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Comprehensive Imaging in Women With Organic Mitral Regurgitation

Implications for Clinical Outcome

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ABSTRACT

OBJECTIVES The purpose of this study was to compare women and men with organic mitral regurgitation (MR) using pre- and post-operative comprehensive imaging and to analyze the effect on outcome.

BACKGROUND Management of organic MR has no sex-specific guideline recommendation, and sex differences on the basis of comprehensive imaging and links to outcome remain largely unknown.

METHODS Comprehensive imaging (MR cause, quantitation, ventricular and atrial measures, and post-operative reverse cardiac remodeling) was analyzed in 217 women and 447 men who underwent operations for organic MR from 1990 to 2000 with long-term follow-up analysis.

RESULTS Pre-operatively, women and men had similar age and ejection fraction. In women, a smaller left ventricle (LV) more often labeled as normal size (23% vs. 13%), left atrium size, and regurgitant volume (all $p < 0.01$) contrasted with higher pulmonary pressure and more heart failure symptoms (41% vs. 19%), which more often triggered surgery (all $p < 0.01$). However, normalizing for body size, LV and left atrial diameters and regurgitant volume were at least as large in women versus men. Similar normalized MR severity was confirmed by similar post-operative reverse cardiac remodeling in women and men (all $p > 0.06$). During follow-up (10.4 ± 3.7 years) women had similar survival as men ($p = 0.5$) but experienced more heart failure (at 15 years: $36 \pm 7\%$ vs. $19 \pm 3\%$; $p = 0.03$; adjusted hazard ratio 1.63 [95% confidence interval: 1.08 to 2.43]; $p = 0.02$) linked to more frequent pre-operative heart failure symptoms ($p < 0.001$).

CONCLUSIONS Women who undergo mitral surgery for organic MR receive similar repair for similar degenerative lesions defined by echocardiography and enjoy similar survival and reverse cardiac remodeling, but they incur excess post-operative heart failure linked to worse pre-operative presentation. Imaging that does not account for body size shows smaller absolute cardiac dimensions and regurgitant volumes, which tends to underestimate MR severity in women. (J Am Coll Cardiol Img 2016;9:388–96) © 2016 by the American College of Cardiology Foundation.

Mitral regurgitation (MR) is the most frequent valvular heart disease (1). Despite similar MR prevalence in men and women (1), few studies have analyzed sex differences (2), and potential sex differences (3,4) are hindered by lack of comprehensive pre- and post-operative imaging. Furthermore, the links between sex differences vis-a-vis imaging, surgical-referral triggers, cardiac reverse remodeling, and post-operative outcomes remain undefined. Because of these uncertainties, U.S. and European guidelines mention no sex-specific differences in management or outcome, do not account for body size of men and women for MR surgical triggers, and refer only to absolute left ventricular (LV) dimensions (5,6). To address these uncertainties, comprehensive imaging data are warranted regarding specific MR cause, quantitative MR assessment, LV and left atrial (LA)

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remodeling before surgery, and reverse-remodeling after surgery. Thus, we analyzed a consecutive cohort of men and women who underwent operations for organic MR with comprehensive imaging and long-term post-operative outcome. We aimed at verifying the null hypothesis that women who underwent mitral surgery for organic MR: 1) had similar clinical presentation, particularly similar MR severity and cardiac remodeling; and 2) had similar clinical and LV outcomes as men. Rejection of these null hypotheses would have major clinical implications for organic MR assessment and management in women, for whom no specific recommendation has yet been made.

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METHODS

We analyzed consecutive patients who underwent mitral surgery for pure, acquired, isolated organic MR (repair or replacement) at Mayo Clinic, Rochester, Minnesota, from 1990 through 2000. Our main cohort of interest required comprehensive imaging defining MR cause, MR quantitation, LV/LA remodeling, and post-operative reverse remodeling, thus including patients with: 1) complete clinical and echocardiographic assessment within 6 months prior to and after surgery; 2) quantitative pre-operative assessment of MR severity; and 3) detailed post-operative outcome (**Figure 1**). A verification cohort (organic MR operated during the same period, irrespective of comprehensive imaging availability) was also analyzed to verify bias-absence. We excluded patients age <18 years, with previous valve surgery, functional MR, cardiomyopathy, or congenital or pericardial disease. MR that was considered "moderate" with surgery indicated for symptoms, LV dysfunction (ejection fraction <60%, end-systolic dimension ≥40 mm), pulmonary hypertension, or atrial fibrillation considered linked to MR was not excluded (7). The study was approved by the Mayo Clinic Institutional Review Board.

DOPPLER ECHOCARDIOGRAPHIC ASSESSMENT. Comprehensive Doppler and 2-dimensional echocardiography provided data prospectively recorded and obtained by direct electronic transfer. Echocardiography was performed pre-operatively at 27 ± 35 days (median 14 days) and post-operatively at 6 ± 10 months. This time frame allows for LV reverse remodeling in MR (8).

MR cause was defined by echocardiography and confirmed by surgical direct valve inspection.

LV and LA dimensions were obtained by 2-dimensional echocardiography. Normal range for left ventricular end-diastolic diameter (LVEDD) used Gardin regression (9). We considered LVEDD enlargement mild-moderate if it was <20% and severe if it was >20% above the upper normal limit. Left ventricular ejection fraction (LVEF), when used unaltered by electronic download, is strongly predictive of outcome in patients with organic MR after surgery (10) and who are under medical management (11,12). LV mass was obtained using a recommended formula (13).

MR severity, quantified by the PISA (proximal isovelocity surface area) method, quantitative Doppler (14), or both, was expressed as effective regurgitant orifice (ERO) and regurgitant volume (RVol). The PISA method was used more frequently (81%) than quantitative Doppler (62%), but use of the 2 methods was attempted as often as possible and correlations between methods remained >0.90 ($p < 0.0001$), with slopes of regressions not different from 1.0, as previously validated (15). Severe MR was considered for RVol ≥60 ml/beat (14) obtained in all patients, whereas incomplete continuous-wave Doppler limited ERO calculation in some patients. However, RVol and ERO are highly correlated ($r = 0.92$) and provide similar categorization power.

All measurements were also indexed by body surface area (BSA) at echocardiography.

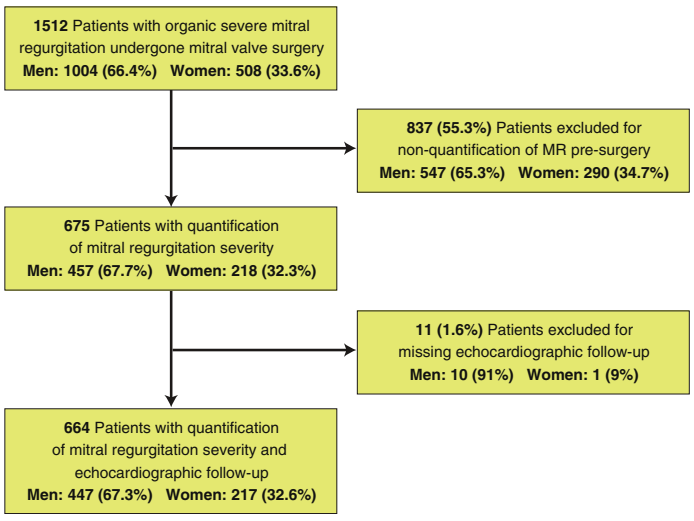
CLINICAL ASSESSMENT AND FOLLOW-UP. Pre-operative clinical data were collected during systematic consultation and echocardiography. Cardiac rhythm was assessed by electrocardiogram. Comorbid conditions were summarized by the Charlson score (16). Cardiovascular history, medications, and follow-up events involved reviewing all medical records, regular follow-up questionnaires, contacts with personal physicians and next of kin, and death certificates. Clinical endpoints were all-cause post-operative mortality and heart failure (HF). HF diagnosis relied on combination of symptoms and signs in Framingham criteria (17), on the basis of a comprehensive review of patients' records, notes, and documents as well as direct consultations/contacts with patients/physicians/next of kin.

STATISTICAL ANALYSIS. Data are presented as percentages for categorical variables and as mean ± SD or median (25th, 75th percentiles) for continuous variables. Distribution of continuous variables was tested by Shapiro-Wilk test. Direct comparison between men and women used Student *t* tests or Wilcoxon rank sum tests for continuous variables and chi-square or Fisher exact tests for categorical variables as appropriate. Survival and HF rates, estimated using the

ABBREVIATIONS AND ACRONYMS

BSA = body surface area
ERO = effective regurgitant orifice
HF = heart failure
LA = left atrial
LV = left ventricular
LVEDD = left ventricular end-diastolic diameter
MR = mitral regurgitation
RVol = regurgitant volume

FIGURE 1 Flow Chart of the Study



Note the selection criteria for the comprehensive imaging main cohort (n = 664) and the total verification cohort (n = 1,512).

Kaplan-Meier method, were compared using the log-rank test. Univariable and multivariable Cox proportional hazards analyses estimated the relative risk of death or HF, which is presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Variables with univariable significant association to outcome and with clinical relevance were included in multivariable models to adjust for sex effect (age, HF symptoms, atrial fibrillation, LVEF, Charlson index, and type of surgery repair/replacement). Changes in echocardiographic variable between baseline and post-operative follow-up were analyzed with 2 way analysis of variance for repeated measurements. Analysis of main and verification cohorts for bias involved models with an interaction term: sex*cohort. All tests were 2-tailed. A p value <0.05 was considered statistically significant. Analyses were performed using JMP version 9.0.1 (SAS Institute Inc., Cary, North Carolina).

TABLE 1 Baseline Clinical Characteristics

	All Patients (N = 664)	Men (n = 447)	Women (n = 217)	p Value
Age, yrs	64 ± 13	63 ± 13	65 ± 14	0.20
Body surface area, m^2	1.91 ± 0.17	2.00 ± 0.16	1.73 ± 0.18	<0.0001
Body mass index, kg/m^2	26 ± 6	26 ± 4	26 ± 9	<0.8
Hypertension	36	35	37	0.60
Diabetes mellitus	5	4	6	0.30
Smoking	47	54	34	<0.0001
Dyslipidemia	43	46	38	0.05
Peripheral vascular disease	3	3	4	0.80
Hypertension	36	35	37	0.60
Coronary artery disease	26	29	20	0.02
COPD	8	6	10	0.07
Cerebrovascular disease	6	6	6	0.70
Atrial fibrillation	24	23	27	0.30
Heart failure symptoms	26	19	41	<0.0001
Charlson Comorbidity Index	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.10
Medical therapy				
ACE inhibitors/ARBs	51	48	59	0.01
Beta-blockers	17	15	24	0.006
Diuretic agents	25	23	31	0.03

Values are mean ± SD, %, or median (25th, 75th percentiles).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease.

RESULTS

CLINICAL PRE-OPERATIVE CHARACTERISTICS. During the study period (January 1990 to December 2000), our main cohort of interest, organic MR surgical correction with comprehensive imaging, included 664 patients. The 1,512 patients who underwent organic MR surgery during that period (irrespective of comprehensive imaging) formed our verification cohort (Figure 1).

Clinical characteristics of the main cohort of interest (Table 1) included 447 (67%) men and 217 (33%) women. Age (64 ± 13 years) was not different, but women presented with more HF symptoms and more drug-prescribed therapy. Conversely, women seldom were smokers or had dyslipidemia or coronary disease, but had borderline more frequent obstructive pulmonary disease. There were no differences in other clinical risk factors, atrial fibrillation, or comorbidities.

PRE-OPERATIVE QUANTITATIVE ECHOCARDIOGRAPHY. Pre-operative echocardiographic characteristics are presented overall and are compared between men and women with and without BSA indexation in Table 2. For nonindexable measures, LVEF was similar in men and women (p = 0.45), whereas systolic pulmonary artery pressure was notably higher in women versus men and was markedly close to the 50-mm Hg threshold that defines pulmonary hypertension (Table 2). All absolute pre-operative measures of LV size and mass or LA dimension in women were smaller than in men. Accounting for normal LV size (9), women were seldom categorized with severe LV dilation versus men (13% vs. 26%; p = 0.0002) and were more often classified as having normal LV size. Hence, all absolute LV and LA measures appear to point toward lesser LV remodeling in women than men. Lesser volume overload appears supported by MR quantitation, with smaller measured RVol and ERO in women versus men. Hence, final interpretation, taking into account the entire information, less

often classified MR as severe in women compared to men (70% vs. 81%; p = 0.002).

The bottom of Table 2 presents BSA-normalized echocardiographic measures, showing women with larger normalized LV and LA versus men. LV mass index remained slightly larger in men. Conversely, BSA-normalized RVol showed no difference between men and women. Therefore, conservative interpretation of BSA-normalized measures is that cardiac remodeling and MR severity are at least as severe in women as in men once body size is accounted for (Table 2).

POST-OPERATIVE ECHOCARDIOGRAPHIC CHANGES. Post-operative echocardiographic measures and changes evaluated in all patients (median 6 months) are shown in Table 3 and Figure 2. Post-operative absolute dimensions were larger in men than women but were mostly close to normal range, although the LA remained enlarged. Post-operative absolute dimension changes (Table 3, bottom) showed marked LVEDD and LA decrease, whereas the decline in LV end-systolic diameter was small. LVEDD decreased by 8 ± 7 mm after surgery, and decreased similarly in men and women (p = 0.06). LVEF, LV mass, and systolic pulmonary artery pressure also decreased significantly after surgery. Changes in the LV and LA showed no sex differences, but change in pulmonary systolic artery pressure was greater in women (p = 0.02), confirming that suppression of volume overload eliminated pre-operative excess pulmonary hypertension in women. When restricted to 324 patients with only later post-operative echocardiography (median 11 months), the analysis showed reverse remodeling as greater in women versus men. Comparison of BSA-normalized LV and LA changes (Figure 2) shows greater and similar reverse remodeling in men and women, reflecting similar suppression of volume overload in men and women by MR surgical correction.

OPERATIVE CHARACTERISTICS. Median duration from first symptom to medical presentation was 6 months (interquartile range: 3 to 12 months), and was not different (p = 0.11) between men (6 months [3 to 12 months]) and women median [25th, 75th percentiles] (6 months [3 to 12 months]). Clinical indication for surgery was different in women versus men (Table 4). MR etiology was predominantly degenerative (89% overall), but less in women versus men (78% vs. 94%; p < 0.001), whereas rheumatic disease prevalence was higher in women (11% vs. 2%; p < 0.001). More women (58% vs. 48%; p = 0.007) underwent mitral surgery for guideline Class I indications (HF symptoms and/or LV dysfunction), driven mainly by symptoms, although ventricular triggers were similar in both sexes (p = 0.25). No difference was found in atrial fibrillation and/or pulmonary hypertension indications. Consequently, early surgery (without Class I, atrial fibrillation/pulmonary hypertension triggers) was less frequent in women than men (26% vs. 39%; p = 0.007) even after excluding rheumatic etiology (p = 0.01).

TABLE 2 Pre-Operative Doppler Echocardiographic Characteristics

	All Patients (N = 664)	Men (n = 447)	Women (n = 217)	p Value
Absolute Doppler echocardiographic measurements				
LVEDD, mm	59 ± 6	60 ± 7	55 ± 6	<0.0001
LVESD, mm	36 ± 6	37 ± 3	34 ± 4	<0.0001
LAD, mm	52 ± 9	53 ± 9	51 ± 10	0.02
LV mass, g	257 ± 60	275 ± 60	220 ± 59	<0.0001
ERO, cm^2	0.57 ± 0.29	0.61 ± 0.31	0.49 ± 0.24	<0.0001
RVol, ml/beat	92 ± 43	98 ± 47	90 ± 35	<0.0001
LVEF, %	63 ± 9	63 ± 9	63 ± 8	0.45
SPAP, mm Hg	45 ± 14	43 ± 13	48 ± 15	<0.0001
Severe MR, %	77	81	70	0.002
LVEDD dimension categorization				
Normal	16	13	23	
Mild-moderate dilation*	62	61	64	0.0002
Severe dilation†	22	26	13	
Indexed Doppler echocardiographic measurements				
LVEDD/BSA, mm/m^2	31 ± 4	30 ± 4	32 ± 5	<0.0001
LVESD/BSA, mm/m^2	19 ± 4	19 ± 3	20 ± 4	<0.0001
LAD/BSA, mm/m^2	28 ± 5	27 ± 5	30 ± 7	<0.0001
LV mass/BSA, g/m^2	135 ± 30	137 ± 28	128 ± 34	<0.0001
RVol/BSA, ml/m^2	48 ± 23	49 ± 24	48 ± 22	0.20

Values are mean ± SD or %. *LVEDD between 100% and 120% of upper limit of normal for the individual. †LVEDD >120% of upper limit of normal.

BSA = body surface area; EF = ejection fraction; ERO = effective regurgitant orifice; LAD = left atrium diameter; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; RVol = regurgitant volume; SPAP = systolic pulmonary artery pressure.

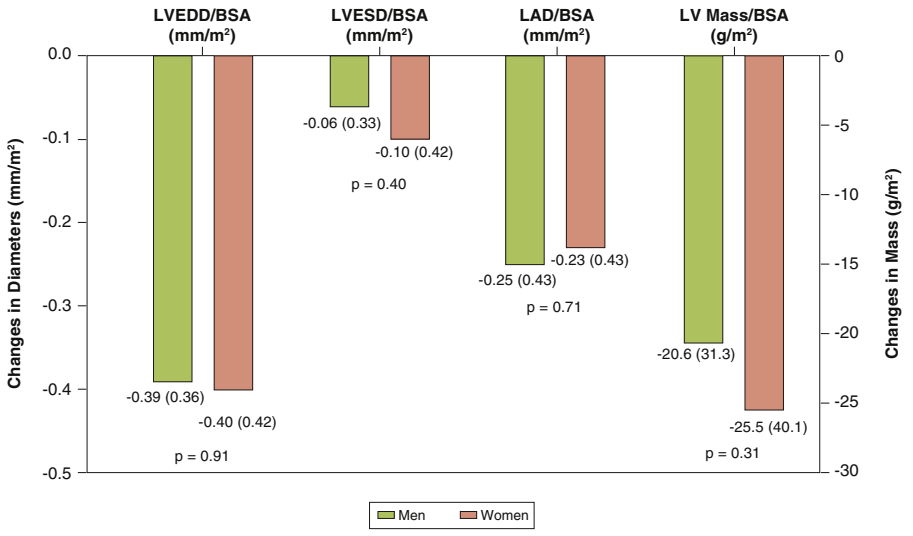
TABLE 3 Post-Operative Absolute and Changes (Δ) in Echocardiographic Characteristics

	All Patients (N = 664)	Men (n = 447)	Women (n = 217)	p Value
Post-operative absolute Doppler echocardiographic measurements				
LVEDD, mm	51 ± 6	52 ± 7	49 ± 6	<0.0001
LVESD, mm	35 ± 7	36 ± 8	33 ± 7	<0.0001
LAD, mm	47 ± 9	48 ± 5	46 ± 7	0.02
LV mass, g	214 ± 60	232 ± 63	183 ± 55	<0.0001
LVEF, %	55 ± 11	54 ± 11	57 ± 10	0.004
SPAP, mm Hg	38 ± 11	37 ± 11	39 ± 12	0.1
Post-operative changes in echocardiography data				
Δ LVEDD, mm	−8 ± 7*	−8 ± 7	−7 ± 6	0.06
Δ LVESD, mm	−2 ± 6†	−2 ± 6	−2 ± 6	0.7
Δ LAD, mm	−5 ± 8*	−5 ± 8	−4 ± 7	0.3
Δ LV mass, g	−42 ± 63*	−41 ± 61	−43 ± 67	0.8
Δ LVEF, %	−8 ± 11*	−8 ± 11	−7 ± 11	0.3
Δ SPAP, mm Hg	−7 ± 13*	−6 ± 13	−9 ± 13	0.02

*p < 0.0001 compared to the baseline data. †p < 0.001 compared to the baseline data.

Abbreviations as in Table 3.

FIGURE 2 Reverse Remodeling After Mitral Regurgitation Surgery Compared in Men and Women



Changes in left ventricular and left atrial dimensions and/or mass indexed to body surface area observed after mitral regurgitation surgery in men **(green bars)** and women **(pink bars)**. Note the similar reverse remodeling in both sexes. BSA = body surface area; LAD = left atrial diameter; LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter. Data are presented by mean (SD).

The type of surgery (Table 4) was predominantly valve repair (91% overall), but was feasible in only 85% of women versus 93% of men (p = 0.0005). Stratified by MR etiology, there was no difference in repair for degenerative MR between sexes, although in the small group of rheumatic MR there were fewer repairs in women (p = 0.01). Consistent with the lower prevalence of coronary disease in women, the need for concomitant coronary bypass surgery (Table 4) was lower in women versus men (17% vs. 25%; p = 0.02).

TABLE 4 Mitral Regurgitation Etiology, Surgical Indications, and Management

	All Patients (N = 664)	Men (n = 447)	Women (n = 217)	p Value
Etiology of mitral regurgitation				
Degenerative mitral disease	89	94	78	
Infective endocarditis	3	3	3	<0.0001
Rheumatic valve disease	5	2	11	
Mixed	3	1	8	
Surgical management				
Mitral valve repair	91	93	85	0.0005
Mitral valve repair by etiology:				
Repair for degenerative disease	94	94	92	0.40
Repair for endocarditis	80	79	83	0.80
Repair for rheumatic disease	50	88	38	0.01
Concomitant CABG	23	25	17	0.02
Bypass time, min	51 (30, 82)	53 (30, 82)	49 (30, 81)	0.30
Triggers for surgery				
Heart failure symptoms and/or ventricular dysfunction)	51	48	58	
Atrial fibrillation and/or pulmonary hypertension	14	13	16	0.007
Early surgery	35	39	26	

Values are % or median (25th, 75th percentiles).
CABG = coronary artery bypass graft.

FOLLOW-UP AND OUTCOMES. During follow-up of 10.4 ± 3.7 years, 212 patients died and 109 had HF, yielding at 10- and 15-year mortality of 24 ± 2% and 42 ± 3% and HF rate of 15 ± 1% and 25 ± 3%, respectively. Women incurred more (p = 0.03) 10- and 15-year post-operative HF (20 ± 3% and 36 ± 7%) than men (13 ± 2% and 19 ± 3%) (Figure 3). After adjustment for LVEF, women had a higher risk of HF (adjusted HR: 1.67 [95% CI: 1.12 to 2.48]; p = 0.01). When age and Charlson index score were added, women remained at higher risk of HF (adjusted HR: 1.65 [95% CI: 1.10 to 2.48]; p = 0.02). After further adjustment for atrial fibrillation and repair performance, women had a higher risk of HF (HR: 1.63 [95% CI: 1.08 to 2.43]; p = 0.02). Results remained similar, excluding concomitant coronary bypass grafting or coronary artery disease.

Analysis of potential interactions with HF incidence focused on pre-operative HF symptoms and MR recurrence. Pre-operative HF symptoms were strongly associated with post-operative HF

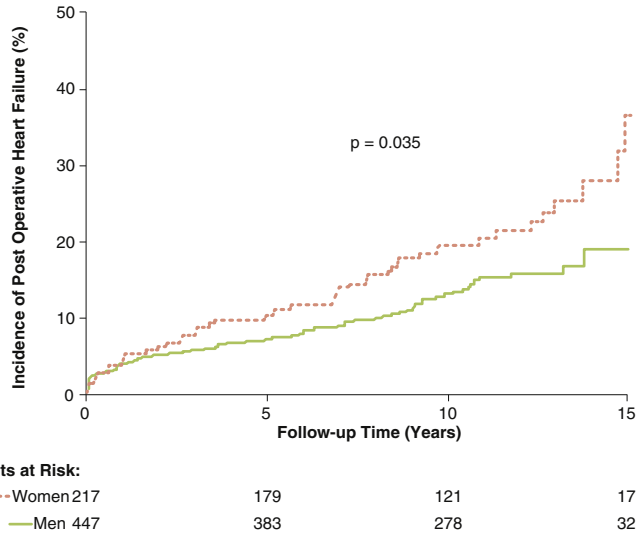
(univariable HR: 3.14 [95% CI: 2.14 to 4.59]; p < 0.0001). Because sex and pre-operative HF symptoms were associated pre-operatively, pre-operative HF symptoms replaced sex in multivariate models that included both variables. Pre-operative HF symptoms remained linked to post-operative HF risk after adjusting for LVEF (adjusted HR: 3.19 [95% CI: 2.13 to 4.75]; p < 0.0001), for added age and Charlson score (adjusted HR: 2.32 [95% CI: 1.52 to 3.51]; p < 0.0001), and for added atrial fibrillation and repair (adjusted HR: 2.34 [95% CI: 1.53 to 3.60]; p < 0.0001).

During follow-up, 62 patients developed moderate or greater recurrent post-operative MR with no sex difference (p = 0.6). Excluding recurrent MR, association between sex and post-operative HF (adjusted for LVEF, age, Charlson index, atrial fibrillation, repair, and coronary artery bypass graft) remained unaffected (adjusted HR: 2.21 [95% CI: 1.35 to 3.56]; p = 0.002). Post-operative transmitral gradient was slightly higher in women (3.9 ± 2.0 mm Hg vs. 3.4 ± 1.6 mm Hg; p = 0.006) but was unrelated to post-operative HF (adjusted HR: 1.03; p = 0.65). Due to altered mitral and pulmonary venous velocity, diastolic LV function cannot be reliably evaluated, and differences in HF between men and women are not linked to detectable differences in residual MR, LV function, or mitral obstruction.

Post-operative survival was 77 ± 2% at 10 years and 58 ± 3% at 15 years, was similar in men and women (Figure 4), and remained similar after all adjustments (all p > 0.20).

CHARACTERISTICS AND OUTCOME IN THE VERIFICATION COHORT. To specify quantitatively volume overload and reverse LV remodeling, our main cohort required pre-operative MR quantitation and post-operative echocardiography. Thus, to assess that these requirements did not bias our series, we verified that the entire series without these requirements (1,004 men vs. 508 women) would result in similar results. Overall, age comparisons (men: 63 years vs. women: 65 years) showed no interaction between cohorts (p = 0.73). HF symptoms were more prevalent in women (47% vs. 26%; p < 0.0001) similarly between the main and verification cohorts (p = 0.37). Prevalence of rheumatic MR was higher in women (12% vs. 2%) without interaction between cohorts (p = 0.15), explaining the lower repair rate in women (p < 0.0001). Differences in LV and LA dimensions between men and women were similar between cohorts (all p > 0.25). Hence, no trend for bias could be detected in baseline and operative characteristics.

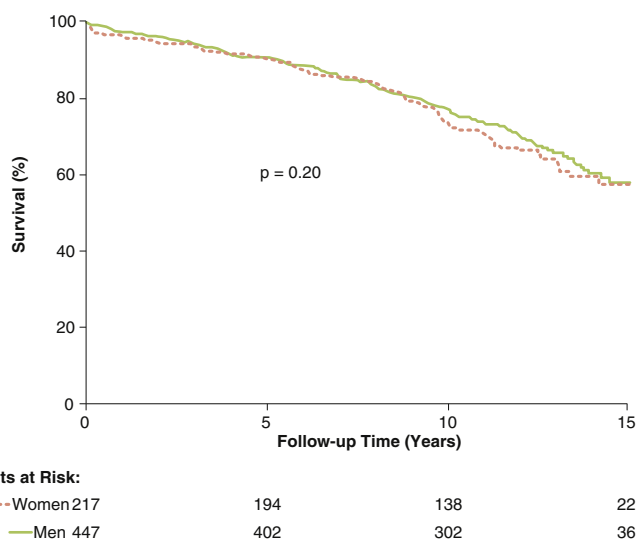
FIGURE 3 Incidence of Post-Operative Heart Failure After Mitral Surgery



Incidence of post-operative heart failure after mitral surgery in men **(solid green line)** and women **(dotted pink line)**. Note the excess heart failure in women.

Outcome analysis with comprehensive adjustment (i.e., similar to the primary cohort of 664 patients) in women versus men displayed no survival difference (p = 0.26), although HF was higher in women versus men (adjusted HR: 1.52 [95% CI: 1.15 to 2.02];

FIGURE 4 Survival in Men and Women After Mitral Surgery



Overall post-operative survival after mitral surgery in men **(solid green line)** and women **(dotted pink line)**.

$p = 0.004$). Adjusting for pre-operative HF symptoms, the larger power brought by the larger sample showed higher HF with pre-operative HF symptoms versus without (adjusted HR: 1.83 [95% CI: 1.4 to 2.4]; $p < 0.0001$) *and* in women versus men (adjusted HR: 1.33 [95% CI: 1.0 to 1.8]; $p = 0.05$), demonstrating that in women, higher post-operative HF did not result from selection biases and displayed very stable HRs under all circumstances.

DISCUSSION

The present study, on the basis of comprehensive imaging in large numbers of men and women with organic MR treated surgically, rejects the null hypothesis of similar characteristics in men and women and shows clinically meaningful differences between the sexes. For MR severity evaluation, women had smaller absolute cardiac cavities (more often labeled as normal size) and smaller RVol than men. Although these misleading differences are superficially interpreted as less severe MR in women, normalization to body size shows that cavity dilation and MR severity are at least as severe in women as in men. Similar volume overload is confirmed by similar reverse LV remodeling in men and women. Nevertheless, because women's pre-operative presentation more often appear to be "benign" by unadjusted imaging, surgical indications are considerably different: surgery is performed more frequently for HF symptoms and less as early surgery in women versus men. Imaging for MR cause shows more rheumatic lesions in women, and thus, mitral repair is slightly less often performed in women. However, for similar degenerative lesions similar repairs are achieved, emphasizing the importance of etiological diagnosis by imaging. The encouraging similar long-term survival highlights similar potential application of early guideline-based indications in men and women. However, women incur more post-operative HF, despite having a lower coronary disease prevalence. Excess post-operative HF in women is linked to worse pre-operative presentation, especially to late surgical indications on the basis of HF symptoms. Thus, these data emphasize comprehensive imaging of MR and cardiac remodeling accounting for body size, carefully interpreted for considering valve repair in women as early as in men.

IMAGING OF LV AND MR IN WOMEN AND MEN. The major adaptive change with volume overload is LV enlargement (18). Although this concept is undisputed (19), a limitation of LV remodeling imaging is that linear measurements imprecisely describe complex 3-dimensional LV volumetric changes (20). Distinguishing normal from abnormally remodeled LV, even using the American Society of Echocardiography's thresholds (13), has limitations due to insufficient healthy population data, particularly in older women with small body size (13). Similarly to LV dimensions, RVol should be interpreted in the context of patients' body sizes. Indeed, although absolute RVol is smaller in women, similar pre-operative volume overload suggested by similar BSA-normalized RVol is uniquely demonstrated by similar LV reverse remodeling after MR surgery and similar post-operative reversibility of pulmonary hypertension. However, because only absolute dimensions are recommended in the guidelines, there is potential for underestimating volume overload and a delay of surgery in women until HF symptoms occur (2), which is linked to worse clinical outcomes in women (2,3). Accounting for body size through BSA normalization has been used in organic MR, whereby end-systolic dimension $\geq$22 mm/m^2 independently determines excess mortality after diagnosis (21). However, this approach, standardized in aortic regurgitation (22), is not yet implemented in clinical guidelines for MR, and specific indexed thresholds will need to be refined.

Thus, accounting for sex and body size in evaluating MR severity and LV remodeling is essential to avoid worse clinical outcomes in women and to warrant careful valve repair consideration without waiting for HF symptoms.

MITRAL IMAGING AND CLINICAL OUTCOME OF MR SURGERY. Recent data suggested that women had less repairs than men and higher mortality (3,4), so pessimistic views have pervaded MR management in women. However, these pessimistic studies, although contradicting earlier reports (10,23), did not resolve whether negative outcomes were intrinsically related to sex or to the patients' presentation. Our extensive phenotypic characterization provides important information linking imaging and outcomes in women. The slightly lower rate of valve repair in women is exclusively related to rheumatic disease, with etiology stratification showing similar repair rates in men and women with endocarditic lesions and, particularly, in those with degenerative MR despite known sex-related morphological differences in this subset (2). Furthermore, potentially lower survival in women post-MR surgery, which would be a considerable disincentive for surgery, was not observed in our study.

Although repair of regurgitant rheumatic mitral valve appears desirable (24), it is challenging given that retractile lesions require complex repair techniques (25). Hence, when undergoing an operation for

the same disease as men, women enjoy reassuringly similar high repair rates and survival. Higher post-operative HF in women is intrinsically tracked back to worse pre-operative presentation with HF symptoms and not to excess LV or valvular dysfunction. Association of pre-operative HF symptoms with poor post-operative outcome is well established (26–28), so the link with post-operative HF (29) is not isolated to this study and is not due to selection bias. Hence, women who come to surgery for HF symptoms are put at risk for post-operative HF. Late presentation with HF and pulmonary hypertension denies the outcome benefits of early surgery (30) mentioned in recent guidelines (6). Later referral in women, influenced by appearances of lower MR severity and lower LV remodeling (2), should be avoidable by accounting for body size.

CLINICAL IMPLICATIONS. Generalization to women of unadjusted LV diameter surgical criteria established in men results in irrelevant criteria almost never reached in women (31) who often undergo surgery after developing severe symptoms. Because guidelines cite unadjusted cardiac dimensions for MR management (5,6), it is essential to attract the attention of practitioners to pitfalls related to body size. This situation is similar to aortic regurgitation, in which women incurred worse outcomes with very similar patterns of underestimation of regurgitation by using nonindexed dimensions (32), yielding a proposal of indexed dimensions for surgical indications (22). This suggestion was adopted by the European guidelines (5) and by the recent U.S. guidelines (6). Improving reliability of MR severity assessment by quantification and accounting for body size may narrow gaps between guidelines and effective implementation in clinical practice (33).

STUDY LIMITATIONS. Requirement of comprehensive imaging for in-depth analysis of sex differences yields strict inclusion criteria. However, conclusions on the basis of this selective cohort are not different from those of the total operated cohort, refuting potential biases due to requirement of comprehensive imaging.

BSA normalization of echocardiographic measurements is controversial. However, cardiac output and BSA are nearly linearly related in normal humans (34,35), and body size determines heart size (36), particularly with increasing age (37), suggesting that it is legitimate to normalize body size differences by BSA. Comparing subjective symptoms across sexes may be questionable, but these are markers of poor outcome in organic MR (26). The study period, used to obtain long-term outcome, involves surgical repair practice that is currently relevant, mature in our center, and applied at very high frequency. Comparing our cohort to recent publications (38), prevalence of asymptomatic patients and of mitral valve repair were at least as high.

CONCLUSIONS

Comprehensive imaging shows that women undergo mitral surgery for organic MR with smaller absolute cardiac dimensions and regurgitant volumes contrasting with more HF symptoms. This contrast is potentially confusing, yielding underestimation of severity of volume overload due to MR. Similar severe volume overload in men and women is demonstrated by normalization to body size with similarly large RVol and post-operative cardiac reverse remodeling in both sexes. Successful operative management by valve repair is similar in men and women for the same lesions. Women do not incur post-operative excess mortality compared with men, and thus should not incur delay or denial of MR surgery. However, women have excess post-operative HF, which can be traced back to their worse pre-operative presentation. Comprehensive imaging accounting for sex and body size in quantifying organic MR severity and cardiac remodeling is warranted to consider similar guideline-based early valve repair in men and women with organic MR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Organic MR severity in women is underestimated compared with men by using absolute echocardiographic measurements that do not take into account the body size, resulting in delayed surgery with more HF symptoms.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Women with organic MR present with worse clinical presentation to surgery and incur post-operative HF more frequently than men.

TRANSLATIONAL OUTLOOK: Accounting for body size in evaluating MR severity and consequences is essential for early consideration of mitral surgery in women to provide similar and excellent outcomes in men and women.

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