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Comprehensive Review

Mitral Regurgitation in Female Patients: Sex Differences and Disparities

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ABSTRACT

Mitral regurgitation is the most common valvular disease, particularly in older adults. Recent literature has consistently supported that there are significant differences in mitral regurgitation outcomes between male and female patients and that this is likely multifactorial. Numerous sex differences in anatomy and pathophysiology may play a role in delayed diagnoses, referrals, and treatments for female patients. Despite the recognition of these discrepancies in the literature, many guidelines that steer clinical care do not incorporate these factors into society recommendations. Identifying and validating sex-specific diagnostic parameters and increasing the representation of female patients in trials of new mitral regurgitation treatment modalities are key factors in improving outcomes for female patients.

Introduction

Valvular heart disease is increasingly prevalent in our aging population. Although there are recognized sex differences in the prevalence of different valvular lesions, sex disparities in outcomes of mitral regurgitation (MR) in female patients are increasingly recognized. Although identification of these differences in the literature is an important and necessary milestone, there have been insufficient guideline and practice-based changes aimed at improving MR outcomes in female patients. Echocardiography remains the imaging modality of choice to screen, diagnose, and surveil patients with MR. Given the prevalence of MR, its associated morbidity and mortality, and the demonstrated disparities in the diagnosis and treatment of these patients, it is imperative that physicians understand both the utility and limitations of current diagnostic criteria in guiding appropriate care for female patients. As new treatment modalities for MR continue to emerge, it is paramount that female patients are well represented in trials and that sex-specific outcomes are analyzed and addressed. This work aims to review the epidemiology, anatomy, pathophysiology, diagnosis, and current treatment modalities for MR in female patients and propose next steps in improving diagnosis and care of female patients with MR. The term sex is used to refer to specific physiologic features and biologic attributes, and sex is commonly categorized as either male or female.[1] Although the authors acknowledge that gender differences play important roles in patient outcomes, this review is focused on sex-specific differences.

Epidemiology

The importance of better understanding MR in today's population cannot be overstated; a growing and aging population has led to an increase in the number of deaths attributable to valvular disease.[2] In a study of patients older than 65 years, >50% of individuals screened[2] with transthoracic echocardiography (TTE) were found to present with mild valvular heart disease, and previously undiagnosed moderate to severe valvular disease was identified in 6.4% of these patients.[3,4] In this cohort, female patients made up to 51.9% of patients diagnosed with valvular heart disease.[4] In an analysis of Swedish patients initially diagnosed with valvular disease, the incidence of any valvular disease was 63.9 per 100,000 person-years, with most diagnoses (68.9%) being made in patients older than 65 years.[3,5] This Swedish analysis revealed

Abbreviations: ASMR, atrial secondary mitral regurgitation; CMR, cardiac magnetic resonance imaging; GDMT, guideline-directed medical therapy; LV, left ventricle; LVEF, left ventricular ejection fraction; MV, mitral valve; MR, mitral regurgitation; PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair.

Keywords: mitral regurgitation; transcatheter edge-to-edge repair; valvular heart disease; women's cardiovascular health.

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that MR made up 24.2% of valvular disease diagnoses,[3,5] but, worldwide, MR represents the most common valvular disease.[6] MR is not only common and underdiagnosed, but it is associated with increased cardiovascular morbidity and mortality.[7] Improvements in both diagnosis and treatment of MR in an aging population have only become more necessary with time.

While the evidence suggests that both sexes are equally likely to develop valvular disease, there are sex-specific differences in the prevalence of certain valve lesions.[6] In particular, among female patients, there is an increased prevalence of mitral valve (MV) disease, such as MV prolapse and rheumatic heart disease.[6] Importantly, as the population ages, so does the proportion of female patients with valvular heart disease, underscoring the need to better understand sex-based differences in diagnosis, treatment, and prognosis.[3,6]

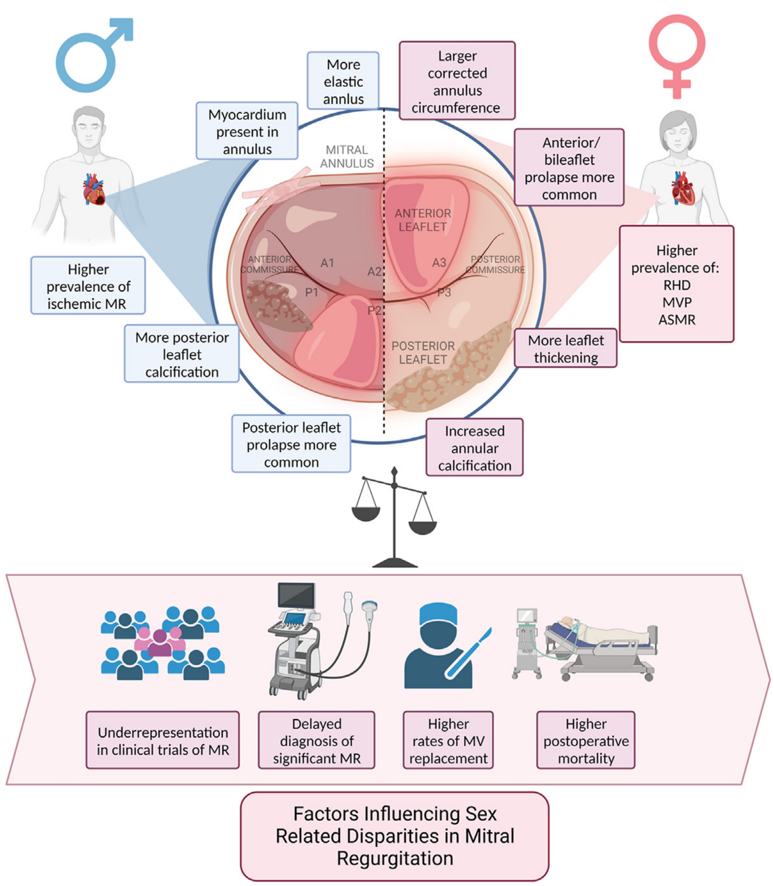
Anatomy of the MV

Sex differences in MV disease begin at the anatomical level. There are discrepancies in mitral annular calcification among sexes; male patient present with more posterior leaflet calcification and female patients with increased risk of annular calcification.[6,8–10] In addition, in a postmortem study by El-Busaid et al, female patients had a less-elastic annulus and a larger annular circumference when correcting for heart weight.[9] The clinical implications of these findings and the potential utility of indexing annular circumference requires further study. Importantly, annular size has been cited as an echocardiographic predictor of poor outcomes after transcatheter edge-to-edge repair (TEER). Multiple recent studies underscore how morphologic changes in the MV apparatus, particularly a dilated annulus, challenge the success of TEER.[11–13]

Mitral valve leaflet morphology varies based on sex as well. Echocardiographic data from the retrospective cohort study by Avierinos et al examining the sex-based differences in MV prolapse found that female patients had more leaflet thickening than male patients, representing more generalized myxomatous degeneration in female patients.[14,15] This study also identified prolapse of the posterior mitral leaflet to be more common in male patients, whereas anterior and bi-leaflet prolapse with myxomatous degeneration are more common among female patients.[14] With rates of durable surgical repair being the highest for isolated posterior leaflet prolapse, female patients may potentially fare worse from suboptimal surgical repair in part because of more complex valvular pathology.[16] Accordingly, given the heretofore described sex disparities in the MV apparatus and their associated effects on MR severity and outcomes, special attention should be paid to identifying these morphologic features on echocardiography in our female population (Central Illustration).

Pathophysiology of MR

Beyond the anatomic level, sex differences in pathophysiology of MV disease may also play an important role in outcomes. Indeed, among patients with both primary mitral regurgitation (PMR) and secondary mitral regurgitation (SMR), sex-based disparities exist. In fact, female patients tend to exhibit a higher prevalence of rheumatic MV disease and MV prolapse relative to male patients, who have a higher



Central Illustration.

Pathoanatomic sex-based differences in mitral regurgitation and associated clinical consequences. Female patients are underrepresented in clinical trials, experience delayed diagnosis of mitral regurgitation, endure higher rates of MV replacement, and experience higher postoperative mortality. ASMR, atrial secondary mitral regurgitation; MR, mitral regurgitation; MVP, mitral valve prolapse; MV, mitral valve; RHD, rheumatic heart disease. Created with BioRender.com.

prevalence of ischemic MR.[8,17,18] Although rheumatic heart disease predominantly affects patients in low-income countries,[19] it continues to disproportionately affect female patients in high-income countries as well.[18,20] The implications of this are significant because patients with rheumatic disease are less likely to experience a successful surgical MV repair.[21]

Among patients with SMR, atrial secondary mitral regurgitation (ASMR) may disproportionately affect female patients.[8] ASMR is characterized by normal leaflet motion, normal ventricular function and normal cardiac dimensions but diminished coaptation surface driven by atrial and atrioventricular annular dilation, a morphologic feature more frequently found in female patients as described earlier.[8] Although the sex differences leading to a higher frequency of ASMR in female patients are still being investigated, it is postulated that female patients may be more prone to advanced left atrial dysfunction and fibrosis, as well as higher inflammatory markers, which may in part be modulated by sex hormones.[8] Furthermore, recent studies have demonstrated that patients with ASMR particularly have worse clinical outcomes after TEER compared to those with PMR.[22,23] Indeed, within this patient cohort, echocardiographic assessments of atrial volume and annular dilation seem to be predictive of suboptimal MR reduction.[22] Given the observed sex disparities in ASMR and the predictive value of left atrial volume index and leaflet-to-annulus index, evaluation of these echocardiographic features may guide patient selection in TEER and mitigate the sex disparities in this vulnerable patient population.[22]

Diagnosis and role of imaging

TTE is the imaging modality of choice used to assess the etiology and severity of MR and to help guide appropriate steps in treatment.[6,24] Relative to cardiac magnetic resonance imaging (CMR) and computed tomography (CT), TTE has superior temporal resolution and excels in assessing leaflet function and in evaluating mobile masses.[6] Transesophageal echocardiography may be a necessary imaging modality when TTE imaging quality is limited, particularly when precisely defining mechanisms of MR, such as pinpointing the scallops responsible for a flail leaflet, or when assessing the feasibility of repair.[6,21,24] Three-dimensional echocardiographic imaging can also accurately provide anatomic measurements of valvular lesions before surgical or transcatheter approaches. Indeed, dedicated pre-procedural echocardiography can identify morphologic predictors which subsequently may guide treatment and thereby reduce morbidity and mortality. CT and CMR do have utility in the diagnosis of MV disease as well. In particular, multidetector CT has been increasingly used in evaluating MV anatomy and left ventricular (LV) outflow tract anatomy when planning percutaneous procedures.[6,25] On the contrary, CMR is useful in quantifying the degree of MR[6] and guidelines recommend the use of CMR in assessing ventricular volumes when there is a discrepancy between imaging modalities,[21] although the standard implementation of CMR in the diagnosis of MR may be limited by both cost and accessibility. A variety of noninvasive imaging modalities—such as stress echocardiography, CMR, or nuclear stress testing—are helpful in establishing the etiology of SMR and viability of the myocardium.[21]

The 2020 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines grade the severity of MR by means of values obtained on TTE, such as left atrial volume, LV volume, effective orifice area, vena contracta, regurgitant volume, regurgitant fraction, and transmitral jet velocity[21] (Table 1). Guidelines recommend that symptomatic patients and asymptomatic patients with severe PMR and LV systolic dysfunction with left ventricular ejection fraction (LVEF) of <60% or LV end-systolic dimension (LVESD) of >40 mm be referred for surgical intervention.[21] However, these guidelines do not consider that female patients generally have smaller cardiac dimensions than male patients[26] or that LVEF may be higher in healthy females than in healthy males.[27] This may contribute to a delay in the diagnosis of MR warranting intervention due to the underestimation of MR severity. Although the ACC/AHA guidelines recommend serial surveillance echocardiography every 6-12 months in patients with moderate to severe MR regardless of sex,[21] these guidelines are largely based on non–body surface area (BSA)–indexed values. Consequently, the sensitivity of these serial surveillance echocardiography assessments to detect meaningful changes in valvular dysfunction may be suboptimal. Further studies, as discussed below, evaluating both the utility and clinical effect of routine assessment of indexed values such as end-systolic LV volume and end-diastolic LV volume may inform future guidelines with regard to MR.

Table 1. Diagnostic criteria for severe mitral regurgitation per ACC/AHA guidelines and identification of sex-specific diagnostic parameters

	Diagnostic criteria for severe MR per ACC/AHA guidelines	Sex-specific diagnostic parameters proposed in the literature
LA volume	Moderate or severe LA enlargement	Requires future study
LV volume	LVESD ≥40.0 mm	Normal LVEDV: female <61 mL/m^2; male <74 mL/m^2 Normal LVESV: female <24 mL/m^2; male <31 mL/m^2
Regurgitant volume	≥60 mL	Requires future study
Regurgitant fraction	≥50%	Requires future study
EROA	≥0.40 cm^2	Requires future study
Vena contract	≥0.7 cm	Requires future study
Central jet MR	>40% LA or holosystolic eccentric jet MR	Requires future study

ACC, American College of Cardiology; AHA, American Heart Association; EROA, effective regurgitant orifice area; LA, left atrial; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation.[6,21,28]

Recent data suggests that normal LV cavity size differs among sexes.[6] In 2022, DesJardin et al[6] underscored the importance of using sex-specific–indexed chamber dimensions in the grading of valvular disease. Recommendations for cardiac chamber quantification published by Lang et al suggest that on 2D echocardiography, female cutoffs for a normal left ventricular end-diastolic volume (LVEDV) index and LV end-systolic volume index are <61 and 24 mL/m^2, respectively. Conversely, in male patients, a normal LVEDV and left ventricular end-systolic volume are <74 and 31 mL/m^2, respectively.[28] Given that atrial and ventricular volume measurements are currently a key component in the assessment of both PMR and SMR and that the cutoffs in guidelines are driven by data from a predominantly male population, it is inevitable that female patients will be underdiagnosed owing to inherently smaller chamber dimensions.[6]

This conclusion is supported by Avierinos et al,[14] who found that at the same level of regurgitation, female patients showed smaller atrial and ventricular cavities compared with male patients after normalization to BSA. In another study examining sex differences in patients undergoing surgery for MR, Mantovani et al[29] found female patients to more frequently present with advanced disease and be referred to surgery due to heart failure symptoms rather than echocardiographic criteria. However, when TTE measurements of MR severity such as LV dilation, left atrial dilation, and regurgitant volume were normalized to patients' BSA of the study BSA, MR severity was equivalent across sexes. The authors postulated that normalizing echocardiographic measurements to BSA will help identify severe MR in female patients earlier and, therefore, result in improved treatment outcomes.[29] Given similar normalization schemes are already used in patients with aortic aneurysms, future application of this principle to MR may provide an

Table 2. Literature supporting that current mitral regurgitation guidelines without sex-specific parameters result in underdiagnosing female patients.

Reference, year	Publication type	Sex differences identified	Suggested changes in practice	Outcomes and findings reported
DesJardin et al,[6] 2022	Review article	Surgical guidelines are not indexed to body size and are not sex specific	Implement either indexed or sex-specific parameters for values such as LV size	NA
Avierinos et al,[14] 2008	Retrospective cohort study	Use of absolute ventricular diameter in female patients presents an issue because of smaller body size	Normalization or indexing of cardiac size to body size	After normalization to BSA, female patients had greater atrial and ventricular enlargement for the same regurgitation severity
McNeely et al,[26] 2016	Quality and outcomes	Underestimation of MR severity in female patients because of unadjusted chamber size	NA	NA
Lang et al,[27] 2005	Guidelines and standards	End-diastolic volumes and end-systolic volumes were smaller in female patients than in male patients	LV size and volume measurements should be reported indexed to BSA	LV volumes and ejection fraction predict adverse outcomes in MR
Mantovani et al,[29] 2016	Retrospective cohort study	Female patients incurred worse outcomes with underestimation of MR	Use indexed dimensions for surgical indications	Female patients rarely meet unadjusted LV diameter surgical criteria and often undergo surgery only after developing severe symptoms
Pfaffenberger et al,[32] 2013	Prospective cohort study	Sex affects heart size	Sex should be considered in the guidelines for surgical referral	Female patients may experience significant left ventricular dilation but present with a LV end-diastolic diameter classified as normal

BSA, body surface area; LV, left ventricle; MR, mitral regurgitation; NA, non-applicable.

opportunity for early referral and improved long-term outcomes in female patients.[30] Because current guidelines lack TTE measurements normalized to BSA, MR is frequently underdiagnosed in female patients,[31] resulting in missed opportunities for early surgical referral and prevention of irreversible cardiac remodeling.[21,26,29] This delay in diagnosis and disparate referral pattern, as discussed below, is associated with increased cardiovascular morbidity and mortality in female patients. Of the numerous factors that contribute to sex inequality in the diagnosis and treatment of MV disease in female patients, inappropriate and/or insufficient echocardiography utilization as a tool for sex-adjusted and BSA-adjusted screening and surveillance of MR remains as a low-hanging fruit that is ripe for change (Table 2).[32]

Treatment of MR

Mitral valve surgery remains the mainstay of PMR treatement.[21] Surgical MV repair is generally preferable to MV replacement for patients with PMR.[21,33] For patients with severe PMR in which surgical risk is prohibitive, percutaneous edge-to-edge MV repair may be indicated.[21,24,33]

Regardless of surgical approach, early surgical referral for PMR is paramount in the treatment and prevention of LV dysfunction.[21] In a large observational study using the Mitral Regurgitation International Database registry, a database of >2000 patients from 6 tertiary care centers in 4 countries, patients who received MV surgery earlier had survival benefits compared with those who were medically managed.[34] Although observational studies such as this are limited by selection bias, the benefit of early surgery in PMR has been consistently supported in the literature and guidelines.[21,35,36] Unfortunately, because of the flaws in the aforementioned current diagnostic criteria, female patients are being referred for surgical repair later than male patients, with more advanced disease and more comorbidities.[26] The consequences of MR disease progression—due to a delay in time to diagnosis—include atrial fibrillation, tricuspid regurgitation, pulmonary hypertension, and decompensated heart failure, all of which portend worse outcomes and increased mortality.[26] Furthermore, because female patients are diagnosed with severe MR at an older age, they present with additional comorbidities such as preoperative cerebrovascular accidents and anemia.[26]

The delay in diagnosis for female patients contributes to decreased referrals for mitral valve surgery compared to their male counterparts.[26] In addition, although repair is associated with improved outcomes,[21,32,37,38] female patients experience lower rates of MV repair than male patients do.[39–41] Vassileva et al[40] found that the MV repair rate for female patients in a study of >47,000 Medicare beneficiaries was 31.9%, whereas the repair rate for male patients was 44% ($P <$ .0001). This analysis also found that female patients experienced a higher in-hospital mortality rate than male patients, which was largely attributed to late presentation.[40] In a study of younger patients, female patients aged 40-59 had a mortality rate approximately 2.5 times higher than male patients with similar comorbidities, with this discrepancy decreasing with age.[42] In a long-term follow-up study of patients undergoing MV surgery conducted by Montavi et al,[29] female patients exhibited similar postoperative mortality rates and reverse cardiac remodeling compared with male patients but disproportionately experienced postoperative heart failure. The sex differences identified in these retrospective analyses underscore the need for future randomized control trials in patients undergoing MR surgery.

SMR treatment differs significantly—the primary aim is treating the LV dysfunction, followed by correction of regurgitation itself.[21] As a first-line treatment, guideline-directed medical therapy (GDMT) includes β-blockers and angiotensin receptor neprilysin inhibitors, which improve LV remodeling and decrease the severity of MR.[43–46] Cardiac resynchronization device therapy reduces the degree of MR by improving atrial-ventricular synchrony, increasing MV closing forces and decreasing LV remodeling.[47,48] Recent data from the PROVE-HF trial suggests that 12 months of sacubitril-valsartan therapy can improve ejection fraction such that patients no longer meet criteria for primary prevention implantable cardioverter defibrillator eligibility, thus reducing the need for procedures and devices in this population.[49] These promising outcomes will need to be investigated specifically in patients with SMR. Unfortunately, recent studies and a meta-analysis shed light on the sex discrepancies that exist in these life-saving treatments—female veterans were significantly less likely to be prescribed appropriate GDMT[50] and female patients were less likely to receive cardiac resynchronization device therapy implantation.[51] This work adds to growing literature supporting that there are significant sex-based disparities in cardiovascular care and underscores the necessity for future studies in mitigating these differences. In particular, it will be important to evaluate if appropriate GDMT titration in female patients can improve outcomes such that the need for procedural intervention in female patients with SMR is reduced.

The evidence for the role of surgical repair in SMR is mixed with some studies demonstrating symptomatic benefit with MV repair in conjunction with coronary artery bypass grafting (CABG).[52,53] However, surgery does not provide a clear mortality benefit.[54–56] There are disparities in surgical outcomes for treatment of SMR as well; a small study

Table 3. Sex differences in surgical mitral valve repair vs TEER.

Intervention	Reference, year	Publication type	Study aim	Study size	Sex differences described
Surgical	Mantovani et al,[29] 2016	Retrospective single-center observational study	Compare presurgical and postsurgical imaging to assess sex differences in surgical outcomes	N = 664 (female: 32.6%; male: 67.3%)	Female patients experience more long-term postoperative heart failure than males do (adjusted HR, 1.52; 95% CI, 1.15-2.02; $P = .004$)
Surgical	Vassileva et al,[39] 2011	Retrospective registry analysis	Examine sex differences in surgical procedural selection and outcomes in patients receiving a surgical intervention for MR	N = 63,754 (female: 51.3%; male: 48.7%)	Female patients are less likely to receive MV repair than males (37.9% vs 55.9%, respectively; $P < .001$). Female patients experience higher in-hospital mortality than male patients do when presenting for MV repair (2.06% vs 1.36%, respectively; $P = .0328$)
Surgical	Vassileva et al,[40] 2013	Retrospective registry analysis	Compare sex differences in long-term survival after MV surgery	N = 47,602 (female: 60.7%; male: 39.3%)	Female patients experience higher in-hospital mortality than male patients do (7.7% vs 6.1%, respectively; P < .0001). Among patients undergoing MV repair, female patients experience similar long-term postoperative survival compared with male patients after risk adjustment (HR, 0.97; 95% CI, 0.92-1.02; $P = .2106$)
Surgical	Johnston et al,[41] 2019	Retrospective cohort study	Examine sex differences in patients undergoing CABG and combined CABG/valve repair surgery	N = 72,824 (female: 24.5%; male: 75.5%)	Female patients experience higher mortality after CABG and combined CABG/MV surgery than male counterparts do (2.7% vs 1.6%, respectively; $P < .001$)
Surgical	Song et al,[42] 2008	Retrospective registry analysis	Examine sex differences in outcomes after MR surgery	N = 24,977 (female: 49%; male: 51%)	Female patients experience higher mortality with MV surgery than male patients do (3.9% vs 2.4%, respectively; $P < .0001$)
Surgical	Giustino et al,[57] 2019	Randomized control trial	Examine sex differences in outcomes after MV surgery for severe ischemic MR	N = 251 (female: 38.2%, male: 61.8%)	Female patients with severe ischemic MR experience higher mortality than male patients do (27.1% vs 17.4%, respectively; $P = .03$) and increased major cardiovascular and cerebrovascular events after MV surgery (49.0% vs 38.1%, respectively; $P = .02$)
TEER	Gafoor et al,[62] 2016	Prospective multicenter trial	Examine the effect of sex on outcomes after percutaneous MV repair	N = 567 (female: 36.2%; male: 63.8%)	Overall survival at the 1-y follow-up after percutaneous MV repair is similar for both sexes (81% in females vs 82.2% in males; $P = .60$) Both sexes experience similar procedural efficacy at the 1-y follow-up, as defined by MR grade ≤2+ (76% of females vs 80% of males; $P < .40$)
TEER	Tigges et al,[63,70] 2016	Retrospective single-center observational study	Examine sex differences in outcomes after percutaneous MV repair	N = 592 (female: 38.9%; male: 61.1%)	Both sexes experience similar short-term procedural success after percutaneous MV repair (OR, 1.02; 95% CI, 0.59-1.77)
TEER	Chan et al,[71] 2021	Retrospective single-center observational study	Examine sex differences in outcomes after percutaneous MV repair in patients with secondary MR	N = 175 (female: 40%; male: 60%)	Female patients are more likely to experience recurrent severe MR after percutaneous MV repair than male patients are (HR, 4.7; 95% CI, 1.2-18.4; $P = .03$)
TEER	Attizzani et al,[70,72] 2015	Prospective single-center observational study	Examine sex differences in outcomes after percutaneous MV repair	N = 171 (female: 38%; male: 62%)	Female patients experience increased residual significant MR after percutaneous MV repair, as defined by MR grade ≥3+ (OR, 2.19; 95% CI, 0.69-6.95)
TEER	Giordano et al,[73] 2015	Retrospective registry analysis	Examine sex differences in baseline characteristics and procedural outcomes in patients undergoing percutaneous MV repair	N = 84 (female: 54%; male: 46%)	Both sexes experience similar long-term improvement in NYHA class after percutaneous MV repair (44.4% in females vs 41.0% in males; $P = .827$)
TEER	Estévez-Loureiro et al,[74] 2015	Retrospective registry analysis	Investigate sex differences in outcomes among patients undergoing percutaneous MV repair	N = 173 (female: 37%; male: 63%)	Both sexes experience similar improvement in NYHA class at 1 mo (77% in females vs 78.3% in males; $P = .851$) and at 6 mo (74.2% in females vs 73.1% in males; $P = .912$)
TEER	Werner et al,[75] 2020	Retrospective registry analysis	Compare differences in baseline characteristics, procedure indication, and outcomes between sexes among patients undergoing percutaneous MV repair	N = 828 (female: 39.5%; male: 60.5%)	Both sexes experience similar mortality after percutaneous MV repair (19.7% in females vs 20.7% in males; $P = .76$). Female patients experience less improvement in NYHA class than males do (NYHA class ≤ II: 54.8% in females vs 68.3% in males; $P < .001$)
TEER	Doshi et al,[76] 2018	Retrospective registry analysis	Examine sex-based differences in outcomes among patients undergoing percutaneous MV repair	N = 521 (female: 42%; male: 58%)	Both sexes experience similar in-hospital mortality rates (3.6% in females vs 2.6% in males; $P = .43$) and similar hospital lengths of stay (7.3 d for females vs. 7.7 d for males; $P = .67$) after percutaneous MV repair
TEER	Kosmidou et al,[77] 2021	Randomized control trial	Assess sex-specific outcomes in patients with secondary MR who undergo percutaneous MV repair	N = 614 (female: 36%; male: 64%)	Female patients treated with percutaneous MV repair experience a smaller decrease in heart failure hospitalizations than male patients do (HR, 1.2; 95% CI, 0.87-1.65; $P = .009$)
TEER	Park et al,[78] 2021	Retrospective registry analysis	Assess sex-based differences in clinical characteristics and outcomes of patients undergoing percutaneous MV repair for secondary MR	N = 1233 (female: 36%; male: 64%)	Both sexes experience comparable procedural efficacy, as defined by MR grade ≤2+ at discharge (93.2% in females vs 94.6% in males; $P = .35$)

(*continued on next page*)

Table 3 *(continued)*

Intervention	Reference, year	Publication type	Study aim	Study size	Sex differences described
TEER	Ya'Qoub et al,[70] 2022	Meta-analysis	Examine sex-based differences in outcomes among patients undergoing percutaneous MV repair	N = 24,905 (female: 45.6%; male: 54.4%)	Both sexes experience similar procedural success (OR, 0.75; 95% CI, 0.55-1.05). Female patients have a higher incidence of periprocedural bleeding (OR, 1.34; 95% CI, 1.15-1.56) and stroke (OR, 1.57; 95% CI, 1.10-2.25). Adjusted long-term mortality is lower among female patients (HR, 0.77; 95% CI, 0.67-0.88)
TEER	Khan et al,[79] 2020	Retrospective registry analysis	Examine sex-based differences in outcomes among patients undergoing percutaneous MV repair	N = 15,264 (female: 47%; male: 52.9%)	There is no significant difference in mortality between sexes among patients undergoing percutaneous MV repair (2.6% in females vs 2.2% in males; $P = 0.16$)
TEER	Paulus et al,[80] 2020	Retrospective single-center analysis	Identify baseline characteristics that predict improvement in functional status after percutaneous MV repair	N = 79 (female: 46.8%; male: 53.2%)	Functional status, as measured by 6-min walk distance, is lower in female patients both before (240 ± 12 m in females vs 288 ± 89 m in males; $P = .034$) and after percutaneous MV repair (267 ± 109 m in females vs 320 ± 94 m in males; $P = .024$)
TEER	Villablanca et al,[81] 2021	Retrospective registry analysis	Compare sex-based differences in outcomes among patients undergoing percutaneous MV repair to patients undergoing MV surgery	N = 5295 (female: 47.6%; male: 52.4%)	Female patients have a lower 1-y mortality rate postpercutaneous MV repair than males do (adjusted HR, 0.80; 95% CI, 0.68-0.94; $P = .008$)

CABG, coronary artery bypass grafting; HR, hazard ratio; MR, mitral regurgitation; MV, mitral valve; OR, odds ratio; TEER, transcatheter edge-to-edge repair.

of 251 patients with severe ischemic MR identified that female patients had a higher mortality rate and worse quality of life than male counterparts after MV surgery.[57]

Transcatheter edge-to-edge repair is an emerging and increasingly popular treatment for patients with SMR. Landmark clinical trials have identified characteristics of MR that are amenable to TEER.[21,58,59] In the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) enrollment criteria included LVEF between 20% and 50%, pulmonary artery systolic pressure of <70 mm Hg, LVESD of <70 mm, and persistent symptoms despite GDMT.[21,60] The COAPT and MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Secondary Mitral Regurgitation) trials studied mortality and heart failure hospitalizations in patients who underwent treatment of SMR with MitraClip (Abbott Vascular) compared with patients treated with GDMT alone.[58,61] Although the COAPT trial demonstrated improved outcomes with MitraClip repair, MITRA-FR failed to demonstrate benefit in mortality or hospitalizations. Importantly, however, the COAPT trial rigorously maximized GDMT by a central eligibility committee before randomization whereas MITRA-FR did not.[58,61] Early data has also been collected from the ACCESS-EU registry, which identified that the MitraClip procedure resulted in 78.9% patients being free from SMR for the first 12 months after the procedure.[62] At 4-year follow-up in the TRAMI registry, low reintervention rates, and stable functional outcomes were reported, but there was a high long-term mortality rate (53.1% at 4-year-follow-up), which was attributed to multiple severe comorbidities in a frail population.[63]

In addition to edge-to-edge repair approaches, it is important to note that there are several emerging and promising percutaneous treatments in patients with SMR. The Carrilon Mitral Contour System (Cardiac Dimensions) has demonstrated efficacy in reducing both MR volume and LV volume by annular reduction in patients that are optimized on GDMT.[64] As recently as September 2022, the Food and Drug Administration granted approval for the Pascal Transcatheter Valve system (Edwards Lifesciences) for patients with severe degenerative MR.[65] This device also shows promise in reducing MR severity after 30 days.[66] Trials evaluating the efficacy of these percutaneous devices are currently enrolling and ongoing.[67] Transcatheter MV replacement is also a promising new therapeutic alternative for patients that are deemed high-risk surgical candidates.[68] Novel techniques in transcatheter MV replacement are emerging with the use of technologies including CardiAQ (Edwards Lifesciences), the Intrepid valve (Medtronic), the Tiara valve (Neovasc), and the Tendyne valve (Abbott).[69] As new devices continue to come to market and percutaneous strategies continue to improve, it is of the utmost importance that female patients be appropriately represented in these clinical trials given the current disparities that exist in treatment outcomes. In the COAPT trial, female patients made up only 36% of subjects and female patients represented <30% of patients in the MITRA-FR trial.[58,61]

Overall, the existing research regarding sex-based differences in percutaneous treatment of SMR is generally promising. The sex disparities observed in surgical MV repair have not been clearly demonstrated in transcatheter edge-to-edge therapies thus far (Table 3).[70–81] In a single-center prospective study of patients treated with MitraClip for SMR, Chan et al[71] found that clinical measures of success, such as New York Heart Association functional class and survival, were equivalent across sexes. The evidence currently supports that both sexes seem to have equivalent procedural success and improvements in functional status at both short-term and long-term evaluation.[62,63,72–76,78] Studies have generally shown equivalent acute procedural mortality across sexes.[62,63,72–76] Data from the EuroSMR registry corroborate that there are no significant sex differences in mortality for up to 2 years after TEER.[78] However, as discussed, female patients seem to be disproportionately affected by ASMR, a subtype of SMR associated with worse outcomes after TEER compared to patients with PMR.[23] Furthermore, in an analysis of the COAPT cohort, the effect of TEER with MitraClip was found to be less pronounced in female patients than in male patients.[77] In addition, a recent meta-analysis found that female patients undergoing TEER with MitraClip showed higher rates of stroke and bleeding relative to male patients, despite female patients having a lower prevalence of preprocedural comorbidities.[70] Conversely, Tigges et al[63] found improved survival in female patients compared with male patients up to 4 years after undergoing MitraClip treatment, although the authors suggested that better preprocedural health played an important role. This is supported by the work of Ya'Qoub et al, which suggests that female patients had lower adjusted mortality on long-term follow-up than male patients did.[70] Long-term outcomes of registries such as TRAMI and ACCESS-EU will be essential to better understanding the effect of TEER on female patients.

Evidence gaps, future research, and a call to action

Echocardiography is essential in the diagnosis of valvular heart disease. Despite recognition of variations in normalized echocardiographic parameters based on sex, many guidelines that steer clinical care do not incorporate these established differences. A likely consequence of these nonspecific treatment thresholds is an exacerbation of health outcomes disparities in female patients suffering from MR. Given the prevalence of MR, its associated morbidity and mortality, and the wide array of effective treatment options, increased awareness of sex-based differences in the pathomorphology of MR and its assessment by echocardiography remains critical. Consensus statements from organizations such as the ACC, the AHA, the European Society of Cardiology, the American Society of Echocardiography, and the Society for Cardiovascular Angiography & Interventions may raise awareness of sex-based cardiovascular disparities and, thereby, encourage high-quality research to investigate and mitigate these differences. Through such endeavors, more refined guidelines that consider sex-specific differences may improve morbidity and mortality in our female population experiencing MR. One potential consideration to help mitigate existing disparities would be adopting new guidelines to incorporate specific sex-based cutoff points, as highlighted by DesJardin et al.[6] An alternative is adjusting atrial and ventricular parameters to normalize for BSA, as underscored by Mantovani et al.[29] Emerging data from observational studies has already identified that indexing values adds diagnostic and prognostic benefits for female patients with MR.[82,83] However, future studies to identify and validate sex-specific echocardiographic criteria and enhanced screening and surveillance initiatives are paramount before implementing sex-based thresholds for diagnosis and referral. Without changes in diagnostic echocardiography that consider physiologic and pathophysiologic differences among both sexes, female patients will likely continue to experience delays in diagnosis and subsequent treatment such as GDMT, TEER, and surgical referral.[32]

Conclusions

Sex differences in MR exist in anatomy, pathophysiology, diagnosis, and treatment. Although some of these differences may be immutable and genetically driven, many disparities can be mitigated. Further studies to identify and validate sex-specific diagnostic criteria, as well as enhanced screening and surveillance initiatives, will likely reduce sex disparities in cardiovascular medicine.

Declarations of competing interest

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