ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 3539–3546
Published online 6 August 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13503

ORIGINAL RESEARCH ARTICLE

Sex differences in prognosis of significant secondary mitral regurgitation

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Abstract

Aims Secondary mitral regurgitation (MR) is more frequent in men than in women. However, little is known about differences in prognosis between men and women with secondary MR. The objective of this study is to investigate the sex distribution of secondary MR and the prognostic differences between sexes.

Methods Patients with significant secondary MR, of both ischaemic and non-ischaemic aetiologies, were identified through the departmental electronic patient files and retrospectively analysed. The primary endpoint was all-cause mortality.

Results A total of 698 patients (mean age 66 ± 11 years) with significant secondary MR were included: 471 (67%) men and 227 (33%) women. Ischaemic heart failure was significantly more common in men (61%), whereas non-ischaemic heart failure was more prevalent in women (63%). Women had significantly smaller left ventricular (LV) volumes when compared with men and more preserved LV systolic function when assessed with LV global longitudinal strain (GLS; 8.5 ± 4.1% vs. 7.5 ± 3.6%; $P = 0.004$). Women more often underwent surgical mitral valve repair (34%) when compared with men (26%), although no differences were observed for transcatheter mitral valve repair. During a median follow-up of 57 [interquartile range 29–110] months, 373 (53%) patients died. Women showed significantly lower mortality rates at 1-, 2- and 5-year follow-up (9%, 16% and 33% vs. 10%, 20% and 42%) when compared with men ($P = 0.001$).

Conclusions Significant secondary MR is more frequently observed in men as compared with women and is associated with worse prognosis.

Keywords Sex; Prognosis; Secondary mitral regurgitation; All-cause mortality

Received: 19 May 2021; Revised: 12 June 2021; Accepted: 19 June 2021
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Introduction

Mitral regurgitation (MR) is one of the most common valvular diseases with a growing incidence, and significant MR is associated with poor prognosis.[1,2] The frequency of significant MR in men and women is comparable.[3] However, when evaluating the aetiology of MR, significant differences are observed: Secondary MR is more prevalent in men, whereas primary MR is more frequently present in women.[3–5] Previous studies have shown differences between men and women undergoing surgical mitral valve repair for primary or secondary MR, with women having a higher mortality risk.[4,6,7] In patients undergoing transcatheter edge-to-edge mitral valve repair with the MitraClip device, no sex differences were observed.[8] However, these studies were mostly performed in patients with primary MR. A recent publication evaluating the sex differences in patients with secondary MR undergoing surgical mitral valve repair showed higher mortality risk in women as compared with men.[9] The factors underlying these differences remain elusive, particularly among patients with secondary MR.[10] Accordingly, the objective of this study is to investigate the sex distribution and long-term prognosis of patients with significant secondary MR.

Methods

Patient population

Patients with significant (moderate and severe) secondary MR were identified between the years 1999 and 2018 through the departmental echocardiographic database of the Leiden University Medical Center (Leiden, The Netherlands). Patients with previous mitral valve intervention were excluded. Baseline demographic, clinical and echocardiographic characteristics were prospectively collected through the departmental clinical database (EPD-Vision 11.8.4.0; Leiden University Medical Center, Leiden, The Netherlands) and were analysed retrospectively. The institutional review board approved this retrospective study of clinically acquired data and waived the need for written patient informed consent.

Clinical variables included heart failure aetiology (i.e. ischaemic vs. non-ischaemic), New York Heart Association (NYHA) functional class, comorbidities and medication use. Body surface area was calculated according to the Du Bois formula.[11] Ischaemic heart failure was defined based on coronary artery disease confirmed by coronary angiography, prior coronary revascularization with percutaneous coronary intervention and/or coronary artery bypass grafting (CABG). Mitral valve intervention included surgical mitral valve repair or replacement and transcatheter edge-to-edge mitral valve repair with the MitraClip device.

Echocardiography

Transthoracic echocardiography was performed with commercially available systems (General Electric Vingmed Ultrasound, Milwaukee, USA), and images were digitally stored for offline analysis (EchoPAC 201.0.0, General Electric Vingmed Ultrasound, Milwaukee, USA). Image acquisition was performed with patients in haemodynamic stable conditions at rest in the left lateral decubitus position. Using 3.5-MHz or M5S transducers, two-dimensional images, M-mode and Doppler data were acquired from parasternal, apical and subcostal views. From the apical two- and four-chamber views, left ventricular (LV) volumes (end-diastolic and end-systolic) were measured and the LV ejection fraction (EF) was quantified using the Simpson biplane method.[12] LV volumes were indexed for body surface area. MR severity was assessed using a multiparametric approach according to current guidelines and graded as moderate (Grade 2), moderate to severe (Grade 3) and severe (Grade 4).[13–15] From standard two-dimensional transthoracic echocardiography, LV global longitudinal strain (GLS) was measured using apical four-chamber, two-chamber and long-axis views of the LV and processed offline using commercially available software (EchoPAC 201.0.0, General Electric Vingmed Ultrasound, Milwaukee, USA).[16] LV GLS is a measure of global shortening of the myocardium and is conventionally expressed as negative values. However, in this study, we have treated this variable as absolute value, and therefore, a higher LV GLS value represents better LV systolic function.

Follow-up

Patients were followed up for the occurrence of the primary endpoint of all-cause mortality. The follow-up started from the date of the first echocardiogram showing significant secondary MR. Data on survival were collected from the departmental cardiology information system (EPD-Vision 11.8.4.0; Leiden University Medical Center, Leiden, The Netherlands), which is linked to the governmental death registry database. Follow-up was complete for all patients.

Statistical analysis

Continuous data are presented as mean ± standard deviation (when normally distributed) or as median with interquartile range (when not normally distributed). An independent sample Student *t*-test or Mann–Whitney *U* test (when appropriate) was used for the comparison of continuous data. Categorical data are presented as absolute numbers and percentages, and a $\chi 2$ test was used for the comparison between groups. To estimate the cumulative survival rates, a Kaplan–Meier analysis was performed, and the log-rank test was used to compare the cumulative survival rates between men and women. Based on the Kaplan–Meier analysis, a post hoc landmark analysis was performed at 36 months of follow-up to evaluate early vs. late outcomes between men and women. Independent associates for all-cause mortality were evaluated using Cox proportional hazards regression analysis. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated and reported. Variables with a *P*-value < 0.05 were considered statistically significant and were included in the multivariable model. All statistical analyses were performed using SPSS for Windows, Version 23.0 (IBM, Armonk, NY, USA), with a two-tailed *P*-value < 0.05 being considered statistically significant.

Results

Patient population

A total of 698 patients (mean age 66 ± 11 years) with significant secondary MR were included. Ischaemic heart failure was present in 53% of the total population. The majority of the patients presented with heart failure symptoms NYHA functional Class III (60%). The mean LVEF was 29 ± 11%,

and the mean LV GLS was 7.8 ± 3.8%. The majority of the patients (82%) had moderate-to-severe or severe MR. *Tables 1 and 2* summarize the baseline clinical and echocardiographic characteristics for the total population and the differences between sexes.

There were 471 (67%) men (mean age 67 ± 10 years) and 227 (33%) women (mean age 65 ± 13). No differences were observed in the prevalence of atrial fibrillation or other cardiovascular risk factors (i.e. hypertension and/or diabetes mellitus). In terms of heart failure aetiology, men more frequently had ischaemic heart failure (61%), whereas women more frequently had non-ischaemic heart failure (63%). Although women had more severe heart failure symptoms as compared with men, the difference did not reach statistical significance. In terms of echocardiographic characteristics, women had significantly smaller LV volumes when compared with men, but no significant difference was observed in LVEF. However, LV systolic function was slightly better in women than in men when assessed with LV GLS (LV GLS 7.5 ± 3.6% in men vs. 8.5 ± 4.1% in women; $P = 0.004$). No differences were observed in MR grade between men and women.

Follow-up

During follow-up, two-thirds of the patients (64%) received cardiac resynchronization therapy, and 308 patients (44%) received mitral valve intervention: 28% underwent surgical mitral valve repair, and 16% received transcatheter edge-to-edge mitral valve repair. Men more frequently received cardiac resynchronization therapy when compared with women. In terms of invasive mitral valve treatment, women more often underwent surgical mitral valve repair (34%), although no differences were observed in transcatheter edge-to-edge

Table 1 Clinical characteristics

	Total population (n = 698)	Men (n = 471)	Women (n = 227)	P-value
Age (years)	66 ± 11	67 ± 10	65 ± 13	0.051
BSA (m^2)	1.92 ± 0.21	1.99 ± 0.19	1.78 ± 0.19	**<0.001**
Atrial fibrillation, *n* (%)	289 (41)	206 (44)	83 (37)	0.071
Hypertension, *n* (%)	275 (39)	175 (37)	100 (44)	0.081
Diabetes mellitus, *n* (%)	167 (24)	120 (26)	47 (21)	0.166
eGFR (mL/min/1.73m^2)	62 ± 26	63 ± 25	61 ± 27	0.417
Heart failure aetiology, *n* (%)				
Ischaemic	370 (53)	287 (61)	83 (37)	**<0.001**
Non-ischaemic	328 (47)	184 (39)	144 (63)	**<0.001**
NYHA class, *n* (%)				
I	34 (5)	26 (6)	8 (4)	0.251
II	170 (24)	116 (25)	54 (24)	0.809
III	415 (60)	282 (60)	133 (59)	0.747
IV	79 (11)	47 (10)	32 (14)	0.108
Medication, *n* (%)				
Beta-blockers	492 (71)	326 (69)	166 (73)	0.288
Diuretics	580 (83)	387 (82)	193 (85)	0.346
ACEi/ARB	565 (81)	390 (83)	175 (77)	0.072
MRA	304 (44)	193 (41)	111 (49)	0.048

Continuous data are presented as mean ± SD or median [interquartile range]. Categorical data are presented as numbers and percentages. Bold indicates statistically significant values. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BSA, body surface area; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association.

Table 2 Echocardiographic characteristics

	Total population (n = 698)	Men (n = 471)	Women (n = 227)	P-value
LVEDVi (mL/m^2)	101 [76–129]	104 [81–132]	92 [68–122]	**<0.001**
LVESVi (mL/m^2)	73 [51–97]	77 [53–98]	66 [44–92]	**<0.001**
LVEF (%)	29 ± 11	29 ± 11	30 ± 12	0.180
LV GLS (%)[a]	7.8 ± 3.8	7.5 ± 3.6	8.5 ± 4.1	**0.004**
MR grade, *n* (%)				
Moderate	125 (18)	87 (19)	38 (17)	0.576
Moderate to severe	305 (44)	210 (45)	95 (42)	0.495
Severe	268 (38)	174 (37)	94 (41)	0.256

Continuous data are presented as mean ± SD or median [interquartile range]. Categorical data are presented as numbers and percentages. Bold indicates statistically significant values. LVEF, left ventricular ejection fraction; LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic volume; LV GLS, left ventricular global longitudinal strain; MR, mitral regurgitation.
[a]LV GLS feasible in n = 660 patients.

mitral valve repair. A summary of device implantation and mitral valve intervention at follow-up and differences between men and women is shown in *Table 3*.

Survival analysis

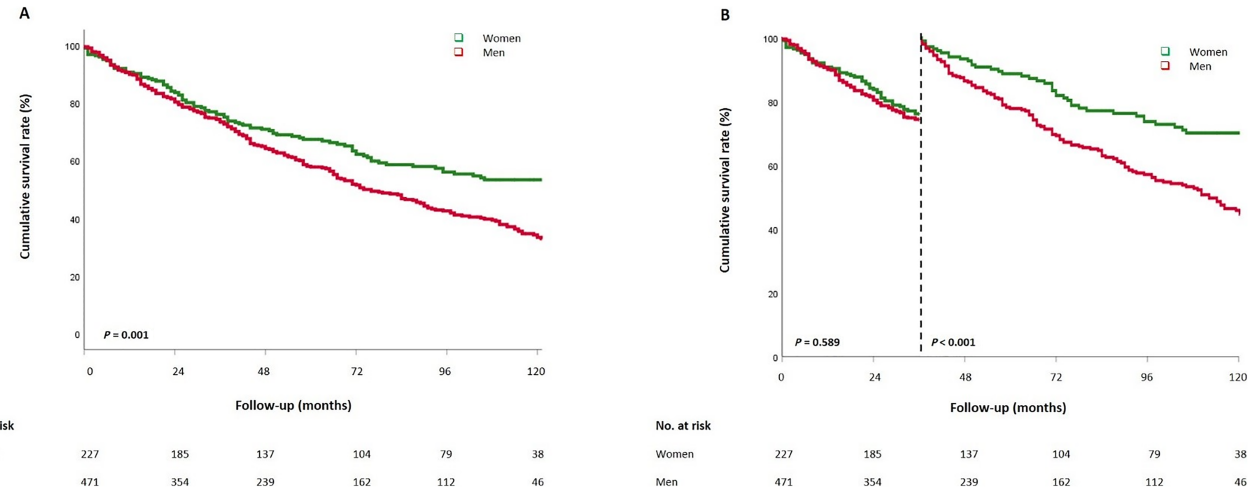
During a median follow-up of 57 [interquartile range 29–110] months, 373 (53%) patients died. Women showed significantly lower mortality rates at 1-, 2- and 5-years follow-up as compared with men (women 9%, 16% and 33% vs. men 10%, 20% and 42%, respectively; P = 0.001; *Figure 1*, Panel A). Based on the Kaplan–Meier curves, an additional landmark analysis was performed at 36 months of follow-up, demonstrating that the differences in survival were significant between men and women after this time point ($P < 0.001$; *Figure 1*, Panel B). In patients with ischaemic heart failure, there was no significant difference in outcome between men and women (P = 0.179; *Figure 2*, Panel A). On the contrary, in patients with non-ischaemic heart failure, a significant difference in outcome between men and women was observed with women having a better outcome as compared with men (P = 0.017; *Figure 2*, Panel B). When considering patients receiving medical therapy only (censored at the moment of intervention), women had lower mortality rates than men (5-year estimated rates 77% in women vs. 62% in men; P = 0.001). On univariable analysis, age, male sex, chronic kidney disease, diabetes mellitus, ischaemic heart failure, LVEF and LV GLS were significantly associated with all-cause mortality (*Table 4*). On multivariable analysis, after correcting for various clinical and echocardiographic parameters, male sex remained independently associated with all-cause mortality (HR 1.423; 95% CI, 1.109–1.826; P = 0.006).

Table 3 Intervention during follow-up

	Total population (n = 698)	Men (n = 471)	Women (n = 227)	P-value
Device therapy, *n* (%)				
Cardiac resynchronization therapy	414 (64)	294 (68)	120 (55)	**0.001**
MV intervention, *n* (%)				
Medical therapy only	387 (55)	279 (59)	108 (48)	**0.004**
Mitral valve repair	198 (28)	122 (26)	76 (34)	**0.037**
Mitral valve replacement	3 (0.4)	1 (0.2)	2 (0.9)	0.206
MitraClip	110 (16)	69 (15)	41 (18)	0.246
Concomitant procedure, *n* (%)[a]				
CABG	60 (9)	46 (10)	14 (6)	0.112
Tricuspid valve annuloplasty	131 (19)	83 (18)	46 (21)	0.264
LV reconstruction	17 (2)	12 (3)	5 (2)	0.782
Cardiac support device (CoreCap)	63 (9)	39 (8)	24 (11)	0.322
MAZE	30 (4)	21 (5)	9 (4)	0.763

Continuous data are presented as mean ± SD or median [interquartile range]. Categorical data are presented as numbers and percentages. Bold indicates statistically significant values. CABG, coronary artery bypass graft
[a]Concomitant procedures with mitral valve treatment.

Figure 1 Kaplan–Meier curves for all-cause mortality.Panel A demonstrates time to all-cause mortality according to sex: women (green) and men (red). Panel B demonstrates the landmark analysis at 36 months of follow-up with time-to-event curves for all-cause mortality according to sex.



DOI: 10.1002/ehf2.13503

Figure 2 Kaplan–Meier curves for all-cause mortality in patients with ischaemic and non-ischaemic heart failure.Panel A demonstrates time to all-cause mortality according to sex in patients with ischaemic heart failure: women (green) and men (red). Panel B demonstrates time to all-cause mortality according to sex in patients with non-ischaemic heart failure.

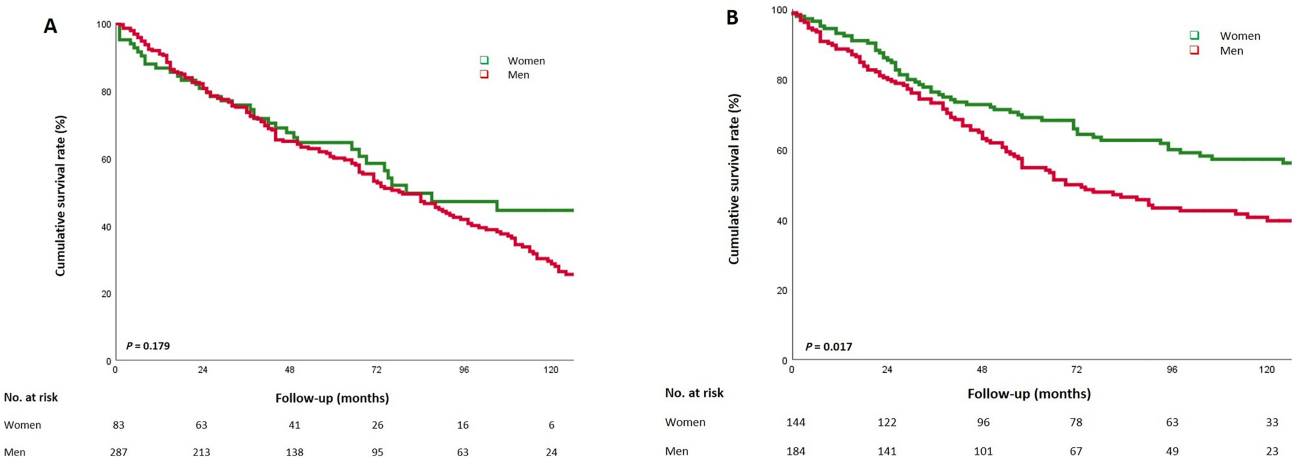


Table 4 Uni- and multivariable Cox regression analyses to identify associates of all-cause mortality

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.030	1.019–1.040	<0.001	1.020	1.009–1.032	0.001
Male sex	1.474	1.175–1.850	0.001	1.423	1.109–1.826	0.006
BSA (m^2)	1.050	0.652–1.689	0.842			
eGFR (mL/min/1.73m^2)	0.977	0.972–0.981	<0.001	0.980	0.975–0.985	<0.001
Hypertension	0.940	0.762–1.160	0.566			
Diabetes mellitus	1.429	1.132–1.805	0.003	1.309	1.021–1.678	0.034
Atrial fibrillation	1.145	0.932–1.406	0.197			
Ischaemic aetiology	1.291	1.052–1.585	0.015	1.071	0.855–1.342	0.550
NYHA classification ≥II	1.026	0.621–1.694	0.920			
Beta-blockers	0.845	0.681–1.048	0.125			
CRT	1.092	0.859–1.390	0.471			
MV intervention[a]	1.051	0.852–1.298	0.642			
LVEF (%)	0.988	0.977–0.998	0.025	0.999	0.985–1.013	0.864
LV GLS (%)	1.082	1.047–1.118	<0.001	1.066	1.024–1.109	0.002

BSA, body surface area; CI, confidence interval; CRT, cardiac resynchronization therapy; EDV, end-diastolic volume; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; MV, mitral valve; NYHA, New York Heart Association.
[a]Combined surgical mitral valve repair, mitral valve replacement and percutaneous edge-to-edge mitral valve repair.

Discussion

The present study shows that significant secondary MR is more frequent in men as compared with women. Ischaemic aetiology is the most frequent underlying mechanism in men, whereas non-ischaemic cardiomyopathy is more frequently observed in women. Men had a worse prognosis, compared with women.

Sex differences in secondary MR

Important differences in prevalence, pathophysiology and prognosis of various cardiovascular diseases have been described between men and women.[17] In mitral valve pathology, two different mechanisms of MR can be distinguished: primary MR (i.e. the result of pathology of the MV apparatus itself) and secondary MR (i.e. the result of changes in the LV geometry due to ischaemic or non-ischaemic heart failure).[18] A large echocardiography-based registry by Monteagudo Ruiz *et al.*[3] described the sex differences among 3309 patients with moderate and severe MR and showed that secondary MR was more prevalent among men vs. women (39.2% vs. 21.8%, respectively). However, the study did not elaborate further on the differences between men and women with significant secondary MR. The randomized clinical trial from the Cardiothoracic Surgical Trials Network (CTSN) comparing mitral valve repair vs. replacement in 251 patients with

ischaemic secondary MR showed that 38% were women, whereas the remaining 62% were men.[9] In the present study, ischaemic aetiology of secondary MR was observed in 61% of men vs. 37% of women. When analysing the clinical and echocardiographic characteristics of the patients enrolled in the CTNS trial,[9] men were comparable with women in terms of age, body mass index, frequency of atrial fibrillation, history of myocardial infarction and renal dysfunction; however, men more frequently had a history of ventricular arrhythmias, whereas women presented more frequently with diabetes mellitus and hypertension. Furthermore, men had larger LV dimensions and effective regurgitant orifice areas when compared with women. However, when the effective orifice regurgitant orifice area was corrected for the LV end-diastolic volume, women had a larger ratio than men, suggesting more severe MR in women than in men. These results are similar to the data reported in this study. However, it should be noted that the present study population is larger and includes both aetiologies of secondary MR (ischaemic and non-ischaemic). Although other studies have compared sex differences in MR,[19,20] this is the first and largest study focusing specifically on secondary MR.

Sex differences in outcomes in patients with secondary MR

Although men with significant secondary MR seem to receive interventional treatment more often than women,[1,21–23] men seem to have a worse prognosis. A study by Estevez-Loureiro *et al*.[8] investigated the effect of gender on results after transcatheter edge-to-edge MV repair with the MitraClip in 173 patients (64 women vs. 109 men) and showed no differences between the sexes in MR reduction, heart failure hospitalization and all-cause mortality. Similarly, data from the German TRAnscatheter Mitral Valve Interventions (TRAMI) registry, including 501 men and 327 women showed no differences in prognosis after successful transcatheter MV repair with the MitraClip.[20] Although those studies consisted mainly of patients with secondary MR, a significant proportion of patients had other aetiologies of MR and sub-analyses concerning only patients with secondary MR were not performed. In contrast, in the randomized CTNS trial, Giustino *et al*.[9] showed that among patients with secondary MR undergoing MV repair or replacement, women had a significantly higher risk for mortality when compared with men (27.1% vs. 17.4%, respectively; $P = 0.03$). The reasons for the worse outcome in women after MV surgery remain unclear. However, it is important to note that both men and women showed similar LV reverse remodelling at 2-year follow-up, whereas women had smaller baseline LV volumes and larger effective regurgitant orifice areas when corrected for LV end-diastolic volume as compared with men, suggesting that women had more severe MR than men at baseline and, after correcting the volume overload with MV repair or replacement, their LVs benefited less. Data on more sensitive measures of LV systolic function such as LV GLS or tissue characterization with cardiac magnetic resonance were not available, but it can be speculated that women have stiffer, more fibrotic LVs than men.

In the present study, including ischaemic and non-ischaemic secondary MR, male gender was independently associated with worse outcome. However, the differences between men and women became evident 3 years after diagnosis of significant secondary MR (*Figure 1*), which could indicate progression of the underlying mechanism of secondary MR (progression of LV remodeling). Although no statistically significant difference was observed between men and women with ischaemic heart failure (possibly due to the low number of women with ischaemic heart failure in the present study), a trend of worse survival was noted in men with ischaemic heart failure. In men, the aetiology of secondary MR was ischaemic heart failure, which is known to respond less well to heart failure therapies and may further progress over time, leading to worse outcome.[24–26]

Study limitations

This is a single-centre retrospective study, which limits the generalizability of the results. In addition, this is a tertiary referral centre where the patients are referred for specific treatments, which may have introduced some selection bias. Patients were identified through the departmental echocardiographic database and not from claims data on outpatient clinic with patients with heart failure. Therefore, the exact prevalence of secondary MR could not be provided. Measures for heart failure such as NT-proBNP unfortunately were not systematically available and therefore could not be provided for the present study. Cardiac mortality was not systematically documented in our centre, and due to the retrospective design of the study, these data could not be acquired. However, to the best of our knowledge, this is the first and largest registry evaluating gender differences and long-term outcome in heart failure patients with secondary MR. The present study did not evaluate changes over time in LV systolic function and dimensions, which could shed more light into the association between heart failure progression and outcomes.

Conclusion

Significant secondary MR is more frequently observed in men as compared with women and is associated with worse prognosis.

Conflict of interest

Nina Ajmone Marsan and Jeroen J. Bax received speaker fees from Abbott Vascular. Victoria Delgado received speaker fees from Abbott Vascular, Medtronic, Edwards Lifesciences and GE Healthcare. The remaining authors have no conflicts of interest to disclose.

Funding

The Department of Cardiology of Leiden University Medical Centre received grants from Biotronik, BioVentrix, Bayer, Medtronic, Abbott Vascular, Boston Scientific Corporation, Edwards Lifesciences and GE Healthcare.

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