Sex differences in outcomes have been noted in many areas of cardiovascular medicine. In mitral valve surgery, this topic is particularly important because in appropriately selected patients, mitral valve repair restores normal life expectancy, which cannot be said for other cardiac surgical operations. Current literature is replete with evidence supporting continued sex inequality in the detection and treatment of mitral valve disease. Women, although just as likely to have significant MR, are less likely to receive surgery than men, and when they do, they have worse observed outcomes after their operation. When women are referred for surgery, they typically present with more comorbidities and later in the disease process and have a lower likelihood of receiving mitral repair, the superiority of which over replacement has been firmly established for degenerative disease.\textsuperscript{1,2}

There is no established medical therapy for degenerative mitral regurgitation (MR), and surgery remains the gold standard for severe MR associated with symptoms and ventricular dysfunction.\textsuperscript{3} Longstanding MR leads to many untoward consequences, including ventricular dysfunction, left atrial enlargement, development of secondary atrial fibrillation, pulmonary hypertension, and tricuspid regurgitation, and if left untreated, it inevitably leads to decompensated heart failure.\textsuperscript{4} Late referral to surgery does not always reverse these negative sequela. It is, therefore, important that this condition is detected early to prevent these untoward consequences and provide patients with the full benefit of their operation.\textsuperscript{5}

Significant differences are noted in the baseline characteristics of women versus men presenting for mitral valve surgery. Women present at an older age, with excess comorbidity burden, including higher incidence of preoperative transient ischemic attack/stroke, atrial fibrillation, heart failure, respiratory failure, anemia, and others, and are more likely than men to have an urgent operation. At the time of mitral valve surgery, women are also more likely to undergo concomitant surgery for atrial fibrillation and tricuspid intervention, presumably reflecting higher incidence of atrial fibrillation and tricuspid regurgitation—factors known to reflect more advanced disease.\textsuperscript{6,7} The higher comorbid burden at presentation offers an explanation of the higher mortality in women undergoing mitral valve surgery compared with men.\textsuperscript{6-8} Data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS ACSD) demonstrated that in patients aged between 40 and 59 years, women had 2.5 times higher risk-adjusted mortality compared with men for isolated mitral valve operations. The survival disadvantage seemed to diminish with age.\textsuperscript{8} In a study of 47602 Medicare beneficiaries with isolated mitral valve surgery, we demonstrated higher operative mortality for women compared with men (7.7\% versus 6.1\%; \(P<0.0001\)), and this was true both for the subset undergoing repair (4.2\% versus 3.5\%; \(P=0.0112\)) and replacement (9.3\% versus 8.2\%; \(P=0.0018\)). After adjustment for differences in baseline characteristics, operative mortality for mitral repair seemed similar between women and men, suggesting that this sex disparity might be largely because of worse preoperative profiles of women compared with men.\textsuperscript{7} Long-term survival differences after mitral valve surgery based on sex have also been reported. A study by Seeburger et al\textsuperscript{9} of 3761 patients undergoing minimally invasive mitral surgery reported 10-year survival of 58\% for women compared with 72\% for men. In the Medicare fee-for-service population, we found that in the subset of patients who underwent isolated mitral repair, long-term survival was worse for women, but this difference disappeared after risk adjustment. When taking sex into account, mitral repair seemed to restore normal life expectancy for men but not for women, and this might help explain the higher observed long-term mortality.\textsuperscript{7}

Lower mitral repair rates for women have been documented across multiple data sources, including the Nationwide Inpatient Sample database, the Medicare database, and the STS ACSD.\textsuperscript{6,7,10} Considering the established superiority of mitral repair over replacement, addressing the lower likelihood of women to receive mitral repair compared with men represents an important opportunity in quality of care initiatives aimed at eradicating healthcare disparities. Compared with replacement, mitral repair is associated with improved survival, better preservation of ventricular function, lower risk of reoperation, and endocarditis, among others. In appropriately selected patients, mitral repair restores normal life expectancy to that of the age- and sex-matched US population.\textsuperscript{12} As a result, mitral valve repair rates have been proposed as a key indicator of quality in mitral valve surgery.\textsuperscript{10} Sex differences in mitral valve morphology and disease lesion have been documented and may partly explain the lower repair rates in women. Higher
incidence of anterior and bileaflet prolapse is more common in women, whereas posterior leaflet prolapse, which is technically easier to repair and, in general, results in higher long-term durability, is more predominant in men. Posterior leaflet calcification and mixed regurgitation/stenosis have been noted more often in women and may further play a role in the ability to repair the valve. Degenerative mitral stenosis (MS) is rare and was almost exclusively found in women in 1 routine echocardiographic study. It was, furthermore, noted to increase with age and was present in 2.5% in patients aged >90 years. Because women live longer than men, it is possible that this entity is detected preferentially in female patients. In many large-scale studies, the cause of mitral valve disease is not reported and has been difficult to ascertain. Consequently, it is unclear whether the lower repair rates in women that are reported might be, in part, because of inclusion of patients with rheumatic mitral disease, considering the significantly higher prevalence of MS in women. A retrospective study of 24,265 echocardiograms between 1984 and 1998 noted similar prevalence of MR in both sexes, whereas the prevalence of MS, although rare, was significantly higher in women compared with men (1.6% versus 0.4%; \( P < 0.001 \)). Nevertheless, despite declining incidence of MS noted in the STS ACSD, we did not observe a trend over time to suggest that repair rates for women are increasing over those for men. Higher hospital and surgeon volumes have been associated with higher repair rates. Targeted referral of complex valve pathology to experienced centers has been proposed as a way to provide better care of patients with mitral valve disease by providing high repair success rates and may be particularly relevant in women to ensure sex equality in care.

Although higher preoperative comorbid burden suggests that women present later in their disease process, it is unclear whether this is driven by patient or physician factors. Sex differences in attitudes toward seeking medical attention have not been extensively studied. Whether sex differences exist with respect to likelihood to seek care in mitral valve disease is unknown but constitutes an important aspect of the multifaceted problem of sex disparity in mitral valve surgery.

Appropriate timing of surgery in patients with MR is extremely important, as early surgery has been associated with improved long-term outcomes. This has now been incorporated in the most recent guidelines that emphasize an aggressive approach in patients with mitral valve disease, including a class IIa recommendation for surgery in asymptomatic patients with severe MR and preserved ventricular function if repair success rate of >95% and operative mortality rate of <1% can be achieved.

Underestimation of regurgitation severity in women according to current guidelines because of lower unadjusted chamber size may lead to decreased referral to surgery in women or delayed referral until severe chamber enlargement is present. Avierinos et al studied >8000 patients with mitral valve prolapse and had extensive follow-up with echocardiographic data. Among patients with severe MR, women were 21% less likely to be referred for surgery, even after adjusting for age, ejection fraction, and regurgitation severity. Whether a less severe symptom profile exists among women is unknown. However, it is likely that morphological differences between sexes are contributing to this referral bias. Women have smaller cardiac dimensions in general, and after matching sexes by the severity of MR, women have significantly smaller ventricular and atrial dimensions. Because American College of Cardiology/American Heart Association guidelines use left ventricular end-systolic dimension ≥4.0 cm, without correction to body surface area, as a class I indication for surgery, it is possible that we are missing a significant segment of the population who would benefit from surgery. Indeed, in the same study, only 5.7% of women compared with 9.6% of men with severe MR had left ventricular end-systolic dimensions that were >4.5 cm (\( P < 0.001 \)). After normalization to body surface area, however, women had larger ventricular and atrial changes than men. Given that quantitative assessment of MR also includes regurgitant volume, among other values, there could also be quantitative underestimation of MR in women or patients with small left ventricles.

Physician bias in diagnosis and referral might also play a role and may be related to differences in symptoms at presentation. Elderly women are less active than their male counterparts and may present with more insidious symptoms, such as fatigue as opposed to shortness of breath, with the latter more likely to trigger a cardiac evaluation. Poor compliance with mitral valve guidelines by treating cardiologists has been documented, but it is unknown whether it contributes to preferential nonreferral or delayed referral for women.

In summary, there continues to be an observed sex disparity in mitral valve surgery. Women present with worse preoperative profile and have a lower likelihood of referral to mitral valve surgery. Furthermore, women receive lower rates of mitral repair, and whether this is because of differences in disease etiology, such as higher prevalence of rheumatic disease and degenerative MS or the presence of complex disease with higher incidence of anterior and bileaflet prolapse needs to be studied further. Guideline-directed referral cutoffs may be contributing to nonreferral or referral for surgery in women at a later disease stage secondary to smaller body size. Finally, higher mortality with mitral valve surgery has been reported compared with men, especially for younger women. Adjustment for baseline characteristics significantly diminishes the disparity in outcomes.

It appears that current evidence strongly supports the role of worse preoperative profiles for women presenting for mitral valve surgery compared with men as the main driver of disparity in outcomes. However, the factors responsible for these findings remain unclear. We believe strong consideration should be given to using sex/body surface area indexing in surgical referral guidelines. Physicians should also more closely monitor their female patients with known MR of lesser grades for symptom development before decompensation. Better compliance with mitral valve guidelines is likely to benefit male and female patients alike. Future areas of investigation must address the potential effect of valve morphology, cause, and etiology, as well as sex differences in attitudes toward seeking medical attention and physician bias leading to delayed diagnosis or referral for surgical intervention. Population health research in this area would play a significant role in the efforts to improve outcomes in women undergoing mitral valve surgery.
Disclosures

None.

References


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