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CLINICAL RESEARCH
Valvular heart disease

Degenerative mitral regurgitation due to flail leaflet: sex-related differences in presentation, management, and outcomes

Jean-Fançois Avierinos[1,2]*, Christophe Tribouilloy [3,4†], Francesca Bursi[5†], Francesco Grigioni[6], Jean-Louis Vanoverschelde[7,8], Noémie Resseguier[9,10], Alexis Théron [2,11], Agnes Pasquet[7,8], Julie Pradier[1], Elena Biagini [12], Andrea Barbieri [13], Hector Michelena[14], Giovanni Benfari[14], Dan Rusinaru[3,4], Stéphane Zaffran[2], David Vancraeynest[7,8], Fréderic Collart[11], Yohann Bohbot [3,4], Benjamin Essayagh [14], and Maurice Enriquez-Sarano[15]

[1]Département de Cardiologie, Centre Hospitalier Universitaire Timone, Assistance Publique Hôpitaux de Marseille, Aix-Marseille Université, 264 rue Saint-Pierre, 13005 Marseille, France; [2]U1251 INSERM, Marseille Medical Genetics, Aix-Marseille Université, 27 Bd Jean Moulin, 13385 Marseille, France; [3]Département de Cardiologie, Centre Hospitalier Universitaire d'Amiens, Amiens, France; [4]EA 7517, Jules Verne University of Picardie, Amiens, France; [5]Department of Health Sciences, University of Milan, Milano, Italy; [6]Research Unit of Cardiovascular Science, Università e Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italy; [7]Service de Cardiologie, Clinique Universitaire Saint-Luc, Brussels, Belgium; [8]Pôle de Recherche Cardiovasculaire, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium; [9]Methodological Support Unit for Clinical and Epidemiological Research, University Hospital of Marseille (APHM), Marseille, France; [10]CEReSS—Health Services and Quality of Life Research, Aix Marseille Université, Marseille, France; [11]Service de Chirurgie Cardiaque, Centre Hospitalier Universitaire Timone, Assistance Publique Hôpitaux de Marseille, Aix-Marseille Université, Marseille, France; [12]Cardiology Unit, St Orsola Hospital, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [13]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy; [14]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA; and [15]Valve Science Center, Minneapolis Heart Institute, Minneapolis, MN, USA

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Abstract

Background and Aims Presentation, outcome, and management of females with degenerative mitral regurgitation (DMR) are undefined. We analysed sex-specific baseline clinical and echocardiographic characteristics at referral for DMR due to flail leaflets and subsequent management and outcomes.

Methods In the Mitral Regurgitation International Database (MIDA) international registry, females were compared with males regarding presentation at referral, management, and outcome (survival/heart failure), under medical treatment, post-operatively, and encompassing all follow-up.

Results At referral, females ($n = 650$) vs. males ($n = 1660$) were older with more severe symptoms and higher MIDA score. Smaller cavity diameters belied higher cardiac dimension indexed to body surface area. Under conservative management, excess mortality vs. expected was observed in males [standardized mortality ratio (SMR) 1.45 (1.27–1.65), $P < .001$] but was higher in females [SMR 2.00 (1.67–2.38), $P < .001$]. Female sex was independently associated with mortality [adjusted hazard ratio (HR) 1.29 (1.04–1.61), $P = .02$], cardiovascular mortality [adjusted HR 1.58 (1.14–2.18), $P = .007$], and heart failure [adjusted HR 1.36 (1.02–1.81), $P = .04$] under medical management. Females vs. males were less offered surgical correction (72% vs. 80%, $P < .001$); however, surgical outcome, adjusted for more severe presentation in females, was similar ($P \geq .09$). Ultimately, overall outcome throughout follow-up was worse in females who displayed persistent excess mortality vs. expected [SMR 1.31 (1.16–1.47), $P < .001$], whereas males enjoyed normal life expectancy restoration [SMR 0.92 (0.85–0.99), $P = .036$].

* Corresponding author. Tel: +33 4 91385737, Fax: +33491384764, Email: jfavierinos@ap-hm.fr
† These authors contributed equally to the study and are co-second authors.

Conclusions Females with severe DMR were referred to tertiary centers at a more advanced stage, incurred higher mortality and morbidity under conservative management, and were offered surgery less and later after referral. Ultimately, these sex-related differences yielded persistent excess mortality despite surgery in females with DMR, while males enjoyed restoration of life expectancy, warranting imperative re-evaluation of sex-specific DMR management.

Structured Graphical Abstract

Key Question

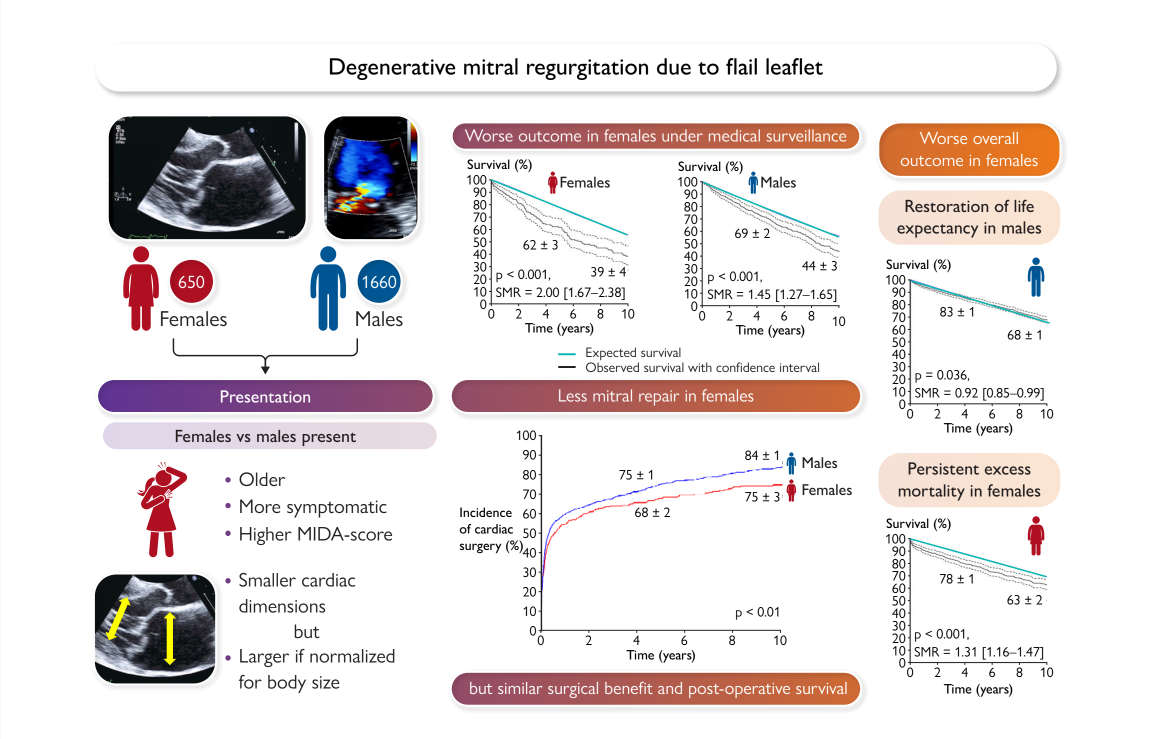
Are there sex-specific differences in presentation, management, and outcomes of severe degenerative mitral regurgitation (DMR)?

Key Finding

Females presented with more severe symptoms, higher MIDA-score, and larger cardiac dimensions normalized to body surface area than males. Females were offered surgery less frequently. Overall outcomes throughout follow-up were worse in females than in males with persistent excess mortality.

Take Home Message

Sex-related differences in patients with DMR involve underestimation of DMR severity, under treatment of DMR and persistent excess mortality in females with DMR as compared to males, warranting re-evaluation of sex-specific DMR management.



Comparison of severe degenerative mitral regurgitation presentation, management, and outcome between males and females. Females vs. males are less referred to tertiary care centers, at a later stage of severe degenerative mitral regurgitation (left), display more severe outcome under medical management (top middle), and are less referred to mitral repair with later indications (bottom middle) but have similar post-operative outcome when operated. They ultimately incur excess overall mortality under medical and surgical management combined, whereas normal life expectancy is restored in males (right). Black solid line denotes observed survival, dotted lines 95% confidence interval, and straight line expected survival. MIDA, Mitral Regurgitation International Database; SMR, standardized mortality ratio.

Keywords Mitral regurgitation • Mitral valve prolapse • Flail leaflet • Female sex • Outcome

Introduction

Mitral valve prolapse (MVP) is frequent, affecting 0.6%–2.4% of the population[1] and is the leading cause for primary mitral regurgitation (MR).[2] Because MR due to MVP, referred as degenerative MR (DMR), is highly repairable,[3] with high technical success,[4] better outcome than valve replacement,[5] and improved survival vs. conservative management,[6] clinical guidelines currently suggest an aggressive surgical approach to severe DMR.[7,8] In this context, guidelines do not mention whether sex influences outcomes and surgical indications.[7,8] While substantial differences have been reported in other valvular diseases, specifically aortic bicuspid valve,[9] regurgitation,[10] or stenosis,[11] knowledge pertaining to MR is discordant, explaining lack of clear recommendations.

While MR overall,[12] and DMR in particular,[2] is as frequent in males and females in the population, males are overrepresented in surgical series of DMR,[3,5] raising interrogations on female carriers of DMR. Surgical series suggested that females vs. males are referred with more symptoms[13,14] and may incur lower repair rates,[15] higher operative mortality,[14–16] more frequent heart failure (HF),[13] and possibly lower post-operative survival.[15,16] Females with MVP do present anatomically differently from males,[17] but it remains unclear whether sex *per se* impacts duration of exposure to MR,[13] clinical profile at diagnosis,[18] and ultimately clinical outcome.[14,17] Moreover, aforementioned differences in presentation, management, and prognosis between sex are often discordant[13,16] and may have suffered from marked aetiology heterogeneity, whereby rheumatic disease[13,16] may have skewed results,[14] warranting analysis in a pure DMR cohort. No data focusing on severe DMR are available to date, with analysis starting from referral to tertiary care centers using uniform criteria in multicenter registries.

The Mitral Regurgitation International Database (MIDA) multicenter registry enrolled patients referred for DMR due to flail leaflets in Europe and North America, providing a large population of males and females with homogeneous MR cause and long follow-up.[19,20] Hence, we examined the null hypothesis that males and females with severe DMR present at referral with similar clinical and echocardiographic characteristics and enjoy the same surgical management and outcome.

Methods

Study design and patient population

Out of all MIDA registries, the present analysis used the original MIDA-Flail registry, which as previously detailed[21] is an international collaborative registry of consecutive patients referred for DMR due to flail leaflet, confirmed by transthoracic echocardiography, in tertiary care centers in Europe (Marseille, Amiens, Bologna, Modena, and Brussels) and in the USA (Mayo Clinic, Rochester, MN). The MIDA investigators/centers are listed in the appendix. Patients were eligible if they had DMR graded ≥ moderate-to-severe and flail leaflet diagnosed by 2D echocardiography[22,23] with comprehensive clinical and echocardiographic evaluation at referral within each institution's echocardiographic laboratory. Exclusion criteria were functional MR, ≥moderate mitral stenosis, ≥moderate aortic valve disease, previous valvular surgery, congenital heart disease, incomplete or unavailable clinical or echocardiographic data, <moderate-to-severe DMR at referral, and patients denying research authorization. History of coronary disease was not exclusive. The first patient was enrolled on the 21 March 1980 and the last patient on the 28 December 2005. The original MIDA-Flail registry included 2472 patients.[21] Patients with missing body surface area (BSA) were excluded from the original cohort for the present analysis. The study was conducted in accordance with institutional guidelines, national legal requirements, and the revised Helsinki Declaration with approval by local institutional review boards.

Clinical and echocardiographic evaluation

Baseline clinical variables were obtained from medical records and vital signs at echocardiography. Baseline transthoracic echocardiograms were performed within routine clinical practice, using standard methods. Left ventricular (LV) and left atrial (LA) diameters were recorded, and ejection fraction (EF) was calculated using 2D-guided dimensions, Simpson biplane method, and/or estimated visually. Diagnosis of flail leaflets was based on failure of leaflet coaptation, with rapid systolic movement of the flail segment into the LA.[22,23] Mitral regurgitation severity was graded by integration of all signs/measures available.[19] Data were used unaltered from original prospective echocardiographic collection of each centers by electronic transfer. Clinical and echocardiographic data were used to calculate the MIDA score for each patient [using age ≥ 65 years, New York Heart Association (NYHA) Classes III–IV, atrial fibrillation, LA diameter ≥ 55 mm, right ventricular systolic pressure > 50 mmHg, LV end-systolic diameter indexed to BSA ≥ 21 mm/m^2,[24] and EF < 60%) as point-markers.[21]

Follow-up

Follow-up started at echocardiographic referral in participating centers until study closure or death. During follow-up, patients were monitored by their personal physicians, and information was harvested on a 2-year schedule basis. Events were ascertained by clinical interviews, detailed questionnaires, review of clinical documents of outside institutions, or by telephone calls to physicians and patients. Autopsy records and death certificates were consulted as possible for attribution of causes of death. Follow-up was complete in 97.2% of patients until death or at least 5 years post-inclusion. Median total follow-up duration was 9.82 years. Last patient date for follow-up was 15 May 2013.

Endpoints and statistical analysis

Baseline qualitative data are expressed as numbers and percentages and quantitative data as means and standard deviations. Comparison between males and females used χ^2 test (or Fisher exact test) and Student's *t*-test (or Mann–Whitney test).

Event incidence rate were estimated using Kaplan–Meier method. Those observed under medical management were analysed by censoring at surgery, if performed. Those occurring after mitral surgery were estimated with time of surgery as time of origin. Those observed during total follow-up, including medical management and post-operative course, were estimated using the entire follow-up. For analysis of all-cause mortality, expected survival was estimated using European and US life expectancy tables and comparison of observed vs. expected survival was performed by estimating standardized mortality ratios (SMR) with 95% confidence intervals (CI) and by matching comparison to year of enrolment. European and US patients were respectively matched to European and US life tables. For US patients, US and not Olmsted County life tables were used, since US patients were not restricted to Olmsted County residents but came from all over the USA. For European patients, country-specific life tables were used. Data were extracted from the Human Mortality Database, Max Planck Institute for Demographic Research (Germany); University of California, Berkeley (USA); and French Institute for Demographic Studies (France), available at http://www.mortality.org. Univariate and multivariate relative survival models of excess mortality vs. expected were analysed.

Primary endpoints were mortality and HF under conservative treatment, after surgical correction of DMR and throughout follow-up including conservative and surgical management. Secondary endpoint was performance of mitral surgery during follow-up. Univariable and multivariable Cox models allowed estimation of crude and adjusted hazard ratios (HR) with 95% CI. Female sex was tested as the main variable of interest univariably and in multivariable analysis with systematic adjustment for MIDA score and comorbidity (Charlson index). Statistical software R Core Team, Foundation for statistical computing, Vienna, Austria, version 4.2.2 (2022), www.R-project.org/, was used for the present analysis.

Results

Study population

The 2310 patients with moderate-to-severe/severe DMR due to flail leaflet were included in five European centers (43% of patients) and 1 American (57%) and involved 1660 males (72%) and 650 females (28%). Overall clinical (*Table 1*) and echocardiographic (*Table 2*) characteristics are typical of DMR with age in the sixth decade and corresponding comorbid conditions, frequent symptoms, and ventricular and atrial dilatation.

Table 1 **Baseline clinical characteristics of 2310 patients with degenerative mitral regurgitation due to flail leaflet according to sex**

Clinical data	Total population ($n = 2310$)	Males ($n = 1660$)	Females ($n = 650$)	*P*
Age (years)	67 ± 13	66 ± 13	69 ± 13	<.0001
BSA (m^2)	1.86 ± 0.2	1.94 ± 0.2	1.65 ± 0.2	<.0001
Comorbidity				
Coronary disease (*n*, %)	249 (11)	188 (11)	61 (9)	.2
Hypertension (*n*, %)	914 (40)	639 (38)	275 (42)	.09
Diabetes (*n*, %)	168 (7)	116 (7)	52 (8)	.4
Infective endocarditis (*n*, %)	161 (7)	121 (7)	40 (6)	.3
Stroke/TIA (*n*, %)	76 (3)	53 (3)	23 (4)	.4
Charlson index	0.91 ± 1.2	0.91 ± 1.3	0.92 ± 1.2	.9
TTE indication (*n*, %)				<.0001
HF symptoms	948 (41)	636 (38)	312 (48)	
CV evaluation	708 (31)	564 (34)	144 (22)	
Non-cardiac indications	654 (28)	460 (28)	194 (30)	
NYHA class				<.0001
I–II	1565 (68)	1176 (71)	389 (60)	
III–IV	745 (32)	484 (29)	261 (40)	
Diuretic treatment (*n*, %)	777 (34)	506 (30)	271 (42)	.0001
Beta-blockers (*n*, %)	412 (18)	273 (16)	139 (21)	.005
ACE inhibitor (*n*, %)	953 (41)	690 (42)	263 (40)	.6
Digoxin treatment (*n*, %)	554 (24)	371 (22)	183 (28)	.003
Atrial fibrillation	709 (31)	496 (30)	213 (33)	.2
EuroSCORE II	1.61 ± 1.54	1.54 ± 1.53	1.80 ± 1.56	.0002

BSA, body surface area; TIA, transient ischaemic attack; TTE, transthoracic echocardiography; HF, heart failure; CV, cardiovascular; ACE, angiotensin-converting enzyme.

Comparing males vs. females (*Tables 1* and *2*), comorbidity, cardiovascular (CV) history, and risk factors were similar. However, females were older and more frequently referred with severe symptoms and HF than males. The trend for more anterior leaflet flail segment and lower DMR severity grading in females did not reach statistical significance. However, higher systolic pulmonary artery pressure in females matched higher HF prevalence. As a continuous variable, ejection fraction (EF) was slightly higher in females, overall in normal range in both sexes, with similar ∼1/4 males and females displaying decreased EF. Absolute cardiac dimensions (LA and LV) were lower in females with lower proportion displaying LV end-systolic diameter ≥ 40 mm. However, females presented with higher indexed cavity diameters normalized for BSA. Integrating comorbidity, older age, more frequent symptoms, and all echocardiographic characteristics, females presented with higher EuroSCORE II and higher MIDA score.

Outcome under conservative management

When considering the entire study population ($n = 2310$ patients) with censoring at cardiac surgery for those operated, mean follow-up under conservative management was 2.05 ± 3.9 years, not different between sexes ($P = .98$). When considering patients without cardiac surgery during follow-up ($n = 517$), mean follow-up under conservative management was 5.3 ± 3.7 years, not different between sexes ($P = .12$).

Mortality

Under conservative management, 396 patients died, 136 females and 260 males. Five- and 10-year survival rates under conservative management are presented in *Table 3* (left panel). Excess mortality was observed in females and in men but was more prominent in females (*Figure 1* and *Table 3* left panel). In Cox models, females incurred higher mortality under conservative management univariately [female sex HR 1.34 (1.11–1.68), $P = .007$] and adjusting for comorbidity (Charlson score) and for all risk factors including age, integrated into MIDA score [adjusted HR 1.29 (1.04–1.61), $P = .02$]. Further adjustment to angiotensin-converting enzyme (ACE) inhibitors and beta-blockers did not affect the impact of female sex on mortality (Supplementary data online). Since one-third of patients had moderate-to-severe DMR (Grade III), multivariable model was further adjusted to MR grade,

Table 2 Baseline echocardiographic characteristics and Mitral Regurgitation International Database score of 2310 patients with severe mitral regurgitation due to flail leaflet according to sex

Echocardiographic data	Total population ($n = 2310$)	Males ($n = 1660$)	Females ($n = 650$)	P
LVEF (%)	64 ± 10	63 ± 10	65 ± 10	.03
LVEF < 60% (n, %)	556 (24)	412 (25)	144 (22)	.16
Flail anterior (n, %)	462 (20)	317 (19)	145 (22)	.08
Flail posterior (n, %)	1848 (80)	1343 (81)	505 (78)	.18
Degree of DMR (n, %)				.2
Moderate-to-severe	850 (37)	597 (36)	253 (39)	
Severe	1460 (63)	1063 (64)	397 (61)	
LVEDD (mm)	58 ± 7	60 ± 7	55 ± 7	<.0001
LVEDD/BSA (mm/m^2)	32 ± 5	31 ± 5	33 ± 5	<.0001
LVESD (mm)	36 ± 7	37 ± 7	33 ± 6	<.0001
LVESD/BSA (mm/m^2)	20 ± 4	19 ± 4	20 ± 4	<.0001
LVESD ≥ 40 mm (n, %)	518 (22)	440 (27)	78 (12)	<.0001
LVESD ≥ 21 mm/m^2 (n, %)	599 (26)	378 (23)	221 (34)	<.0001
LA (mm)	51 ± 9	51 ± 9	49 ± 9	<.0001
LA/BSA (mm/m^2)	28 ± 6	27 ± 5	30 ± 6	<.0001
sPAP (mmHg)	44 ± 17	43 ± 16	46 ± 19	.0002
MIDA score	4.3 ± 3.0	4.0 ± 3.0	5.0 ± 2.9	<.0001

LVEF, left ventricular ejection fraction; DMR, degenerative mitral regurgitation; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LA, left atrium diameter; sPAP, systolic pulmonary artery pressure; MIDA, Mitral Regurgitation International Database.

Table 3 Survival rates in males and females under conservative management (left panel) and during total follow-up including conservative and surgical management (right panel) and comparison with expected survival using US and European country-specific life tables

	Conservative management			Total follow-up		
	Males	Females	P*	Males	Females	P*
Five-year survival	69 ± 2%	62 ± 3%	.007	83 ± 1%	78 ± 1%	.009
Ten-year survival	44 ± 3%	39 ± 4%		68 ± 1%	63 ± 2%	
Comparison with expected survival (SMR)	1.45 (1.27–1.65) $P' < .001$	2.00 (1.67–2.38) $P' < .001$	<.001	0.92 (0.85–0.99) $P' = .036$	1.31 (1.16–1.47) $P' < .001$	<.001

SMR, standardized mortality ratio.
P', comparison of observed survival to expected. P*, comparison of males vs. females.

which did not affect impact of female sex on mortality (Supplementary data online).

Cardiovascular mortality

Under conservative management, 162 deaths were deemed CV, 69 in females and 93 in males. Five-/10-year rates of CV mortality were 21 ± 2%/40 ± 4% in females vs. 12 ± 2%/28 ± 3% in males ($P < .001$, *Figure 2*, left). Females incurred higher CV mortality univariably [HR 1.88 (1.37–2.59), $P < .0001$] and adjusting for comorbidity and MIDA score [adjusted HR 1.58 (1.14–2.18), $P = .007$]. Further adjustment to ACE inhibitors and beta-blockers did not affect the impact of female sex on CV mortality (Supplementary data online). Further adjustment to MR grade did not affect the impact of female sex on CV mortality (Supplementary data online, *Data*).

Heart failure

Under conservative management, 222 patients developed ≥1 HF episode, 77 females and 145 males. Five-/10-year HF rates were 31 ± 3%/41 ± 4% in females vs. 22 ± 2%/35 ± 3% in males ($P = .02$; *Figure 2*, right). Females incurred higher HF rates univariably

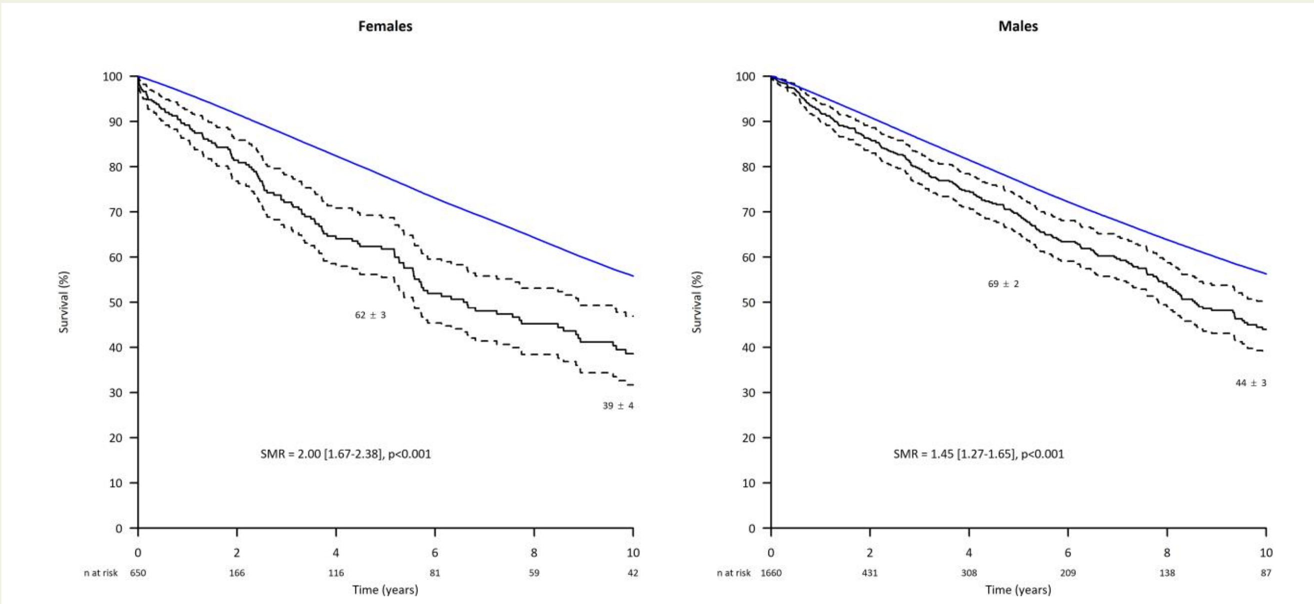


Figure 1 Comparison of observed to expected survival under conservative management in 650 females (left) and 1660 males (right) with severe degenerative mitral regurgitation (DMR) due to flail leaflet. Excess mortality is observed in both sexes but is more prominent in females. Black solid line denotes observed survival, dotted lines 95% confidence interval, and straight line expected survival. SMR, standardized mortality ratio

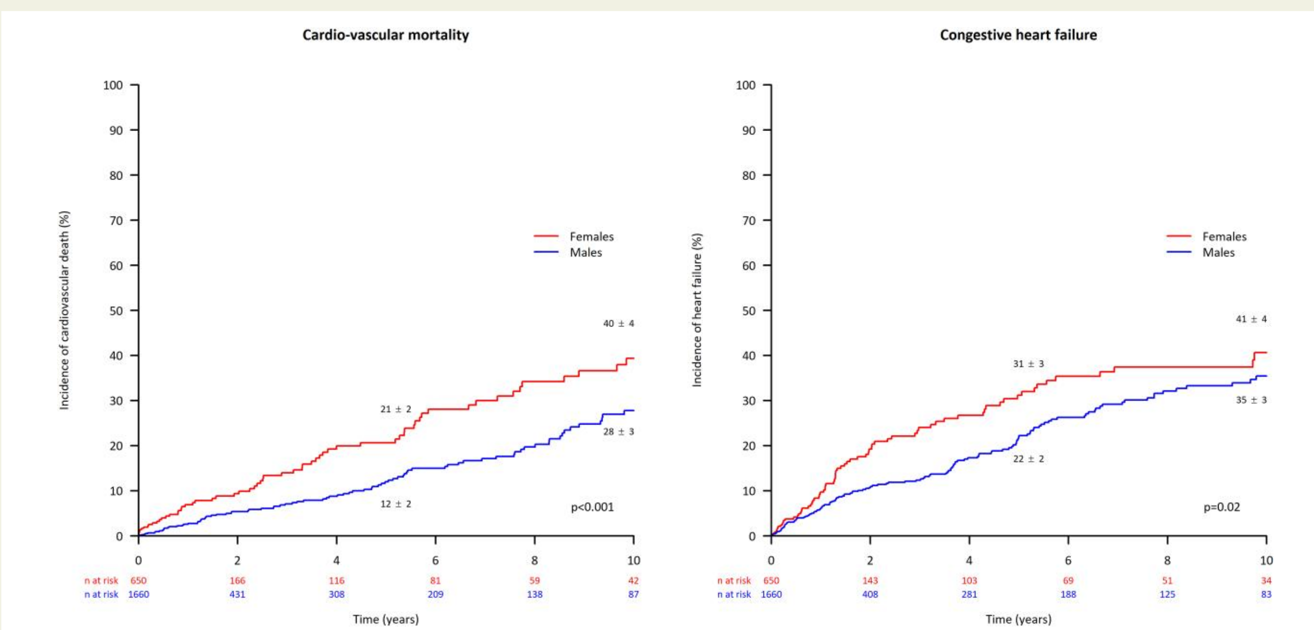


Figure 2 Cardiovascular (CV) mortality (left) and heart failure (HF, right) under conservative management in 2310 patients with severe degenerative mitral regurgitation due to flail leaflet according to sex. Females medically followed incur higher CV mortality and HF than males

[HR 1.44 (1.08–1.89), $P = .01$] and adjusting for comorbidity and MIDA score [adjusted HR 1.36 (1.02–1.81), $P = .04$]. Further adjustment to ACE inhibitors and beta-blockers did not affect impact of female sex on HF (Supplementary data online). Further adjustment to MR grade did not affect impact of female sex on HF (Supplementary data online).

Surgical management and indications

During follow-up, 1793 patients underwent DMR surgical correction (88% repair). Females were less offered surgery ($n = 471$, 72%) than males ($n = 1322$, 80%, $P < .001$), had lower associated coronary artery bypass (15% vs. 23%, $P < .0001$), and tended to have less repair than males (85% vs. 89%, $P = .052$). Age at surgery was 67 ± 13 years in

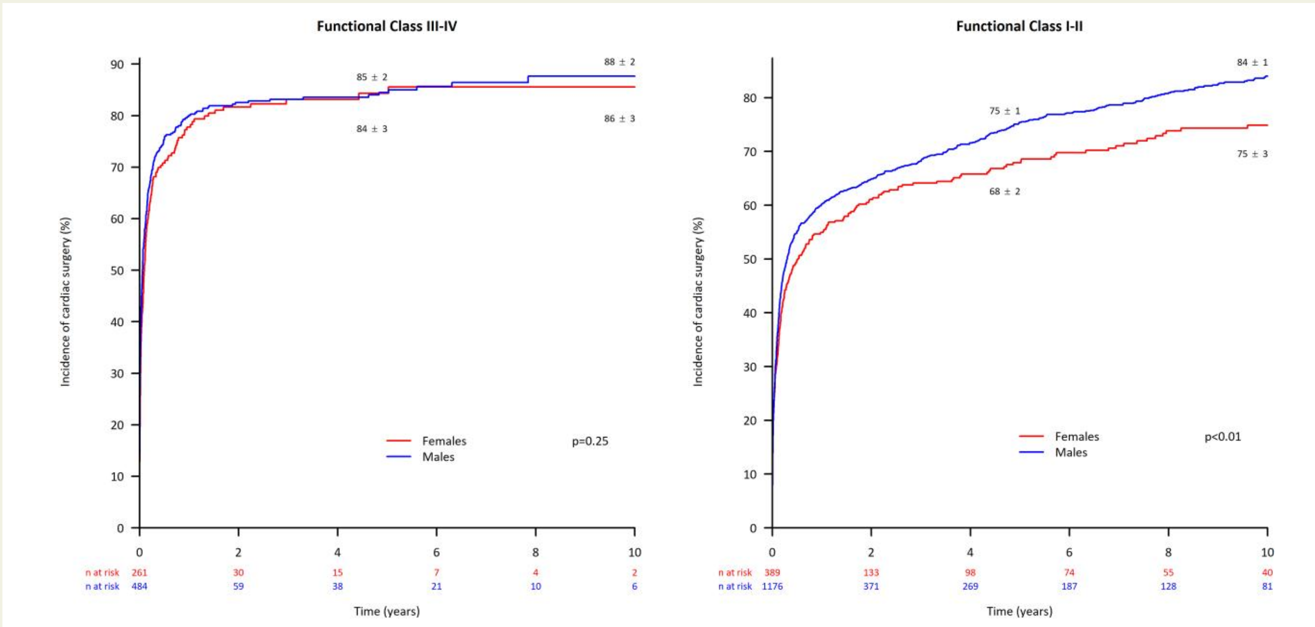


Figure 3 Cumulative rates of mitral surgery during follow-up in 2310 patients with severe degenerative mitral regurgitation due to flail leaflet according to sex and functional class at referral. Rates of surgical correction are similar within the same timeframe between sex in symptomatic patients, whereas a- or minimally symptomatic females are less and later offered surgery than a- or minimally symptomatic males

females and 64 ± 12 years in males ($P < .0001$). Supplementary data online, *Tables S1* and *S2*, depict baseline clinical and echocardiographic characteristics of those 1793 operated patients according to sex. Indications for surgery were severe symptoms in 72% of operated females vs. 57% of operated males ($P < .0001$). Only 4% of operated females had surgery for LV dilatation criteria alone vs. 11% of operated males ($P < .0001$). Personal physician preference was the sole indication for surgery in 16% of females vs. 23% of males ($P < .0001$). Five-/10-year rates of DMR surgical correction were slightly lower in females (74 ± 2%/80 ± 2%) than in males (78 ± 1%/86 ± 1%, $P = .06$) but highly different according to functional status at referral. Among Classes III–IV patients, EuroSCORE II was similar in females and males (2.18 ± 1.89 vs. 1.94 ± 1.95, $P = .11$) as were surgical correction rates within a similar time frame. Among a-minimally symptomatic patients, rates of surgical correction were much lower and surgery was delayed in females (*Figure 3*), despite a more severe presentation as attested by older age, larger cavity diameters indexed to BSA despite lower absolute values, higher systolic pulmonary pressure, and higher MIDA score, reflecting a more advanced DMR stage in a-minimally symptomatic females. Of note one-third of a-minimally symptomatic females reached or exceeded the threshold of left ventricular end-systolic diameter (LVESD) ≥ 21 mm/m^2 vs. less than one-fourth of a-minimally symptomatic males. Lastly, EuroSCORE II was higher in a-minimally symptomatic females as compared with a-minimally symptomatic males (1.54 ± 1.23 vs. 1.37 ± 1.28, $P = .02$), reflecting this more advanced presentation in this subset despite the lack of symptoms. Supplementary data online, *Tables S3* and *S4*, depict baseline clinical and echocardiographic characteristics of 1565 a-minimally symptomatic patients (NYHA Classes I–II at referral) according to sex. Stratified by functional class, females had access to mitral surgery, similar to males when highly symptomatic [adjusted HR 0.91 (0.77–1.08), $P = .28$] but much lower when a-minimally symptomatic [HR 0.81 (0.71–0.93), $P = .002$] even adjusting for comorbidity/MIDA score [adjusted HR 0.87 (0.78–0.97), $P = .009$].

Post-operative outcome

Operative mortality was 2.1% in females and 1.4% in males ($P = .3$). Mean post-operative follow-up was 7.5 ± 2.8 years, similar between sexes ($P = .8$). During post-operative follow-up, 508 patients died, 144 females (44 CV) and 364 males (127 CV). Five-/10-year post-operative survival was similar between sexes (88 ± 2%/75 ± 2% in females vs. 89 ± 1%/75 ± 1% in males, $P = .7$). Female sex was univariately associated with post-operative mortality vs. male sex [HR 1.34 (1.07–1.69), $P = .01$] but was not when adjusting for baseline comorbidity/MIDA score [adjusted HR 1.21 (0.97–1.55), $P = .09$]. Post-operatively, 203 patients developed HF (67 females and 136 males). Five-/10-year rates of post-operative HF were 9 ± 1%/16 ± 2% in females vs. 7 ± 1%/12 ± 1% in males ($P = .03$). Female sex was univariately associated with post-operative HF [HR 1.40 (1.02–1.92), $P = .03$] but did not reach significance adjusting for baseline comorbidity/MIDA score [adjusted HR 1.26 (0.92–1.73), $P = .15$].

Overall outcome throughout follow-up

Mean total follow-up under conservative and surgical management was 9.2 ± 5.4 years.

Total mortality

During total follow-up, 904 patients died (280 females and 624 males). Five- and 10-year overall survival rates under conservative and surgical management are presented in *Table 3* (right panel). Excess mortality compared with expected remained highly significant in females but disappeared in males (*Figure 4* and *Table 3*, right panel). In Cox models, female sex was associated with total mortality univariably [HR 1.46 (1.27–1.70), $P < .0001$] and remained independently so adjusting for comorbidity/MIDA score [adjusted HR 1.35 (1.17–1.57), $P < .0001$]. Further adjustment to time-dependent surgery did not alter the negative independent impact of female sex on total mortality

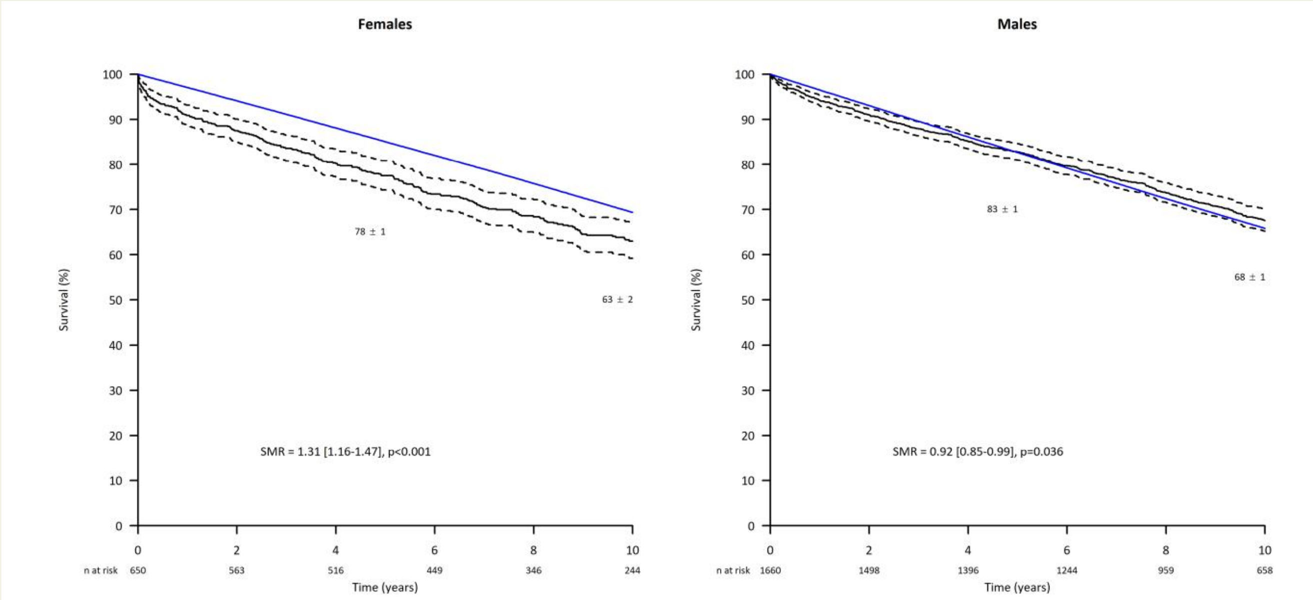


Figure 4 Comparison of observed to expected overall survival including conservative and surgical management in 650 females (left) and 1660 males (right) with severe degenerative mitral regurgitation due to flail leaflet. Normal life expectancy is restored in males, whereas females still display excess mortality despite surgical management. Black solid line denotes observed survival, dotted lines 95% confidence interval, and straight line expected survival. SMR, standardized mortality ratio

[adjusted HR 1.26 (1.09–1.46), $P = .002$], while mitral surgery showed an independent protective effect [adjusted HR 0.58 (0.51–0.67), $P < .0001$]. Further adjustment to ACE inhibitors and beta-blockers did not affect the impact of female sex on total mortality (Supplementary data online). Further adjustment to MR grade did not affect, the impact of female sex on total mortality (Supplementary data online).

Total cardiovascular mortality

Overall, 333 patients died from CV cause (113 females and 220 males). Five-/10-year rates were 10 ± 1%/17 ± 2% in females vs. 7 ± 1%/13 ± 1% in males ($P = .002$). Female sex was associated with total CV mortality univariably [HR 1.41 (1.13–1.78), $P = .003$] and remained independently so adjusting for comorbidity and MIDA score [adjusted HR 1.26 (1.01–1.58), $P = .04$]. Further adjustment to time-dependent surgery attenuated the negative independent impact of female sex on CV mortality [adjusted HR 1.20 (0.97–1.50), $P = .09$], while mitral surgery kept a strong independent protective effect [adjusted HR 0.26 (0.21–0.33), $P < .0001$]. Further adjustment to ACE inhibitors and beta-blockers did not affect the impact of female sex on total CV mortality (Supplementary data online). Further adjustment to MR grade did not affect the impact of female sex on total CV mortality (Supplementary data online).

Total heart failure

Overall, 425 patients developed at least 1 episode of HF (144 females and 281 males). Five- and 10-year rates were 17 ± 2% and 24 ± 2% in females vs. 12 ± 1% and 18 ± 1% in males ($P < .001$). Female sex was associated with total HF univariably [HR 1.43 (1.17–1.74), $P < .001$] and adjusting for comorbidity/MIDA score [adjusted HR 1.35 (1.09–1.63), $P = .006$]. Further adjustment to time-dependent surgery did not alter the negative independent impact of female sex on total HF [adjusted HR 1.32 (1.07–1.61), $P = .008$], while beneficial impact of mitral surgery was weaker [adjusted HR 0.83 (0.70–1.03), $P = .08$]. Further adjustment to ACE inhibitors and beta-blockers did not affect the impact of female sex on total HF (Supplementary data online). Further adjustment to MR grade did not affect the impact of female sex on total HF (Supplementary data online).

A-minimally symptomatic patients

Restriction of the analysis to a-minimally symptomatic patients (NYHA Classes I–II at referral) did not affect the negative impact of female sex on overall outcome (Supplementary data online).

Propensity score matching

Propensity score matching between males and females was performed using all baseline variables known as outcome risk factors in DMR as variables of adjustment, namely age, Charlson score, symptoms, atrial fibrillation, MR grade, and LVEF. Cavity diameters and BSA were not included due to their sex-specific nature. Propensity score matching resulted in the identification of 635 matched pairs by sex, whose baseline characteristics are presented in Supplementary data online, *Tables S5 and S6*. While some adjusted HRs did not reach significance due to the loss of power linked to the loss of sample size, the trends were all similar to those observed in the entire cohort. Female sex HRs are presented as Supplementary data online.

Interaction between year of inclusion and sex

Only 25% of our cohort was enrolled before 1995. Comparing three periods, before 1995, 1995 to 2000, and after 2000, no difference was observed in terms of age of patients at referral ($P = .09$) and sex distribution ($P = .5$). No interaction was observed between inclusion year ranges and sex regarding symptoms ($P = .9$), LV end-diastolic diameter ($P = .61$), LV end-systolic diameter ($P = .38$), LVEF ($P = .41$), LA diameter ($P = .6$), systolic pulmonary artery pressure ($P = .18$), and EuroSCORE II ($P = .75$). No interaction was observed between year of inclusion and impact of sex on mortality under conservative treatment ($P = .1$), on rates of mitral surgery ($P = .14$) and on total mortality through all follow-up ($P = .9$). Further adjustment to date of inclusion in addition to Charlson score and MIDA score in multivariable models did not alter the negative impact of female sex on outcome under conservative management, both for mortality [adjusted HR 1.27 (1.02–1.59), $P = .03$] and HF [adjusted HR 1.34 (1.01–1.78), $P = .04$]. It did not affect the lower access of females to mitral surgery [adjusted HR 0.86 (0.78–0.96), $P = .007$], neither the negative impact of female sex on overall outcome throughout follow-up, both for total mortality [adjusted HR 1.25 (1.08–1.45), $P = .002$] and total HF [adjusted HR 1.29 (1.05–1.58), $P = .01$].

Discussion

Our study conducted among 1660 males and 650 females from first referral for clinically significant DMR due to flail leaflets in US and European tertiary care centers shows considerable sex-specific differences in presentation, management, and outcome. Females are a minority of patients with DMR due to fail leaflet in tertiary centers and are referred at an older age, with more symptoms and more often with HF and elevated pulmonary pressure. Females present with smaller hearts and less frequent systolic diameter reaching guideline-based thresholds but have more severe cardiac enlargement normalized to their smaller BSA. Excess mortality vs. expected under conservative management is notable in both sexes but is more pronounced in females, with excess cardiac mortality/HF independently of comorbidity and other determinants of outcome. Females remain longer under medical management and are less referred to mitral surgery than males, particularly among a-minimally symptomatic patients. Ultimately, these differences in presentation and management culminate into major differences regarding total prognosis after referral including medical and post-operative outcome, as males enjoy normal life expectancy restoration, whereas females display persistent excess mortality and higher HF rates despite surgery (*Structured Graphical Abstract*).

Females with degenerative mitral regurgitation

Epidemiological evidence regarding population-based sex-related susceptibility to DMR, i.e. MR caused by various forms of MVP, is scant.[25] The fundamental discordance comes from the reported female predominance among all carriers of MVP,[26] contrasting with surgical[3] and medical[21] tertiary care series of patients with 'significant' DMR displaying large male predominance. This imbalance may be related to male sex association with more severe DMR[27,28] or to underreferral of females with DMR to diagnostic echocardiogram or centers of expertise. This latter hypothesis is supported by the well-balanced sex distribution among patients with clinically 'significant' MR reported by systematic population screening of all-cause MR[29] or in population-based series of organic MR,[2] suggesting that female sex underrepresentation in clinical series is mostly linked to center-of-expertise referral after DMR diagnosis.[30] Underreferral reasons would be extremely complex to analyse, but a possible contributor to referral bias affecting females is their 'small' heart dimensions despite actual more severe cardiac remodelling accounting for BSA[13,17] as confirmed by the present analysis. Referral bias is particularly vexing, since it amplifies undertreatment and thus has considerable implications in DMR management and outcome in females.

Degenerative mitral regurgitation management and outcome in females

Degenerative mitral regurgitation major management tool is mitral valve repair,[3,31] which provides improved outcome over valve replacement at all ages,[5] even in the oldest patients and without sex interaction, making the issue of valve repair in females crucial to address.[25] Valve repair feasibility in females was reported to be lower in national databases of all-cause MR,[15] with the caveat of heterogeneity both of surgical expertise according to centers and of MR aetiology.[16] Conversely, single-expert centers suggested similarly achievable repair rates in males and females with homogeneous DMR.[13,14] In our multicenter setting, we observed slightly lower repair procedures in females with DMR due to flail leaflet, unlikely responsible for the observed small divergence in post-operative outcome. Data on sex-specific post-operative outcome are confusing. Results from national databases suggested excess post-operative mortality in females,[15] but subsequent single-center studies showed alternatively either excess post-operative mortality,[16] excess post-operative HF,[13] or conversely similar outcome,[14] in females vs. males. In that regard, our multicenter study, enrolling only patients with DMR, showed absolute post-operative outcomes slightly lower in females but essentially due to older age, higher mitral severity score, and higher risk at referral, since after adjustment for such worse presentation, survival and HF were not significantly different. Worse post-operative outcome seems thus not intrinsically related to female sex, neither to different repair rates, but to their later presentation at a more advanced stage of the disease.[13] Multiple registries have reported improved survival in patients treated by early surgery,[6,32,33] and clinical guidelines have evolved to rank highly mitral surgery indications in asymptomatic patients without signs of ventricular dysfunction, at low surgical risk and high repair probability.[7,8] Our multicenter cohort shows that females and males with similar severe HF symptoms at referral are equally and promptly sent to mitral surgery, confirming that severe symptoms are unanimously accepted as strong surgical signal. Conversely, among patients with no or minimal symptoms, females are less and later referred to surgery. Yet, clinical and echocardiographic presentation in this subset attested a more advanced DMR stage in females despite lack of symptoms, consistent with higher EuroSCORE II, which should have been an incentive to prompt surgery. This differential management, leaving more females subject to DMR risks under medical surveillance, ultimately translates into overall excess mortality in females vs. restoration of life expectancy in males. Including mitral surgery as time-dependent variable in multivariable models attenuated and but did not suppress the negative impact of female sex on overall outcome throughout follow-up, reinforcing the hypothesis of delayed referral to tertiary care centers where surgery is indicated and of deferred surgical performance. Lower access to mitral surgery of a-minimally symptomatic females despite adjustment for comorbidity and all MR-related characteristics included in the MIDA score may also suggest contribution of sex-specific social behaviour since females are often caregivers, reluctant to care for themselves.[25,34] But more addressable in managing females is DMR staging,[21,35] with DMR severity being downgraded in females despite similar valve lesions or regurgitation assessment.[13] The present study is on line with the recent call for research data to elucidate sex disparities in DMR management and outcome[36] by adding new evidence of the risk of misinterpretation of DMR consequences if smaller BSA of females is not accounted for.[13,17] Irrespective, sex-specific care needs to address all these factors to homogenize DMR management between males and females and promptly correct excess mortality and excess HF endured by females with DMR.

Clinical implications

Females with severe MR are underrepresented among patients to whom surgical treatment is offered, likely because the seriousness of their valve disease may be underestimated.[13] Systematic use of BSA-adjusted cavity diameters, accepted for aortic regurgitation, has not been implemented for DMR in recent guidelines,[7,8] despite the reported prognostic value of indexed LVESD.[24] Quantitative DMR assessment by regurgitant orifice area and volume[37,38] should be performed as recommended by current guidelines.[7,8]

Limitations

Retrospective identification of patients with DMR may be considered a limitation, but all assessment/measurements were performed prospectively at baseline, with uniform diagnosis, in a multicenter, consecutive process, allowing gathering a very large cohort providing unique insights regarding females with DMR. This large cohort extends considerably preliminary data in community/tertiary populations[39] and provides crucial new information on excess mortality in females. Extensive follow-up of all individuals from community diagnosis to ultimate expert centers/intervention referral, to elucidate subtle mechanisms underpinning referral biases/undertreatment affecting females with DMR, would be unrealistic. Negative outcome impact of female sex was inferred from adjustment of multivariable models to all widely acknowledged variables impacting outcome included in the MIDA score and Charlson comorbidity score. Adjustment to B-type natriuretic peptide (BNP) level could not be performed since serum BNP level was not available. However, its use is not recommended for DMR management in current guidelines.[7,8] The wide timeframe of enrolment exposes to changes in echocardiographic practices, but the election of flail leaflet in the MIDA registry,[19] as in the first seminal outcome studies dedicated to primary MR,[23] is widely accepted as a pertinent surrogate for severe primary MR[23] and included in the recommended integrative grading.[40] It also exposes to evolution with time of clinical practices but which appeared to apply equally to males and females as no interaction was observed between year of inclusion, sex-related specificities of clinical and echocardiographic presentation of DMR, and female sex impact on outcome. Likewise, forcing into multivariable models, the period of patients' inclusion did not alter neither the negative impact of female sex on outcome nor the lower access of females to mitral surgery similarly observed throughout all timespan of inclusion. Remote last date of follow-up can be perceived as restraining the applicability of our data to current practice and limiting outcome analysis, but it was an a priori decision not to renew follow-up at a more recent date. Indeed, since study closure, no sex-specific guidelines mentioned sex-specific DMR management making unlikely significant changes in routine practice capable to alter the outcome penalty observed in females. In addition, recalling patients for follow-up would have added deaths to the count but almost exclusively after 10 years of follow-up, while the difference between males and females in terms of outcome was mostly observed within the first years of follow-up and sustained afterwards with all differences established at 5 years. Due to these facts, and the considerable and quite complete follow-up up to 10 years, it appeared unessential to engage into a renewed follow-up collection that would have added few to the present results.

Conclusion

Females with DMR due to fail leaflet represent a minority of DMR patients referred to tertiary centers at an older age and with a more advanced DMR stage than males. Despite this serious presentation, females remain longer under medical management, are less referred to mitral repair, and incur higher excess mortality under medical management vs. males. While feasibility of valve repair is only slightly lower in females and post-operative survival and HF are not independently linked to sex, the overall outcome is profoundly affected by the risks incurred under medical management. Encompassing all phases of follow-up, males enjoy restoration of their life expectancy, while females continue to incur excess mortality despite surgical management. These data represent an urgent call to apply the current guideline-based trend towards early surgery for DMR, particularly in females, in order to provide all patients with optimized outcomes.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

M.E.-S. received honoraria from Edwards LifeSciences, Artivion, and HighLife.

Data Availability

No data were generated or analysed for or in support of this paper.

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Ethical Approval

Ethical approval was not required.

Pre-registered Clinical Trial Number

None supplied.

Appendix

MIDA investigators:

C. Tribouilloy, F. Trojette, C. Szymanski, D. Rusinaru, G. Touati, J. P. Remadi (University of Amiens, France).

F. Grigioni, A. Russo, E. Biagini, F. Pasquale, D. Pacini, G.D. Gargiulo (University of Bologna, Italy).

J. Boulif, C. de Meester, G. El Khoury, B. Gerber, S. Lazam, A. Pasquet, P. Noirhomme, D. Vancraeynest, J.-L. Vanoverschelde (Université Catholique de Louvain, Belgium).

J. F. Avierinos, F. Collart, A. Theron, G. Habib (University of Marseille, France).

A. Barbieri, F. Bursi, G. Modena, G. Boriani (University of Modena, Italy).

J. Maalouf, H. Michelena, V T. Nkomo, M. Enriquez-Sarano (Mayo Clinic, Mayo Medical School, Rochester MN, USA).

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