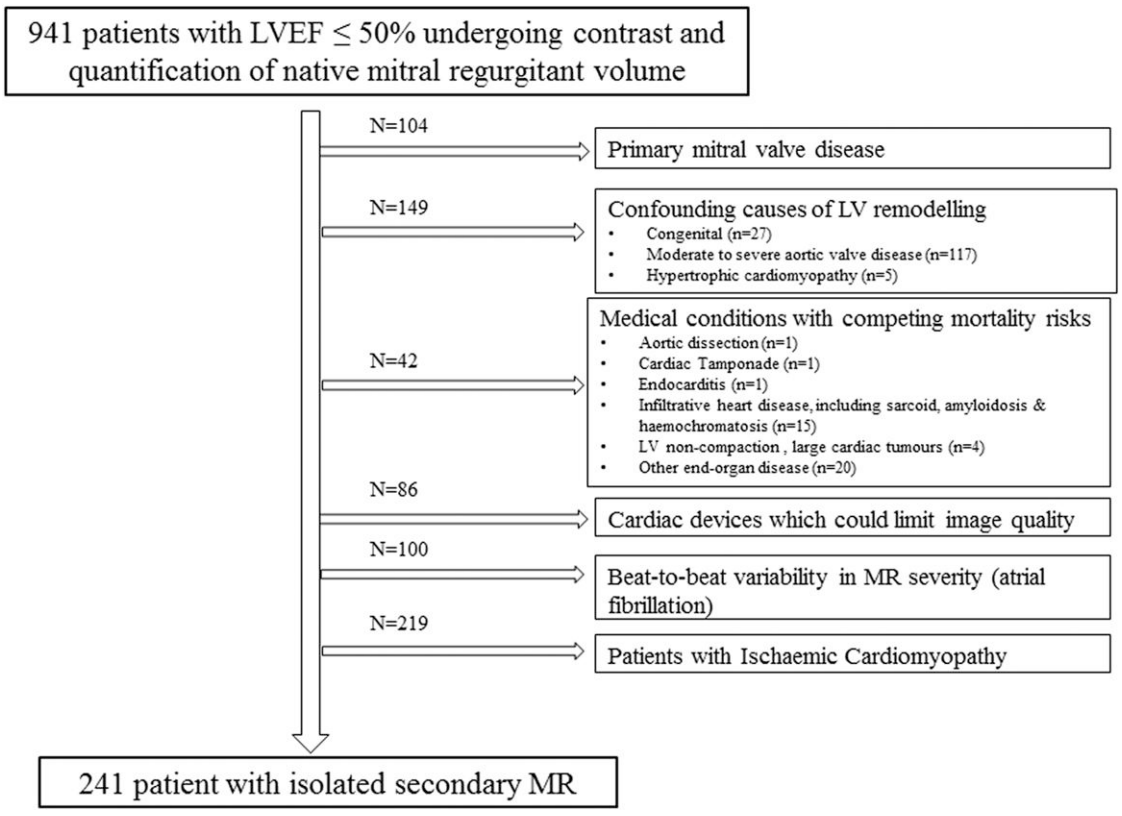


Figure 1 Flow chart showing the details of the patient inclusion in the study. LV, left ventricle; MR, mitral regurgitation.

quantification of native MR were enrolled into the DEBAKEY CMR Registry (NCT04281823), a prospective observational registry. Baseline medical history and medication use were recorded at the time of CMR via a comprehensive patient interview by a registered nurse or cardiac imaging fellow. Patients were excluded if they had (i) primary MR as described by the recent recommendation of the American Society of Echocardiography[12]; (ii) associated factors that could affect LV remodelling (congenital heart disease, concomitant aortic valve dysfunction, or hypertrophic cardiomyopathy); (iii) competing mortality risk based on clinical history or CMR findings (infiltrative heart disease or other end-organ diseases) that could shorten life expectancy; (iv) cardiac devices (pacemaker/defibrillator) that could affect optimal image quality; (v) atrial fibrillation at the time of imaging due to inherent beat-to-beat variability in the quantity of MR; and (vi) ischaemic heart disease based upon a prior history of coronary revascularization or significant obstructive epicardial coronary artery stenosis (≥70%). Details of exclusion are listed in *Figure 1*. The institutional review board at Houston Methodist Research Institute approved the study, and patients provided written and informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

CMR imaging

CMR images were acquired using either 1.5 or 3.0 T clinical scanners (Siemens Avanto, Aera, and Skyra, Siemens Healthineers, Erlangen, Germany) with phased-array coil systems. In all patients, anatomical and functional assessment of the LV was performed on a stack of short-axis cine images acquired at 1 cm interval, as well as three apical views using steady-state free precession sequences with a typical flip angle of 65°–85°; repetition time of 3.0 ms; echo time of 1.3 ms; in-plane spatial resolution of 1.7–2.0 mm × 1.4–1.6 mm; slice thickness of 6 mm, with 4 mm interslice gap; and temporal resolution of 35–40 ms. Flow across the aortic valve was assessed using phase-contrast imaging with typical flip angle of 25°–30°, repetition time of ∼5 ms, echo time of 2.4 ms, reconstructed in-plane spatial resolution of ∼2.0 × 2.4 mm, slice thickness of 6 mm, and temporal resolution of ∼40–50 ms. Late gadolinium enhancement (LGE) images were obtained approximately 10 min after the administration of intravenous gadolinium contrast (gadopentetate dimeglumine or gadoterate meglumine, 0.15 mmol/kg) using phase-sensitive segmented inversion-recovery gradient echo sequence.

CMR image analysis

LV and RV volumes [end-diastolic volume (EDV), end-systolic volume (ESV)], EF, and LV mass were measured as per recommended guidelines.[13] The left atrial volume (LAV) was measured using the biplane area length. Total LV stroke volume was derived by subtracting LVESV from LVEDV. Forward stroke volume was determined from contouring of phase-contrast images at the aortic root by correction for baseline flow offset. LV and RV volumes and forward stroke volume were indexed to body surface area for reporting purposes. MR volume (MRvol) was calculated as the difference between LV stroke volume and forward stroke volume. MR fraction (MRF) was calculated as the percentage of MRvol in relation to the total stroke volume (MR volume/stroke volume × 100%). The presence and extent of scar by LGE was determined in all LV segments by a level III trained CMR interpreter blinded to all clinical outcome data.

Pulmonary hypertension

Systolic pulmonary artery pressure (sPAP) was assessed using echocardiography. Echocardiographic data available within a time interval of ±30 days of CMR were used. The sPAP was calculated as 4 × (peak tricuspid regurgitant velocity by continuous-wave Doppler in m/s)^2 + estimated right atrial pressure.[14] The diameter of the inferior vena cava and its change with

Table 1 Baseline characteristics of the population

Variables	Total ($N = 241$)	RVEF ≥45% ($n = 93$)	RVEF <45% ($n = 148$)	*P*-value
Age (years), median (IQR)	56 (43, 64)	59 (47, 66)	52 (40, 62)	**0.004**
Male gender	127 (52.7)	35 (37.6)	92 (62.2)	**<0.001**
BMI (kg/m^2)	29.8 ± 7	29.1 ± 6.6	30.2 ± 7.2	0.12
NYHA Class III or IV, *n* (%)	86 (36)	15 (16)	71 (48)	**<0.001**
Hypertension, *n* (%)	138 (57.3)	56 (60.2)	82 (55.4)	0.46
Diabetes, *n* (%)	47 (19.5)	21 (22.6)	26 (17.6)	0.34
CKD, *n* (%)	48 (19.9)	19 (20.4)	29 (19.6)	0.87
ACEI/ARB, *n* (%)	119 (49.4)	39 (41.9)	80 (54.1)	0.07
Beta-blocker, *n* (%)	185 (76.8)	68 (73.1)	117 (79.1)	0.29
Diuretics, *n* (%)	163 (67.6)	42 (45.2)	121 (81.8)	**<0.001**
Imaging characteristics				
LV EDVI (mL/m^2), median (IQR)	127.7 (103.1, 160.6)	107.6 (93.9, 132.4)	139.5 (117.1, 170.9)	**<0.001**
LV ESVI (mL/m^2), median (IQR)	86.7 (62.0, 118.7)	64.4 (51.1, 81.7)	102.6 (78.0, 137.0)	**<0.001**
LV mass index (mg/m^2), median (IQR)	88.2 (73.3, 105.2)	82.2 (68.4, 100.2)	93.9 (77.1, 112.0)	**<0.001**
LVEF (%), median (IQR)	33.0 (22.0, 41.0)	41.0 (37.0, 47.0)	25.0 (19.5, 33.0)	**<0.001**
LAVI (mL/m^2), median (IQR)	66.4 (52.7, 81.8)	54.5 (41.8, 66.0)	73.0 (58.8, 89.4)	**<0.001**
RV EDVI (mL/m^2), median (IQR)	91.9 (75.6, 117.3)	76.8 (60.9, 87.9)	104.2 (86.7, 127.9)	**<0.001**
MRV (mL), median (IQR)	21.0 (14.0, 30.0)	18.0 (12.0, 25.0)	23 (16.0, 31.0)	**0.002**
MRV ≥24 (mL), *n* (%)	98 (41)	26 (28.0)	72 (49.0)	**0.001**
MRF (%), median (IQR)	29.0 (19.0, 38.0)	22.0 (15.0, 29.0)	33.0 (25, 43.0)	**<0.001**
MRF ≥25 (%), *n* (%)	146 (60.6)	35 (37.6)	111 (75.0)	**<0.001**
LGE, *n* (%)	111 (46.1)	34 (36.6)	77 (52.0)	**0.02**
Scar burden (%), median (IQR)	0.0 (0.0, 3.0)	0.0 (0.0, 2.0)	2.0 (0.0, 3.5)	**0.001**
Composite end-point, *n* (%)	42 (17.4%)	9 (9.7%)	33 (22.3%)	**0.01**
Death, *n*	25	8	17	
Heart transplant, *n*	8	1	7	
LVAD, *n*	9	0	9	

Bold letters suggest a significant *P*-value <0.05.
IQR, interquartile range; BMI, body mass index; NYHA, New York Heart Association; CKD, chronic kidney disease (GFR < 60 mL/min); ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; LV, left ventricle; EDVI, indexed end-diastolic volume; ESVI, indexed end-systolic volume; EF, ejection fraction; LAVI, indexed left atrial volume; RV, right ventricle; MRV, mitral regurgitation volume; MRF, mitral regurgitation fraction; LGE, late gadolinium enhancement; LVAD, left ventricular assist device.

respiration and hepatic venous flow were used to estimate the right atrial pressure.[14] An estimated sPAP ≥ 40 mmHg was defined as significant pulmonary hypertension.

Outcomes

The main objective of the study was to determine the correlates of RVD, which was defined as RVEF < 45%.[15] Clinical outcome data on death, heart transplantation, or left ventricular assist device (LVAD) implantation at follow-up were also collected. Clinical outcome data were tracked by annual phone interviews with participants or review of available medical records/contact with the referring clinic. The last date of end-point collection was 30 September 2019. Follow-up was curtailed at 8 years due to scarcity of patients beyond this point.

Statistical analysis

Continuous variables were expressed as mean with standard deviation or median with interquartile range (IQR) depending on the normality of distribution. Student's *t*-test was used to compare means, and Mann–Whitney *U* test was used to compare medians. Categorical variables were expressed as absolute numbers along with their percentages and compared using χ^2 test. Univariable and multivariable binomial logistic regression was performed to determine the factors associated with RVD (<45%). Freedom from composite event was depicted by the Kaplan–Meier curves and stratified by RVEF ≥45% vs. <45%. Differences between groups were compared by the log-rank test.

Cox proportional hazard modelling was performed to determine the characteristics associated with the composite events. MRvol and MRF were introduced as continuous as well as categorical variable in separate logistic regression models. The selection of covariates for the multivariable models was based on both the clinical importance and the least absolute shrinkage and selection operator method with the cross-validation selection option.[16] Collinearity was tested between variables by performing collinearity diagnostics using variance inflation factor. An interaction test was also performed between RVD and MRF (≥30%) for composite events as there was an association between these two variables. The performance of the models was determined by the C-statistic. As recent studies[17,18] have shown that secondary MR carries an increased risk of poor prognosis even at lower volumes, we determined optimal cut-offs of MRvol and MRF related to RVD by receiver operating characteristic curve and Youden index. Pearson correlation test was used to determine correlation coefficient (*R*) between LVEF and RVEF. All the analyses were performed on Stata version 16.1 (StataCorp LLC, College Station, TX, USA). A *P*-value of <0.05 was considered statistically significant.

Results

The patient flow diagram is shown in *Figure 1*. Of the 241 in the study cohort, 148 (61%) had RVD (RVEF <45%). The baseline characteristics of the study cohort along with those with and without RV dysfunction are listed in *Table 1*. The patients with RVD were younger [52 (40–62) years vs. 59 (47–66) years] and more often male (62% vs. 38%). Among the imaging parameters, patients with RVD had larger LV and RV volumes, lower LVEF and LV stroke volume, higher LAV, and higher prevalence of LGE and larger median LV scar extent. Six patients had mitral valve intervention at follow-up (four surgical valve repair and two percutaneous clips).

Secondary MR and RV dysfunction

Patients with RVD had higher median MRvol [23 mL (IQR 16–31 mL) vs. 18 mL (IQR 12–25 mL), $P = 0.002$) and MRF [33% (IQR 25–43%) vs. 22% (IQR 15–29%), $P < 0.001$] in comparison with those without RVD. In multivariable analyses, both MRvol and MRF as a continuous variable were associated with increased odds of RVD with OR 1.05 (95% CI 1.01–1.10, $P = 0.01$) and OR 1.09 (95% CI 1.04–1.14, $P < 0.001$), respectively. In the study cohort, the optimal threshold of MR parameters that was related to RVD was MRvol ≥ 24 mL (sensitivity 49% and specificity 72%) and MRF ≥ 30% (sensitivity 62% and specificity 76%). Using these cut-offs, both MRvol ≥ 24 mL (OR 2.44, 95% CI 1.40–4.26, $P = 0.002$) and MRF ≥ 30% (OR 5.30, 95% 2.96–9.49, $P < 0.001$) were associated with higher odds of RVD. These associations persisted even after adjusting for other clinical and imaging covariates in multivariable analysis: MRvol ≥ 24 mL (OR 3.57, 95% CI 1.45–8.79, $P = 0.01$) and MRF ≥ 30% (OR 5.46, 95% CI 2.23–13.25, $P < 0.001$). The details of univariable and multivariable analyses are listed in *Table 2*. Among other parameters associated with RVD were male sex, LV mass, and LVEF and LAV.

Since LVEF is strongly correlated with RVEF ($R = 0.74$, $P < 0.001$), we further interrogated if increasing MRF (tertiles) is associated with impairment of RV function among different strata of LV dysfunction (tertiles of LVEF). The results are demonstrated in *Figure 2*. With increasing degree of secondary MR, increasing proportion of RVD was observed across all three tertiles of LVEF. The overall trend for the increasing RVD was significant between the different groups ($P < 0.001$).

Secondary MR and relationship with pulmonary artery pressure

Subgroup analysis was performed on patients with available data on pulmonary artery pressures using echocardiography. Data on sPAP were available in 96 (40%) patients within the ±30 days interval of CMR. Of these, 69 patients (72%) had sPAP ≥ 40 mmHg. Patients with MRF ≥ 30% had significantly higher proportion of patients with sPAP ≥ 40 mmHg in comparison with those with MRF < 30% (81% vs. 61%, $P = 0.04$). Moreover, in comparison with patients with sPAP < 40 mmHg, those with sPAP ≥ 40 mmHg had higher number of patients with RVD (86% vs. 59%, $P = 0.01$).

RV dysfunction and outcome

During the median follow-up period of 3.4 years (IQR 2.2–5.9 years), 42 (18%) patients suffered an adverse event of all-cause mortality ($n = 25$), LVAD implantation ($n = 9$), or heart transplantation ($n = 8$). Patients with RVD (<45%) had increased incidence of events compared with those without RV dysfunction (≥45%): 19% vs. 8% ($P = 0.03$). Increasing RVEF was independently associated with a lower risk of adverse events (adjusted HR 0.98; 95% CI 0.95, 1.00; $P = 0.047$). When stratified using a cut-off of 45%, RVD (RVEF < 45%) was associated with increased risk of events (log-rank $P = 0.046$; *Figure 3*). The interaction test between MRF (≥30%) and presence of RVD for outcome was not significant ($P = 0.61$). Detailed univariable and multivariable data of Cox regression are presented in *Table 3*. Due to high degree of collinearity between LVEF and RVEF (variance inflation factor of 22), LVEF was not introduced in the same multivariable model. A separate multivariable model demonstrates that LVEF was also significantly associated with events. However, there was no significant difference in the outcome discrimination between the two models with a C-statistic difference of 0.01 (95% CI −0.03, 0.05; $P = 0.59$).

Discussion

These single-centre data utilizing CMR demonstrate that secondary MR severity is associated with RVD among patients with NICM. Although RVD is strongly associated with LV dysfunction, increasing severity of secondary MR is associated with increasing prevalence of RVD across different degrees of LV dysfunction. Furthermore, the current study demonstrates a higher sPAP among patients with more severe secondary MR explaining the possible mechanism of RVD in patients with NICM.

In a recent study among patients with ICM ($N = 560$, mean LVEF 24 ± 10%), it was demonstrated that patients with significant secondary MR [effective regurgitant orifice area (ERO) ≥0.2] had a lower RVEF in comparison with those without significant MR.[11] Moreover, they found that increasing severity of MR by ERO was associated with declining RVEF.[11] However, NICM patients are a completely different subset of the population, and the results of ICM cannot be elaborated directly on these patients. It was demonstrated previously that, compared with ICM, NICM more frequently involves the RV causing its dysfunction.[8–10]

La Vecchia *et al.*[8] studied 153 patients comprising ICM ($n = 61$) and NICM ($n = 92$) patients and found that NICM patients had nearly 50% higher incidence of RVD despite both groups having similar LVEF. They further demonstrated that NICM patients may have RVD without associated pulmonary hypertension. This supports the hypothesis that NICM may have RVD due to a global cardiomyopathy process that affects both the LV and the RV.

A study investigated the correlates of RV dysfunction using CMR in a large series of NICM patients ($n = 423$).[19] They found that the strongest correlate was LVEF.[19] Similarly, our study also demonstrates that RVD is strongly related to the degree of LV dysfunction among patients with NICM. Despite this, secondary MR seems to have an additional impact on RV systolic function independent of LVEF. Although it was previously theoretically assumed, this is the first study to demonstrate it. We observed increasing prevalence of RVD with increasing severity of secondary MR across different degrees of LV dysfunction. This demonstrates that secondary MR severity has an impact on RVD, and it is not all related to the underlying molecular mechanism causing the LV dysfunction.

Primary MR is different than secondary MR as it results in a larger regurgitant volume and hence higher volume overloading of the LV and LA along with a higher LV end-diastolic pressure resulting in higher pulmonary artery pressure.[20] It has been shown that RV systolic function is inversely related to the increased pulmonary pressure, which is directly related to the severity of primary MR.[21,22] Moreover, RVD is shown to be reversible in patients with primary MR and improves after valvular corrective surgeries.[23] However, this concept cannot be directly applied to patients with secondary MR, since patients with HF and secondary MR can have higher filling pressure and pulmonary artery pressure due to the LV systolic dysfunction itself. The current study demonstrates that despite small MRvol, secondary MR does impact the pulmonary artery pressure and cause RVD independent of the LV systolic function.

Clinical implications

In patients with secondary MR, RVD has not been a focus of previous studies. This was mainly due to a lack of treatment options for secondary MR. However, more recently, the COAPT trial demonstrated that transcatheter mitral valve edge-to-edge repair led to a 60% reduced risk of HF hospitalization and 38% reduced risk of all-cause mortality in

Table 2 **Factors associated with RVEF (≤45%)—univariable and multivariable logistic regression ($n = 241$)**

	Univariable		Multivariable (continuous MRV)		Multivariable (MRV ≥/<24 mL)		Multivariable (continuous MRF)		Multivariable (MRF ≥/<30%)	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age (years)	0.97 (0.96, 0.99)	0.01	0.99 (0.96, 1.02)	0.48	0.98 (0.96, 1.01)	0.30	0.98 (0.95, 1.01)	0.22	0.99 (0.96, 1.01)	0.32
Male gender	2.72 (1.59, 4.65)	**<0.001**	3.89 (1.62, 9.31)	**0.002**	4.19 (1.73, 10.16)	0.002	6.45 (2.43, 17.15)	**<0.001**	5.32 (2.10, 13.47)	**<0.001**
Hypertension	0.82 (0.48, 1.39)	0.46	1.59 (0.61, 4.14)	0.34	1.77 (0.67, 4.66)	0.25	1.49 (0.56, 4.00)	0.43	1.34 (0.50, 3.56)	0.56
Diabetes	0.73 (0.38, 1.39)	0.34	0.66 (0.24, 1.81)	0.42	0.71 (0.25, 1.96)	0.50	0.66 (0.23, 1.88)	0.44	0.66 (0.23, 1.85)	0.43
ACEI/ARB	1.63 (0.96, 2.75)	0.07	0.88 (0.39, 1.99)	0.76	0.83 (0.37, 1.89)	0.66	0.89 (0.38, 2.07)	0.79	0.84 (0.36, 1.94)	0.68
Diuretics	5.44 (3.04, 9.76)	**<0.001**	2.04 (0.85, 4.88)	0.11	2.08 (0.86, 5.01)	0.10	1.89 (0.76, 4.69)	0.17	2.02 (0.81, 5.00)	0.13
LV mass index (mg/m^2)	1.02 (1.01, 1.03)	**0.001**	0.97 (0.95, 0.99)	**0.01**	0.97 (0.95, 0.99)	**0.01**	0.97 (0.95, 0.99)	**0.01**	0.98 (0.96, 1.00)	**0.02**
LVEF (%)	0.84 (0.81, 0.88)	**<0.001**	0.82 (0.77, 0.87)	**<0.001**	0.82 (0.77, 0.87)	**<0.001**	0.83 (0.78, 0.88)	**<0.001**	0.83 (0.78, 0.88)	**<0.001**
LAVI (mL/m^2)	1.04 (1.03, 1.06)	**<0.001**	1.02 (1.00, 1.04)	**0.04**	1.02 (1.00, 1.04)	**0.02**	1.02 (1.00, 1.04)	0.06	1.02 (1.00, 1.04)	**0.03**
MRV (mL)	1.04 (1.01, 1.06)	**0.003**	1.05 (1.01, 1.10)	**0.01**						
MRV ≥24 (mL), *n* (%)	2.44 (1.40, 4.26)	**0.002**			3.72 (1.49, 9.30)	**0.01**				
MRF (%)	1.08 (1.05, 1.11)	**<0.001**					1.09 (1.04, 1.14)	**<0.001**		
MRF ≥30 (%), *n* (%)	5.30 (2.96, 9.49)	**<0.001**							5.60 (2.27, 13.79)	**<0.001**
LGE	1.88 (1.11, 3.20)	**0.02**	0.90 (0.38, 2.14)	0.82	0.77 (0.32, 1.86)	0.56	0.85 (0.34, 2.12)	0.73	0.78 (0.32, 1.90)	0.59
			C-statistic = 0.92		**C-statistic = 0.92**		**C-statistic = 0.93**		**C-statistic = 0.92**	

Bold letters suggest a significant *P*-value <0.05.
LV, left ventricle; EF, ejection fraction; MRV, mitral regurgitation volume; MRF, mitral regurgitation fraction; LGE, late gadolinium enhancement; LAVI, indexed left atrial volume; ACEI, angiotensin-converting enzyme inhibitors; ARB, aldosterone receptor blocker; OR, odds ratio; CI, confidence interval.

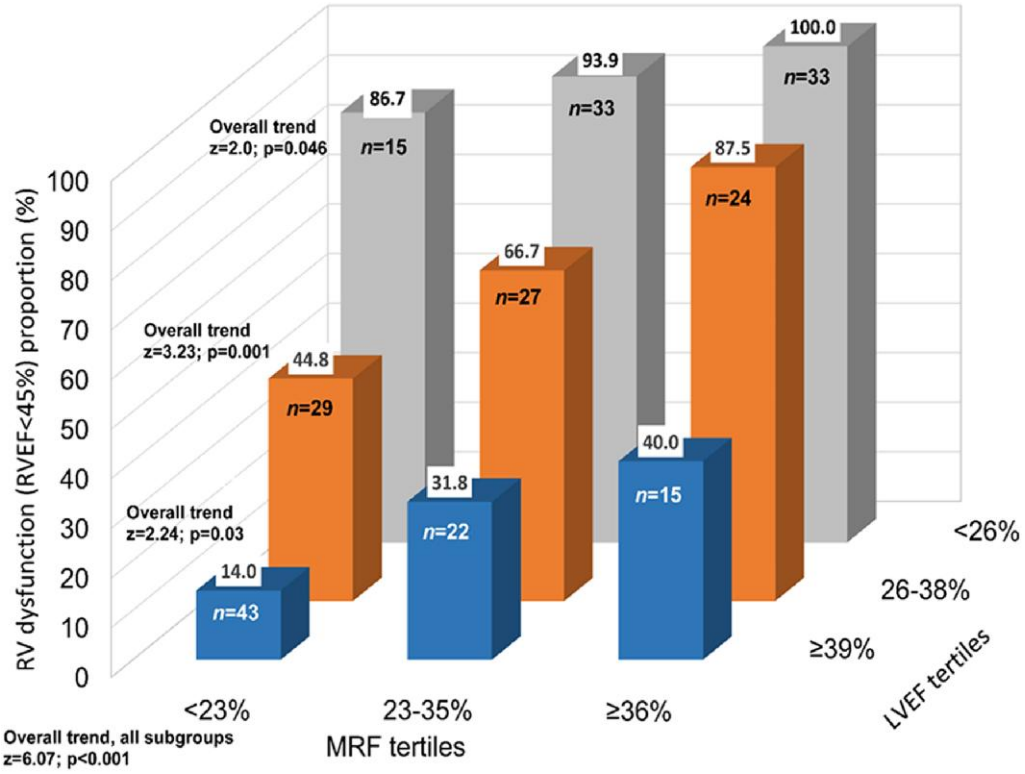


Figure 2 Impact of secondary MR on RV dysfunction across different severity of LV dysfunction. Bar diagram showing the prevalence of RVD (<45%) with increasing severity (tertiles) of mitral regurgitation fraction across different tertiles of LVEF. RVEF, right ventricular ejection fraction; RV, right ventricle; MRF, mitral regurgitation fraction; LVEF, left ventricular ejection fraction.

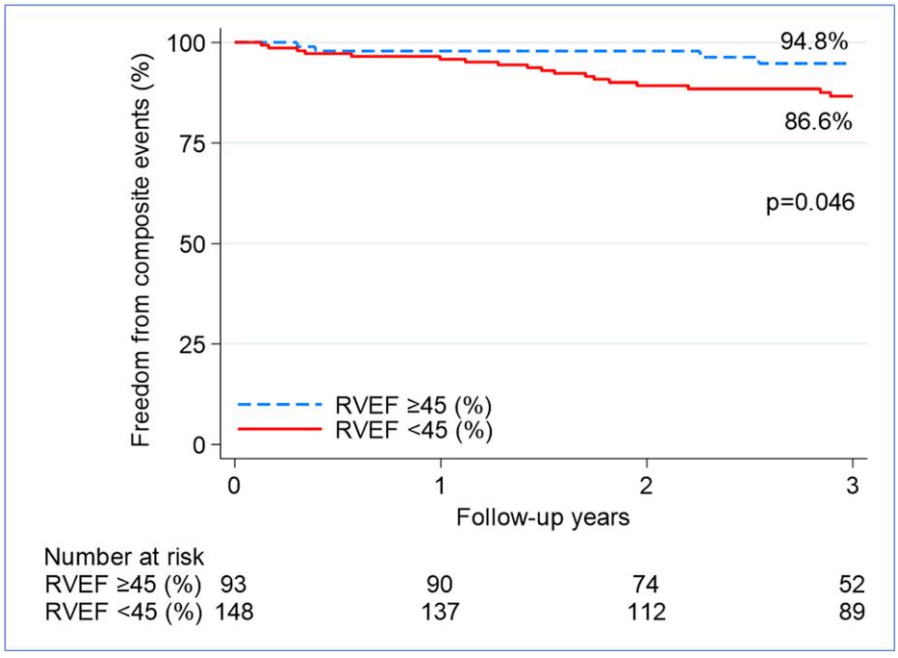


Figure 3 Prognostic significance of RV dysfunction. Kaplan–Meier curve showing the comparative freedom from composite events of death, LVAD implantation, or heart transplantation among total population divided based on RVD (45% cut-off). RVEF, right ventricular ejection fraction.

Table 3 Univariable and multivariable Cox regression analyses for the factors associated with study outcome

	Univariable		Multivariable, Model 1[a]		Multivariable, Model 2[a]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years), median (IQR)	1.00 (0.98, 1.02)	0.95	1.00 (0.98, 1.02)	0.99	1.00 (0.98, 1.03)	0.96
Male gender	1.31 (0.71, 2.42)	0.39				
Hypertension, *n* (%)	1.49 (0.78, 2.83)	0.22				
Diabetes, *n* (%)	1.17 (0.56, 2.44)	0.68				
CKD, *n* (%)	1.61 (0.81, 3.20)	0.18	1.88 (0.91, 3.90)	0.09	1.85 (0.89, 3.84)	0.10
Diuretics, *n* (%)	2.85 (1.20, 6.77)	**0.02**				
LV ESVI (mL/m^2), median (IQR)	1.01 (1.00, 1.01)	0.04				
LV mass index (mg/m^2), median (IQR)	1.01 (0.99, 1.02)	0.31				
LVEF (%), median (IQR)	0.96 (0.93, 0.99)	**0.01**			0.96 (0.93, 0.99)	**0.02**
LAVI (mL/m^2), median (IQR)	1.01 (1.00, 1.02)	0.07				
RVEF (%), median (IQR)	0.98 (0.96, 1.00)	**0.04**	0.98 (0.95, 1.00)	**0.047**		
MRV ≥24 (mL), *n* (%)	1.02 (0.56, 1.88)	0.94				
MRF ≥30 (%), *n* (%)	1.69 (0.90, 3.15)	0.10				
Scar burden (%), median (IQR)	1.06 (1.03, 1.09)	**<0.001**	1.06 (1.03, 1.09)	**<0.001**	1.06 (1.03, 1.09)	**<0.001**
C-statistic (95% CI)			0.67 (0.59, 0.76)		0.68 (0.60, 0.77)	
Discrimination improvement (95% CI)					0.01 (−0.03, 0.05); $P = 0.59$	

Bold letters suggest a significant *P*-value <0.05.
CKD, chronic kidney disease; LV, left ventricle; ESVI, indexed end-systolic volume; EF, ejection fraction; LAVI, indexed left atrial volume; RV, right ventricle; MRV, mitral regurgitation volume; MRF, mitral regurgitation fraction.
[a]Model 1 includes RVEF and Model 2 includes LVEF.

patients with secondary MR.[24] This study has resulted in a paradigm shift in the management of secondary MR, necessitating a deeper understanding on the implications of secondary MR among which include the effect of secondary MR on RVD. A sub-study of the COAPT trial showed that advanced RVD at baseline was a marker of poor prognosis even among patients randomized to device therapy.[25] Our study shows that secondary MR despite its lower MRvol has an impact on RV systolic function among patients with NICM. Not all RVD in NICM is solely related to the advanced cardiomyopathy process.

While the study may not immediately change clinical practice, it sheds light on several clinically relevant aspects. First, it demonstrates a clear link between secondary MR and RVD in NICM patients, suggesting that addressing MR may play a role in managing RVD in this population. This finding could inform treatment decisions for NICM patients with secondary MR, potentially favouring interventions like TEER that address both issues. Secondly, the study highlights the prognostic significance of RVD in NICM, potentially allowing for improved risk stratification and patient management. Identifying patients with RVD could help healthcare professionals prioritize interventions and monitor these patients more closely. Furthermore, the study lays the groundwork for future research with more direct clinical applications. Understanding the mechanisms underlying the MR–RVD link could pave the way for the development of targeted therapies specifically aimed at preventing or managing RVD in NICM patients. We believe that these findings, while not immediately practice changing, offer valuable insights that can contribute to the advancement of clinical knowledge and the development of future therapeutic strategies for NICM patients with secondary MR.

Limitations

This is an observational study from a single centre. The findings of the study need to be confirmed in a larger multicentre cohort. In the current study, we specifically excluded aetiologies such as sarcoidosis and amyloidosis that can directly involve the RV; however, there can still be other idiopathic aetiologies that may cause RV involvement. Moreover, patients with prior cardiac devices like pacemaker and defibrillators were excluded due to the interaction of these devices with the image quality that may limit the accurate quantification of secondary MR. Only a subgroup of patients had the estimated sPAP echocardiographic data available for analysis of the effect of pulmonary hypertension of RVD in our patient cohort. A larger data set including non-invasive pulmonary pressure assessment as well as invasive right heart catheterization data could have provided more convincing insight into the mechanism of RVD in our patient cohort. Nonetheless, this study provides novel data on the impact of secondary MR on RVD in patients with NICM.

Conclusion

In this prospective cohort of patients with NICM and reduced LVEF, where CMR is utilized to quantify secondary MR and RV function, it is demonstrated that secondary MR is independently associated with increased prevalence of RVD among patients with NICM—this is prognostically important. RVD among NICM patients is not always related to the inherent cardiomyopathy process affecting the LV, but may also be affected by the degree of secondary MR.

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Conflict of interest: None declared

Data availability

Because of confidentiality issues, data sets and study materials are safeguarded by the Houston Methodist Research Institute and cannot be made available to outside parties.

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