European Heart Journal - Imaging Methods and Practice (2025) **3**, qyaf021
https://doi.org/10.1093/ehjimp/qyaf021

ORIGINAL ARTICLE

Sex differences in cardiac remodelling in ischaemic cardiomyopathy and functional mitral regurgitation: impact on prognosis

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Received 1 October 2024; accepted after revision 8 February 2025; online publish-ahead-of-print 19 March 2025

Abstract

Aims

Sex differences in prognosis of functional mitral regurgitation (FMR) associated with ischaemic cardiomyopathy (ICM) demonstrate the need to identify sex differences in cardiac remodelling. This study aimed to characterize sex differences in cardiac remodelling associated with FMR in the setting of ICM, sex interactions with cardiac remodelling and FMR severity, and predictors of all-cause mortality or heart transplantation using cardiac magnetic resonance (CMR) imaging.

Methods and results

Consecutive patients with ICM referred to CMR between 2002 and 2017 were reviewed. Eligible 790 patients [mean age: 62.0 (standard deviation = 11.2] years and 24.7% females] were evaluated over a median follow-up of 5.8 years. There were 773 subjects with complete data for survival analysis, with 449 primary events. Coronary artery disease risk factors, medications, and previous coronary revascularization were similar in females and males (all $P > 0.05$). Indexed left ventricular and right ventricular (LV and RV) volumes were larger in males ($P <$ or =0.005 for all comparisons) with similar slope of increasing LV and RV volumes in the setting of increasing FMR (all $P > 0.05$, for interactions). However, indexed left atrial volume was similar in males and females ($P = 0.696$), after adjusting for FMR severity. After adjusting for medical risk factors and post-CMR procedural interventions, females demonstrated increased risk of primary clinical composite point with enlarging LV volumes [hazard ratio: 1.04 (95% confidence interval: 1.01–1.06), $P = 0.034$].

Conclusion

Because females with increasing LV size and FMR severity demonstrated significantly increased risk of adverse outcomes, our findings suggest the importance of deriving sex-specific CMR selection criteria for therapeutic management of FMR in the setting of ICM.

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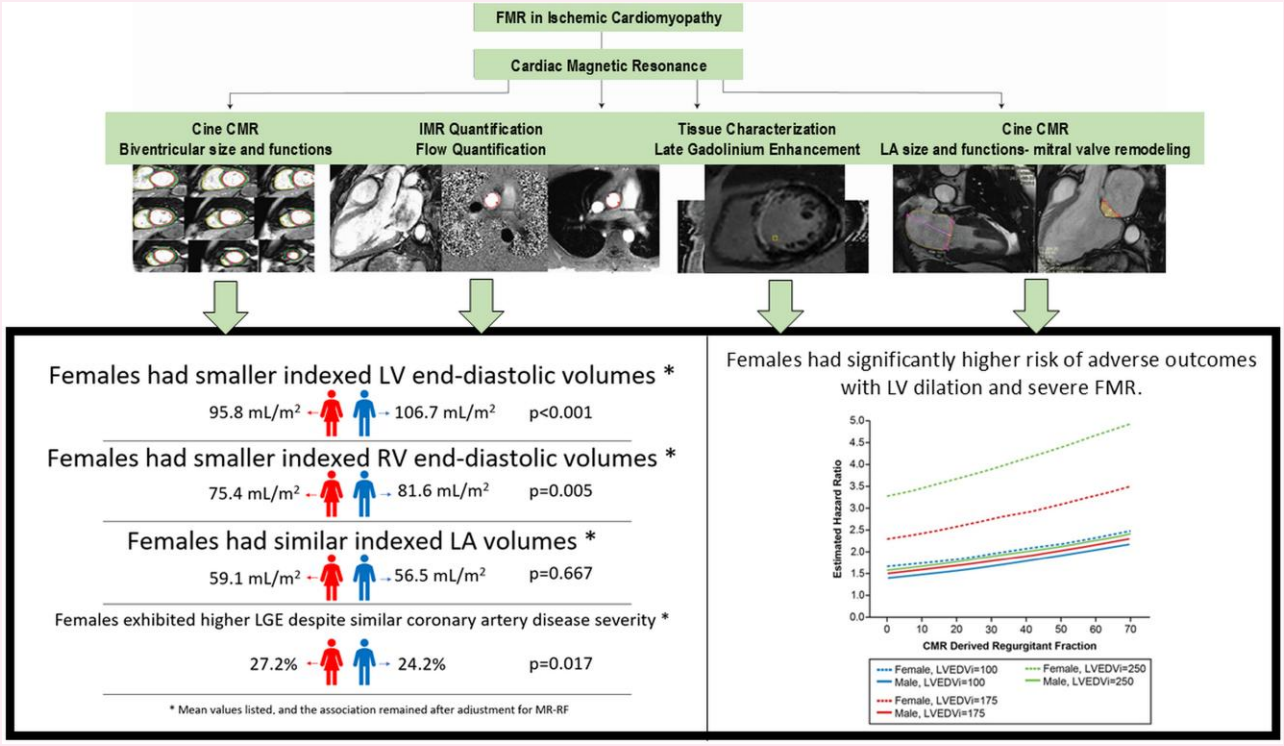
Graphical Abstract



Key findings of the current study. CMR imaging provides comprehensive assessment of functional mitral regurgitation in ischaemic cardiomyopathy and enables the ability to discern sex differences in remodelling. CMR, cardiac magnetic resonance; IMR, ischaemic mitral regurgitation; LV, left ventricular; LVEDV, LV end-diastolic volume; RV, right ventricular.

Keywords functional mitral regurgitation • coronary artery disease • ischaemic heart disease • cardiac magnetic resonance imaging • echocardiography • gender

Introduction

Functional mitral regurgitation (FMR) in ischaemic cardiomyopathy (ICM) is primarily caused by left ventricular (LV) remodelling and sub-valvular dysfunction after ischaemic injury and is the most common form of FMR.[1] The presence of FMR is associated with a poor prognosis, even when the FMR is mild,[2,3] and the risk increases significantly as the severity of FMR worsens.[3–7] Additionally, FMR contributes to progressive, maladaptive LV remodelling, which often leads to heart failure (HF) events.[6,7]

Although few studies have examined sex differences in the prognosis of FMR in ICM,[8] most have included patients with both ischaemic and non-ischaemic causes of mitral regurgitation.[9–11] With the increasing use of cardiac magnetic resonance (CMR) imaging to assess FMR[12,13] and its advantages over echocardiography (ECHO),[14,15] we aimed to explore sex differences in cardiac remodelling and function in response to FMR using CMR in a population with ICM. We hypothesized that these sex-related differences in cardiac remodelling would be linked to distinct survival outcomes.

Methods

Study population

This retrospective cohort study reviewed consecutive ICM patients who were referred for CMR between 2002 and 2017 ($n = 1071$). ICM was defined as LV dysfunction [LV ejection fraction (LVEF) ≤50%] with evidence of obstructive coronary artery disease (CAD, defined by >70% stenosis in one or more epicardial coronary artery on angiography). Patients with acute myocardial infarction at the time of coronary angiography were excluded. Clinical data were collected through medical chart review, and medication use was recorded within 6 months of the CMR. The primary composite clinical endpoint was all-cause mortality or heart transplantation. Deaths were confirmed through death certificates, online obituaries, or verification with family members. The study was approved by the Institutional Review Board, which waived individual consent, and conducted in accordance with the Helsinki Declaration.

CMR assessment

CMR examinations were performed on 1.5 and 3 Tesla magnetic resonance imaging scanners (Sonata and Avanto, Siemens Medical Solutions, for imaging between 2002 and 2006, and Philips Achieva XR/Ingenia, for imaging between 2007 and 2017). These scanners used a maximum gradient strength of 40–45 mT/m and a maximum slew rate of 200 T/m per second with electrocardiographic gating. Ventricular chamber measurements were obtained from short-axis cine images, following established guidelines.[16] Left atrial (LA) endocardial borders were manually traced in apical two- and four-chamber views, just after mitral valve (MV) closure and immediately before MV opening, to estimate minimal and maximal LA volumes (LAVs), respectively, using the biplane area-length method.[17] LA emptying fraction (LAEF) was calculated as (maximal LAV−minimal LAV)/maximal LAV × 100%.

MV geometry variables, including the mitral annular diameter (MAD), MV tenting area (MVTa), and MV tenting height (MVTh), were measured as described previously and indexed to body surface area (BSA).[18,19] MR quantification was based on the regurgitant fraction (MR-RF), calculated using the formula: (LV stroke volume minus aortic phase contrast forward flow)/LV

stroke volume.[12] Late gadolinium enhancement (LGE) images were acquired in long- and short-axis views, 10–15 min after the injection of 0.2 mmol/kg gadolinium dimeglumine. LGE was identified as areas with signal intensity >2 standard deviations (SDs) above the user-defined viable myocardium and was quantified as a percentage of the total LV myocardium (infarct mass divided by total LV mass).[18] The peri-infarct area was characterized as regions with signal intensity of 2–3 SDs higher than the user-specified myocardium.[18] Image analysis was performed using third-party post-processing software (cvi42, Circle Cardiovascular Imaging Inc, Calgary, Canada).

Statistical analysis

Data were presented as mean ± SD, median (inter-quartile range), or absolute number and percentages. Sex differences in imaging biomarkers were assessed using Wilcoxon two-sample tests and χ^2 tests. Linear regression models were built to assess the relationships, with indexed LV end-diastolic volume (LVEDVi) (or other markers) as the dependent variable and MR-RF, sex, their interaction, and a quadratic term for MR-RF (if statistically significant) as the independent variables.

Cox proportional hazards regression models were constructed to test sex and its interactions with LGE, MR-RF, and LVEDVi as predictors of primary clinical endpoint. A medical risk score from a previous study,[20] which included age, sex, body mass index, diabetes mellitus, glomerular filtration rate, hypertension, dyslipidaemia, medications (beta-blocker and angiotensin-converting enzyme inhibitor/receptor blocker), and an interaction term for sex and diabetes mellitus, was modified for this study by removing sex and the interaction between sex and diabetes mellitus, while including sex as a main effect in the Cox regression model.

The following variables were adjusted for in the multivariable Cox models: treatment group (medical vs. revascularization), the modified medical risk score as described above, incomplete revascularization, LGE, MR-RF, implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT), pre-CMR coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), post-CMR MV repair, LVEDVi, and indexed MVTh. As in the previous model,[20] we included the interaction between LGE and MR-RF, considering LGE and MR-RF as both continuous and categorical (i.e. LGE of ≤15, 16–29, and ≥30%; MR-RF of <35 and ≥35%) variables. The interactions of sex with LGE, MR-RF, and LVEDVi were then tested using a Wald test, with a significance level set at 0.05.

Statistical analysis was performed using SAS 9.4 (SAS Institute Inc. 2013, Cary, NC, USA) and IBM SPSS Statistics 23 (IBM SPSS Statistics for Windows, Version 23.0. 2016, Armonk, NY, USA: IBM Corp.), with a significance level of 0.05.

Results

Study population

Of the 1071 patients who underwent CMR, 790 patients met the inclusion criteria. A total of 281 patients were excluded from the original

Table 1 Clinical characteristics of the study population stratified by sex

	Males (*N* = 595)	Females (*N* = 195)	*P*-value
Baseline clinical characteristics			
Age, mean (SD), years	62.2 ± 10.8	61.5 ± 12.3	0.858
Body mass index, mean (SD), kg/m^2	29.0 ± 5.4	28.6 ± 6.8	0.099
Glomerular filtration rate, mean (SD), mL/min/1.73 m^2	81.6 ± 35.1	83.0 ± 40.5	0.893
Diabetes mellitus, *n* (%)	230 (38.7%)	70 (35.9%)	0.491
Hypertension, *n* (%)	334 (56.1%)	111 (56.9%)	0.847
Dyslipidaemia, *n* (%)	333 (56.0%)	101 (51.8%)	0.310
CAD severity[a], *n* (%)			0.088
1	173 (30.2%)	72 (37.3%)	
2	178 (31.0%)	65 (33.7%)	
3	209 (36.4%)	52 (26.9%)	
4	14 (2.4%)	4 (2.1%)	
Pre-CMR CABG/PCI, *n* (%)	264 (44.4%)	80 (41.0%)	0.414
Medical risk score, mean (SD)	0.692 ± 0.637	0.623 ± 0.711	0.356
Medications, *n* (%)			
Acetylsalicylic acid	534 (92.2%)	168 (89.4%)	0.220
Statin	474 (79.7%)	141 (72.3%)	0.077
ACEi/ARB	461 (77.5%)	143 (73.3%)	0.236
Beta-blocker	425 (71.4%)	146 (74.9%)	0.351
MRA	189 (31.8%)	58 (29.7%)	0.597
Furosemide	198 (33.3%)	68 (34.9%)	0.683
Post-CMR interventions, *n* (%)			
Post-CMR CABG	309 (51.9%)	79 (40.5%)	0.006*
Post-CMR PCI	27 (4.5%)	9 (4.6%)	0.964
Post-CMR MV surgery	116 (19.5%)	41 (21%)	0.642
Post-CMR ICD implantation	184 (31.0%)	57 (29.2%)	0.656
Post-CMR CRT implantation	53 (8.9%)	15 (7.7%)	0.599

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CMR, cardiac magnetic resonance imaging; CRT, cardiac resyncronization therapy; MRA, mineralocorticoid receptor antagonist.

[a]Coronary artery disease severity was graded according to the findings from the coronary angiography within 1 year of the CMR.

*A *P*-value of <0.05 demonstrates statistical significance.

cohort due to incomplete data, concomitant degenerative MV disease, missing aortic phase contrast imaging, poor quality CMR cine/LGE images, and mixed ICM/non-ICM aetiologies.

The mean age of the cohort was 62.0 (SD = 11.2) years, with 24.7% females. Clinical characteristics of the study population, stratified by sex, are shown in *Table 1*. There were no significant differences between males and females in terms of age, comorbidities, and medication use ($P > 0.05$). The proportions of males and females who had undergone revascularization prior to CMR were similar ($P = 0.414$), although more males underwent surgical revascularization following the index CMR ($P = 0.006$).

Biventricular remodelling and functions, assessed using CMR and stratified by sex, are summarized in *Table 2*. Females had significantly smaller indexed LV and right ventricular (RV) volumes (all $P < 0.05$), but demonstrated significantly higher LGE ($P = 0.017$), despite similar CAD severity ($P = 0.088$) and peri-infarct areas compared with males ($P = 0.063$). Females also had higher RV ejection fraction (RVEF) than males ($P = 0.002$), while LVEF was similar between sexes ($P = 0.489$).

MV and LA remodelling and function, also stratified by sex, are summarized in *Table 2*. Females had similar indexed MAD and MVTa compared with males ($P = 0.891$ and 0.740, respectively) but less MVTh ($P = 0.001$). Indexed LAV (LAVi) and LAEF were comparable between sexes ($P = 0.667$ and $P = 0.240$, respectively).

Table 2 Imaging characteristics of the study population stratified by sex on CMR

	Males (*N* = 595)	Females (*N* = 195)	*P*-value
Cardiac remodelling and functions			
Indexed LVEDV, mean (SD), mL/m^2	106.7 ± 45.5	95.8 ± 50.3	<0.001*
Indexed LV end-systolic volume, mean (SD), mL/m^2	139.6 ± 44.6	127.3 ± 50.2	<0.001*
Indexed LV mass, mean (SD), g/m^2	95.0 ± 41.2	79.7 ± 30.4	<0.001*
LVEF, mean (SD), %	25.7 ± 8.97	26.93 ± 9.59	0.489
Indexed RV end-diastolic volume, mean (SD), mL/m^2	81.6 + 28.2	75.4 + 27.4	0.005*
Indexed RV end-systolic volume, mean (SD), mL/m^2	49.2 ± 25.7	43.8 ± 24.9	0.002*
RVEF, mean (SD), %	41.9 ± 13.2	45.07 ± 14.90	0.002*
Indexed MAD, mean (SD), cm/m^2	1.70 ± 0.28	1.70 ± 0.28	0.891
Indexed MVTa, mean (SD), cm^2/m^2	0.81 ± 0.39	0.82 ± 0.40	0.740
Indexed MVTh, mean (SD), cm/m^2	0.57 ± 0.24	0.51 ± 0.21	0.001*
LAVi, mean (SD), mL/m^2	56.5 + 32.3	59.1 + 41.7	0.667
LAEF, median (IQR), %	36.8 (15.4)	35.2 (15.5)	0.240
LV LGE (2 SD), mean (SD), %	24.2 + 15.4	27.2 ± 15.5	0.017*
Peri-infarct area (2–3 SD), median (IQR),%	5.9 (3.2)	6.4 (3.5)	0.063
Mitral regurgitation severity			
Mitral regurgitant fraction, median (IQR), %	9.0 (25.0)	10.9 (29.8)	0.121

CMR, cardiac magnetic resonance imaging; IQR, inter-quartile range.
*A *P*-value of <0.05 demonstrates statistical significance.

Relationships of MR-RF with cardiac remodelling stratified by sex

Indexed LV and RV volumes increased with increasing MR-RF ($P < 0.001$ for all comparisons), with males having larger indexed LV and RV volumes ($P \leq 0.003$ for all comparisons). The difference in indexed cardiac volumes between men and women remained constant, unaffected by MR-RF values ($P = 0.379$, $P = 0.790$, $P = 0.378$, and $P = 0.158$, respectively, for interactions) (*Figure 1*). Although LAVi also increased with increasing MR-RF ($P < 0.001$), after adjusting for FMR severity, LAVi was similar in males and females ($P = 0.696$), with no significant interaction between MR-RF and sex in the relationship of MR-RF with LAVi ($P = 0.812$) (*Figure 2*).

There was no significant relationship between MR-RF and LGE ($P = 0.471$). After adjusting for MR-RF, females had slightly higher LGE compared with males ($P = 0.020$), with no interaction between MR-RF and sex in the relationship of MR-RF with LGE ($P = 0.958$). The relationship of MR-RF with MV geometry variables indexed by BSA and LV end-diastolic volume (LVEDV) is shown in Supplementary data online, Results and *Figures S1* and *S2*, respectively.

Relationships of MR-RF with cardiac functions stratified by sex

Patients with worse FMR had lower LVEF and RVEF and LAEF ($P < 0.001$ for all). There was a significant interaction between MR-RF and sex in the relationship of LVEF and RVEF, where females had significantly lower LVEF and RVEF in the presence of higher MR-RF ($P = 0.042$ and $P = 0.023$, respectively). However, LAEF was similar between sexes, after adjusting for MR-RF ($P = 0.746$), with no interaction between MR-RF and sex in the relationship with LAEF ($P = 0.979$) (*Figure 2*).

Outcomes assessment

Over a median follow-up of 5.8 years (range: 0 days to 19.4 years), there were 449 deaths or heart transplantations (females: 3 transplants, 113 deaths; males: 16 transplants, 317 deaths). The final Cox proportional hazards regression model to assess the effect of sex on the primary clinical composite endpoint suggested that after adjusting for medical risk factors and treatment, the following factors independently were associated with increased risk: incomplete revascularization, higher medical risk score, absence of an ICD, larger myocardial infarct size (higher LGE %), at least moderate LGE at high MR-RF, lower MVTh, larger LVEDVi, and females with larger LVEDVi (*Table 3*) (*Figure 3A*). Females not only demonstrated increased risk with enlarging LV volumes (*Figure 3B*) but also with increasing LV dilation and MR-RF severity compared with males (*Figure 3C*). However, the interactions between female sex and MR-RF or female sex and LGE were not statistically significant.

Discussion

Our large CMR study highlights sex differences in cardiac remodelling and their impact on outcomes in ICM. Key findings are as follows (*Graphical Abstract*): Despite consistently smaller LV/RV volumes, women demonstrated (i) larger amount of scar (LGE), (ii) similar MV geometry when indexed by BSA but greater degree of distortion

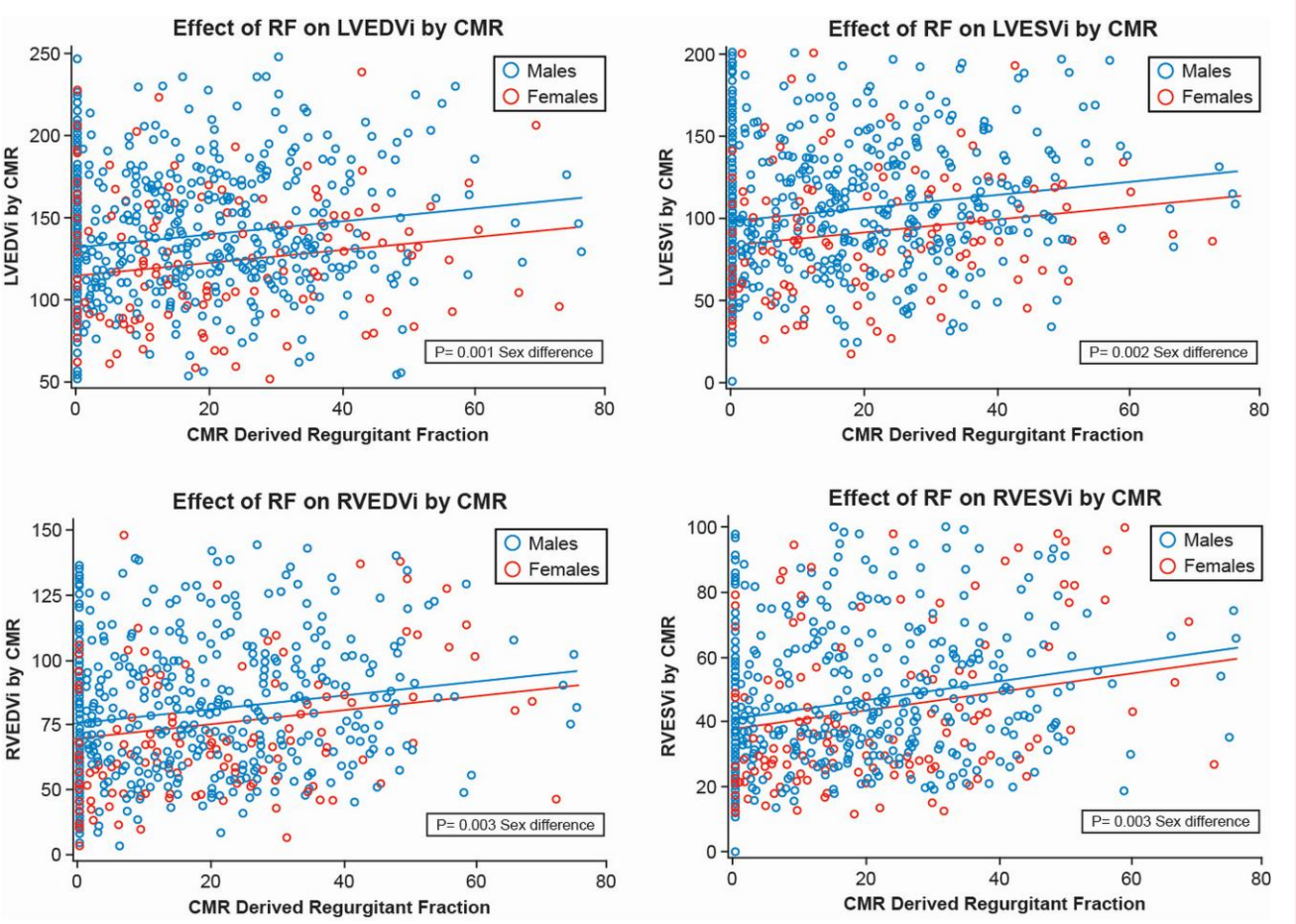


Figure 1 Distribution of indexed volumes and mitral regurgitation severity on CMR. Top row: LVEDVi by CMR (left) and LVESVi by CMR (right); bottom row: RVEDVi by CMR (left) and RVESVi by CMR (right) to severity of mitral regurgitation measured by CMR-derived RF by sex. CMR, cardiac magnetic resonance imaging; LVESVi, indexed LV end-systolic volume; RF, regurgitant fraction; RVEDVi, indexed RV end-diastolic volume; RVESVi, indexed RV end-systolic volume.

when indexed by LVEDV, (iii) similar LAVi and LAEF, and (iv) higher LVEF and RVEF in the absence of severe MR but lower LVEF and RVEF when MR-RF was severe. Our study also demonstrated sex differences in primary composite endpoint based on severity of LV dilation, where females with larger LVEDVi had increased risk of all-cause mortality or heart transplantation compared with males with similar LVEDVi, and the risk progressively increased with worsening FMR in ICM.

Previous CMR studies in healthy volunteers and acute myocardial infarction patients have consistently shown that females had smaller LV than males, even when indexed to body size.[21,22] LV size and mass were also found to be smaller in females on ECHO in the Cardiothoracic Surgical Trials Network study that evaluated 251 patients with severe ischaemic mitral regurgitation (IMR).[8] Findings from our large CMR study of patients with ICM add to the current body of knowledge by demonstrating a consistent continuum of smaller indexed LV volumes across increasing levels of FMR in females, even in the presence of increased LGE than men despite similar CAD severity. This blunted compensatory LV dilation in the setting of increased myocardial infarct size observed in females was accompanied with an increased distortion of MV geometries relative to LV size. Our study also demonstrated that while women with less severe FMR exhibited more preserved LV and RV systolic function than men, biventricular systolic dysfunction was significantly more pronounced in women with severe FMR, suggesting limited compensatory mechanisms in women.

Dilation and functional impairment in LA have been reported in ICM patients in observational studies[23–25] and study cohorts of FMR that also included subjects with non-ischaemic aetiology.[26] As previously demonstrated in the context of HF with lower ejection fraction[27] and after coronary artery bypass surgery,[28] females are likely to have relatively larger LAVi, compared with men, due to potentially higher LV filling pressures.[29] In our study, despite smaller LV and RV sizes, females had similar LAVi and MV geometry with increasing MR-RF, which indicates 'disproportionate' remodelling of the LA. Indeed, MV geometry variables being similar with males when indexed with BSA but being greater when indexed by LVEDV when adjusted for MR-RF suggest 'disproportionate' LA remodelling. Likewise, the degree of impairment shown in LAEF across the increasing severity of IMR was equivalent in females and males, emphasizing reduced LA functions in females

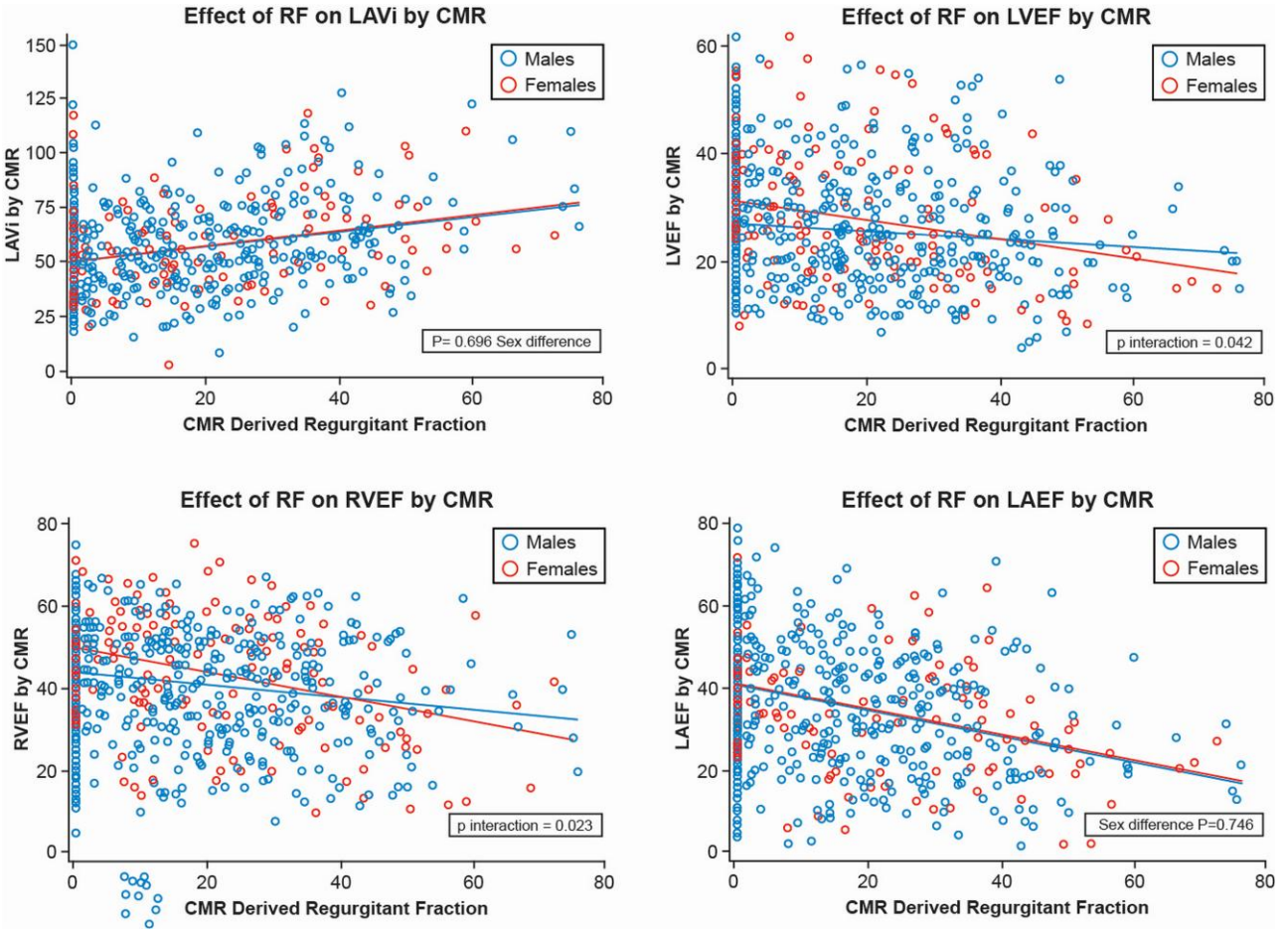


Figure 2 Distribution of cardiac functions and mitral regurgitation severity on CMR. Top row: LAVi by CMR (left) and LVEF by CMR (right); bottom row: RVEF by CMR (left) and LAEF by CMR (right) to severity of mitral regurgitation measured by CMR-derived regurgitant fraction by sex. CMR, cardiac magnetic resonance imaging; LAEF, LA emptying fraction.

even while impairment in LVEF and RVEF was not worse than in males until MR-RF reached the threshold of 40%.

Our study also identified LGE% and larger LVEDVi as strong predictors of increased risk over a median follow-up of 5.8 years. Notably, lower MVTh was linked to a higher risk of adverse events, possibly due to asymmetric tethering patterns in FMR.[30]

While there are limited data on sex differences in FMR outcomes in ICM,[8,9] our findings highlight how sex-specific cardiac remodelling in response to FMR severity impacts long-term outcomes. Females with larger LVEDVi showed a higher risk of mortality and heart transplantation compared with males with similar LV volumes. Furthermore, the risk increased progressively with worsening FMR. Interestingly, while MR-RF severity did not significantly interact with sex in predicting outcomes, LVEDVi was a more important determinant of adverse events in females. As LVEDVi increased beyond 100 mL/m^2, females had a significantly higher risk, and this risk was almost three times higher than in males when LVEDVi approached 200 mL/m^2. Moreover, even with normal LV size (LVEDVi = 100 mL/m^2), females had a higher rate of adverse events as MR-RF increased.

When we explored differences between males and females for various subgroups defined by LGE, RF, and LVEDVi, we found that females had a higher absolute risk than males when LGE $\leq$ 15 and LVEDVi ranged between 100 and 200. For example, when RF < 35%, the 1-year event rate for females was 30% compared with 11% for males; at 3 years, the event rates were 42 vs. 25%, respectively, and at 5 years, the event rates were 55 vs. 32%. In the subgroup with RF $\geq$ 35%, the differences in event rates between females and males were even more pronounced, though the sample size was small. This trend for higher absolute risk in females for low LGE and LVEDVi between 100 and 200 suggests the need for sex-specific therapeutic management strategies, but validation of this exploratory analysis is a critical next step.

This sex-specific and discordant impact of LV dilation on risk has significant implications on the current FMR selection criteria, defined by effective regurgitant orifice area/LVEDV ratio on ECHO for identifying patients likely to benefit from percutaneous MV therapeutic interventions.[15] The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) study showed that an enlarged LV adversely impacts mortality and HF hospitalizations.[31] However, Bartko *et al.*[32] revealed that 'disproportionate FMR' was linked with higher mortality, suggesting that outcomes

of valve-specific treatment is not only related with the severity of FMR but also with accompanying structural changes in the left atrium and the myocardium itself. In addition, studies that investigated sex differences in outcomes after MV surgery for severe IMR[8] or after MitraClip™ for FMR[10,11] demonstrated that although more females had 'disproportionate FMR' due to the presence of consistently smaller LV volumes, they did not demonstrate improved outcomes. Our data suggest that females should potentially be considered for more aggressive therapeutic intervention with smaller LV volumetric thresholds and possibly smaller MR-RF thresholds given that they have smaller LV sizes even after indexing to body size. Women also demonstrated more significant biventricular systolic dysfunction in the setting of severe FMR and demonstrated significantly higher risk of adverse outcomes with LV dilation and severe FMR. Furthermore, women in our study demonstrated disproportionately larger LAVi and decreased LAEF, suggesting that sex-specific LA size and mitral geometric thresholds should also be considered and developed in addition to sex-specific LV morphologic thresholds, in the evaluation of and derivation of optimized patient selection criteria for therapeutic management strategies for FMR.

Table 3 Final multivariable model for predicting primary composite clinical endpoint

Independent variables	Estimated HR (95% confidence interval)	*P*-value
Medical risk score	1.93 (1.64, 2.28)	<0.001*
LGE%		<0.001*
16–29 vs. ≤15%	1.10 (0.84, 1.43)	
≥30 vs. ≤15%	1.61 (1.25, 2.07)	
ICD	0.67 (0.53, 0.85)	0.001*
CRT	1.14 (0.81, 1.61)	0.449
Pre-CMR CABG/PCI	1.02 (0.84, 1.24)	0.869
MV repair/replacement	1.09 (0.85, 1.41)	0.498
Female sex	0.74 (0.42, 1.31)	0.308
LVEDVi (per 10 units)	1.05 (1.02, 1.08)	0.004*
Mitral RF ≥35%	0.84 (0.51, 1.39	0.507
MVTh	0.33 (0.13, 0.80)	0.014*
Treatment: revascularization	1.17 (0.94, 1.45)	0.157
Incomplete revascularization	1.38 (1.12, 1.68)	0.002*
Interaction of scar and RF[a]:		0.037*
Moderate (16–29%) vs. low (≤15%) LGE% at Low RF (<35%)	1.10 (0.84, 1.43)	
High (≥30%) vs. low LGE% at low RF	1.61 (1.25, 2.08)	
Moderate vs. low LGE% at high RF (≥35%)	1.95 (1.04, 3.67)	
High vs. low LGE% at high RF	3.63 (2.03, 6.53)	
LVEDVi (per 10 units) × female sex	1.04 (1.01, 1.06)	0.034*

RF, regurgitant fraction.
[a]<35 and >35% for RF; <15, 16–29, and >30% for scar.
*A *P*-value of <0.05 demonstrates statistical significance.

Study limitations

Our study is a single-centre, observational study with a relatively small proportion of females, though ischaemic aetiology is more common in males in FMR cohorts.[9] Second, sex differences in the management of CAD may have influenced the severity of ICM and FMR, potentially impacting our findings. As a referral centre, our cohort may represent a sicker patient profile. Fourth, the decision to perform CMR was at the discretion of the physician, and patients with contraindications were excluded, introducing possible selection bias. Also, including patients who underwent CMR within 1 year of the coronary angiography may have led to selection bias due to the dynamic nature of LV remodelling before and/or after the ischaemic insult. Additionally, our study population includes a spectrum of patients with varying degrees of MR-RF, not only those with at least moderate FMR; however, this is in accordance with the natural distribution of FMR severity as FMR is skewed towards lower severity.[33] Nevertheless, the ability to include a wide spectrum of FMR enables the ability to further evaluate correlates of FMR with sex-specific remodelling. Last, since follow-up data were collected until 2018, none of the patients had been eligible for mitral transcatheter edge-to-edge repair or recently approved HF medications (i.e. angiotensin receptor/neprilysin

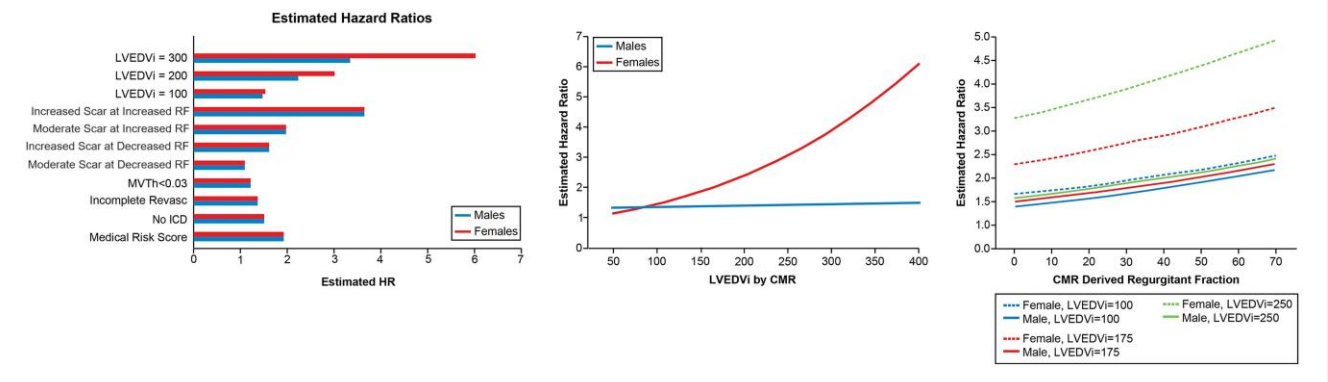


Figure 3 Multivariable Cox regression model to predict primary composite clinical endpoint. Estimated hazard ratios of significant predictors from final model (left), model-based estimated hazard ratios for the interaction of sex and LVEDVi (middle), and model-based estimated hazard ratios as a function of LVEDVi and severity of mitral regurgitation measured by CMR-derived RF (right). CMR, cardiac magnetic resonance imaging; HR, hazard ratio; RF, regurgitant fraction.

inhibitor or sodium–glucose cotransporter-2 inhibitors), which could influence outcomes.

Conclusion

CMR is a powerful imaging modality that provides comprehensive assessment of FMR in the setting of ICM and enables the ability to discern sex differences in remodelling. Our study reveals significant sex-specific differences in biventricular, MV geometry, and LA remodelling and function. While females had smaller indexed LV and RV volumes, they exhibited higher LGE, indicating more extensive myocardial fibrosis despite similar CAD severity. In addition, females demonstrated greater biventricular dysfunction in the presence of increasing MR-RF severity. Notably, females had a higher risk associated with larger LV volumes and worsening MR-RF compared with males. These findings suggest the importance of deriving sex-specific CMR selection criteria for more tailored therapeutic management to improve outcomes in FMR in ICM.

Supplementary data

Supplementary data are available at *European Heart Journal - Imaging Methods and Practice* online.

Consent

The need for written informed consent was waived by the institutional review board due to the retrospective study design.

Funding

This study was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health under 1R01HL170090-02 (grant recipient: D.H.K.).

Conflict of interest: W.H.W.T. is a consultant for Sequana Medical, Cardiol Therapeutics, Genomics plc, Zehna Therapeutics, Renovacor, Boston Scientific, WhiteSwell, Kiniksa Pharmaceuticals, CardiaTec Biosciences, and Intellia and has received honorarium from Springer Nature and American Board of Internal Medicine. Dr. D.H.K. is funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health under 1R01HL170090-02. D.H.K. also had a research agreement with Circle cvi42. The other authors have no conflict to declare.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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