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Article

Sex-Based Differences in Early Outcomes Following Mitral Valve Surgery for Degenerative Disease

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Abstract

Objectives: To determine whether sex-based differences exist following surgery for degenerative mitral valve disease. **Methods**: Using a national database, we analysed data on mitral valve surgery for degenerative disease (n = 22,658) between January 2000 and March 2019 in the UK. We split the cohort into men (n = 14,681) and women (n = 7977) and compared background characteristics, intraoperative variables and early postoperative outcomes. Our primary outcome was hospital mortality; secondary outcomes included re-exploration for bleeding, prolonged admission (>10 days) and mitral replacement. We used binary logistic regression models for all outcomes, with multiplicative interaction terms to determine the nature of any differences. **Results**: Women presented older (70 $\pm$ 11 years *vs.* 67 $\pm$ 11 years, $p < 0.001$) with worse symptom profiles (New York Heart Association Class III–IV 57% *vs.* 44%, $p < 0.001$). They had higher rates of preoperative atrial fibrillation (39% *vs.* 35%, $p < 0.001$) and tricuspid disease requiring surgery (21% *vs.* 15%, $p < 0.001$). They had lower repair rates (66% *vs.* 76%, $p < 0.001$), higher mortality (3% *vs.* 2%, $p < 0.001$) and were more likely to have a prolonged admission (48% *vs.* 40%, $p < 0.001$). Female sex was an independent predictor of mortality (odds ratio (OR): 1.52, 95% CI: 1.21–1.90, $p < 0.001$). Age and Canadian Cardiovascular Society (CCS) score showed significant interactions with sex. The relationship between advancing age and mortality was found to be more pronounced in women. **Conclusions**: (1) Female sex is an independent predictor of hospital mortality, prolonged hospital admission and mitral valve replacement. (2) The relationship between female sex and mortality is exacerbated by worsening CCS score and advancing age. (3) Women have significantly lower repair rates.

Keywords

degenerative; mitral; valve; disease; sex; differences

Introduction

Degenerative mitral valve disease (DMD) is a progressive disorder characterised by leaflet thickening as well as thickening and elongation of the chordae tendinae; left untreated, the sequelae include left atrial enlargement, secondary atrial fibrillation, and tricuspid regurgitation[1]. These consequences disrupt quality of life and reduce life expectancy. Surgical correction is the treatment of choice for DMD. In the context of symptomatic disease, mitral valve repair (MVr) is the gold standard, with data demonstrating clear prognostic benefits when compared with mitral valve replacement (MVR) [2–9].

Sex-based outcome discrepancies are reported across the literature in various medical and surgical specialties. Discrepancies have been demonstrated in a range of cardiac sub-specialties [10–12]. The publications have demonstrated unfavourable outcomes for women undergoing surgery, including reduced long-term survival.

A recently published meta-analysis examining sex-specific outcomes after mitral valve (MV) surgery highlighted the lack of studies with sufficient sample sizes and concluded a need for further large studies in the area [13]. The purpose of this analysis was therefore to examine the relationship between sex and early postoperative outcomes specifically in patients with degenerative MV disease, using a large cohort of patients from a national database.

Materials and Methods

Data Acquisition

A retrospective cohort study was planned using the UK National Adult Cardiac Surgery Audit (NACSA) data, maintained by the National Institute for Cardiovascular Outcomes Research (NICOR). All cardiac surgical centres in the UK are required to submit data to NICOR using a standardized data submission form, including a range of preoperative and intraoperative variables as well as early postoperative outcomes from the index admission. The

database therefore contains clinical information on all patients undergoing cardiac surgery in the UK. Maintenance and validation are regularly undertaken by the use of reproducible cleaning and maintenance algorithms, with return to individual centres for local validation. Access was solicited from NICOR to examine the relationship between demographic, and operative characteristics with early clinical outcomes. Identifiable patient information was removed, the requirement for patient informed consent was waived and the dataset was adapted for use with statistical analysis software. The dataset was resurveyed for non-adult or duplicate results, with removal planned as appropriate.

Missing Data

The following variables had missing data for $\geq$5% of patients: redo sternotomy (5%), coronary disease (13%), preoperative acute kidney injury (AKI; 29%), concomitant tricuspid valve surgery (TVS; 65%), concomitant coronary artery bypass graft (CABG; 26%), concomitant ablation (23%), postoperative stroke/transient ischemic attack (TIA; 15%), postoperative dialysis (13%), return to theatre for bleeding and/or cardiac tamponade (8%). The nature of missingness in the dataset was investigated using Little's test, which returned a significant result ($p < 0.001$), indicating that data were not completely missing at random. We imputed missing values with '0' in these variables (i.e., the event did not occur). This is a reasonable assumption, since the proportion of patients with no event (i.e., 0) in these variables reflect the rates of these events in cardiac surgery populations reported in the literature.

Inclusion and Exclusion Criteria

We included patients undergoing MV surgery for primary degenerative disease, with or without concomitant coronary artery bypass grafting (CABG), tricuspid valve surgery (TVS) or ablation for atrial fibrillation. We excluded patients presenting as emergency or salvage cases, as well as patients presenting with any aetiology other than primary degenerative disease. We excluded patients presenting in a pre-operative critical state, defined as being in shock, requiring dialysis, requiring mechanical assistance or intra-aortic balloon pump (IABP). We also excluded patients undergoing concomitant major aortic, or aortic valve surgery.

Outcomes

Hospital mortality was our primary outcome of interest. Secondary outcomes were rates of MV replacement, prolonged hospital admission (defined as >10 days) and postoperative return to theatre for bleeding and/or tamponade.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). All data are presented descriptively by group (men and women) using means and standard deviation or median and interquartile ranges for continuous variables and counts and percentages for categorial variables. Univariable analyses were conducted to examine differences in background characteristics, intraoperative variables and postoperative outcomes by group. For categorical variables, chi-squared test was used. Where expected values were less than 5, Fisher's exact test was used. For continuous variables, the independent *t*-test was used. We used Cochran-Mantel-Haenszel tests to compare trends in repair rates over time between men and women across four-year time periods (2000–2003, 2004–2007, 2008–2011, 2012–2015 and 2016–2019).

To investigate the independent association of sex with hospital mortality, we used a binary logistic regression model. We pre-defined a threshold of $p < 0.25$ in the univariable analyses for inclusion in the multivariable model. We also used binary logistic regression models to examine the independent relationship of sex with all secondary outcomes (re-exploration for bleeding and prolonged admission). When conducting the regression model for MVR, we excluded intraoperative covariates. We used the Box-Tidwell test with a Bonferroni correction to test the assumption of linearity. Based on this assessment, continuous independent variables were found to be linearly related to the logit of the dependent variables in all models.

In order to better understand how different covariates impacted the relationship between sex and mortality, we planned to repeat the binary logistic regression modelling with the inclusion of multiplicative interaction terms. The same list of covariates was used each time. We did so iteratively, each time including multiplicative interaction terms between a different covariate and sex. For covariates that were found to have a significant interaction with sex, we then calculated the odds ratios for sex in patients with and without that variable. This was done by repeating the regression models in all cases with the characteristic, and then in those without it.

As a sensitivity analysis, we conducted univariable comparisons between men and women in the complete-case population to ensure no significant deviation from the study cohort (see **Supplementary Material**). There was no significant difference in the complete-case population compared to the study population. Hosmer and Lemeshow's test did not return a statistically significant result in any model, indicating good model fits.

Results

Study Cohort

After applying inclusion and exclusion criteria (see Fig. 1) our final study sample consisted of 22,658 consecutive patients undergoing surgery for primary degenerative MV disease; there were 7977 (35%) women and 14,681 (65%) men.

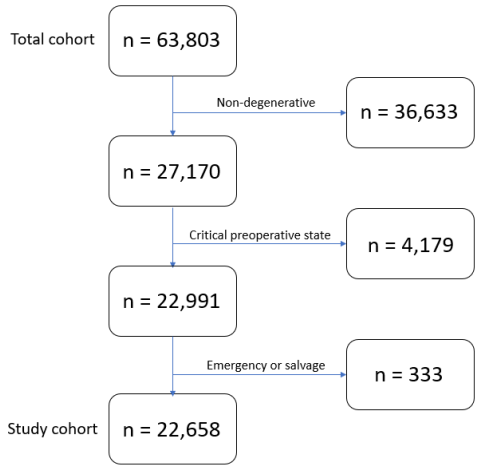

Fig. 1. Schema showing the study population.

Univariable Analysis

Tables 1 and 2 show the demographic, clinical characteristics and operative characteristics in women *vs.* men. Fig. 2 shows that women were more likely to present for surgery with markers of advanced disease, presenting older (70 ± 11.0 years *vs.* 67 ± 11.3 years, $p < 0.001$) with more advanced breathlessness (NYHA III–IV: 57% *vs.* 44%, $p < 0.001$), more likely to require concomitant tricuspid valve surgery (21% *vs.* 15%, $p < 0.001$) and as urgent referrals more frequently (14% *vs.* 12%, $p < 0.001$). They were also more likely to have preoperative atrial fibrillation (39% *vs.* 35%, $p < 0.001$), however rates of concomitant ablation did not differ between women and men (16% *vs.* 18%, $p = 0.111$).

Women had lower rates of coronary disease (19% *vs.* 29%, $p < 0.001$) and were accordingly less likely to receive concomitant CABG (16% *vs.* 26%, $p < 0.001$). They had greater rates of concomitant TVS (21% *vs.* 15%, $p < 0.001$). They more likely to suffer from MV stenosis or mixed disease (10% *vs.* 3%, $p < 0.001$). There were no differences in rates of diabetes, hypertension, active smoking, acute kidney injury or chronic obstructive pulmonary disease (COPD).

In terms of intra-operative variables, women had lower mean cardiopulmonary bypass time (CPB; 118 ± 46.6 mins *vs.* 131 ± 51.6 mins, $p < 0.001$) and lower mean aortic cross clamp time (87 ± 36.1 mins *vs.* 97 ± 38.2 mins, $p < 0.001$). They were significantly more likely to receive MVR than men (34% *vs.* 24%, $p < 0.001$) and in patients receiving MVR women were more likely to receive a bioprosthesis (67% *vs.* 64%, $p = 0.006$).

Compared with men, women had higher mortality rates (3% *vs.* 2%, $p < 0.001$) and lower return to theatre for bleeding and/or cardiac tamponade (5% *vs.* 6%, $p < 0.001$). There were no differences in rates of stroke, postoperative dialysis or deep sternal wound infection.

Repair Rate Trends

Fig. 3 shows the repair rates for degenerative disease over time in men and women. They rose from 33% to 67% in men and from 17% to 49% in women. Women had lower repair rates across all time periods ($p < 0.005$).

Multivariable Analysis

We included 16,257 (72%) patients in the multivariable models for hospital mortality, prolonged admission and re-exploration for bleeding; 16,746 (74%) patients were included in the model for receiving a replacement (see Table 3). Table 4a and Table 4b show the modifying effect of sex on the relationship between preoperative variables and postoperative outcomes.

Hospital Mortality

After adjusting for confounders, female sex was an independent predictor of mortality (OR: 1.52, 95% CI: 1.21–1.90, $p < 0.001$). This was modified by age ($p = 0.01$) and CCS score ($p = 0.036$). Female sex was only found to be an independent predictor of mortality in patients aged 64–74 (OR: 2.34, 95% CI: 1.57–3.50). There was no effect in patients with CCS score 0, however there was a significant relationship in patients with CCS scores I–II (OR: 1.73, 95% CI: 1.12–2.67) and III–IV (OR: 2.49, 95% CI: 1.20–5.20). See Table 3 for other independent predictors of mortality.

Return to Theatre

Female sex was a protective factor against re-exploration for bleeding (OR: 0.68, 95% CI: 0.59–0.80, $p < 0.001$). This was modified by year of admission ($p < 0.001$) and concomitant TVS ($p = 0.038$) (see Table 4a and Table 4b). Other protective factors against return to theatre include active smoking status (OR: 0.61, 95% CI: 0.40–0.93) and year of admission falling within 2016–2019 (OR: 0.65, 95% CI: 0.45–0.94) (see Table 3).

Table 1. Demography, comorbidities and clinical characteristics of men and women undergoing mitral valve surgery for degenerative mitral valve disease in a UK population (2000–2019).

Variable	Women (n = 7977)	Men (n = 14,681)	*p*-value	Missing
Age, years [Mean (SD)]	70 (±11.0)	67 (±11.3)	**<0.001**	2 (0%)
BMI, kg/m^2 [Mean (SD)]	25.7 (±5.2)	26.4 (±4.3)	**<0.001**	490 (2%)
NYHA class			**<0.001**	129 (1%)
I–II	3368 (43%)	8244 (56%)		
III–IV	4556 (58%)	6361 (44%)		
CCS score			**0.004**	286 (1%)
I	5650 (72%)	10,417 (71%)		
II–III	1743 (22%)	3376 (23%)		
IV–V	464 (6%)	722 (5%)		
Diabetes	592 (8%)	1101 (8%)	0.849	94 (0%)
Hypertension	4122 (52%)	7424 (51%)	0.103	166 (1%)
Active smoker	314 (4%)	635 (4%)	0.182	193 (1%)
Preoperative AKI	53 (1%)	114 (1%)	0.346	6663 (29%)
Urgency			**<0.001**	4 (0%)
Elective	6867 (86%)	12,940 (88%)		
Urgent	1108 (14%)	1739 (12%)		
Previous MI	521 (7%)	1195 (8%)	**<0.001**	211 (1%)
Re-do sternotomy	507 (6%)	1004 (7%)	0.164	1176 (5%)
Preoperative COPD	921 (12%)	1631 (11%)	0.326	296 (1%)
Previous stroke/TIA	513 (7%)	843 (6%)	**0.035**	517 (2%)
PVD	287 (4%)	611 (4%)	**0.041**	129 (1%)
Preoperative AF	3016 (39%)	5056 (35%)	**<0.001**	570 (3%)
Coronary disease	1299 (16%)	3672 (25%)	**<0.001**	2860 (13%)
EF range			**<0.001**	213 (1%)
Good	4281 (54%)	7523 (52%)		
Moderate	1650 (21%)	3338 (23%)		
Poor	1965 (25%)	3688 (25%)		
MV lesion			<0.001	342 (2%)
Regurgitation	7094 (90%)	14,050 (97%)		
Stenosis	381 (5%)	248 (2%)		
Mixed	378 (5%)	165 (1%)		

Numbers are n (%) unless otherwise indicated. The denominators used to calculate the percentages take into account the missing values for each variable. Bold indicates statistical significance. Abbreviations: NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; AKI, acute kidney injury; IMD, index of multiple deprivation; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; AF, atrial fibrillation; EF, ejection fraction; MV, mitral valve; BMI, body mass index; TIA, transient ischemic attack.

Prolonged Hospital Admission

Female sex was an independent predictor of prolonged admission (OR: 1.21, 95% CI: 1.12–1.30, $p < 0.001$). This was modified by age ($p = 0.043$), body mass index (BMI) ($p = 0.02$) and concomitant TVS ($p = 0.05$) (see Table 4a and Table 4b).

Mitral Valve Replacement

Female sex was an independent predictor of receiving MVR (OR: 1.35, 95% CI: 1.25–1.47). This effect was modified by the presence of MV stenosis (see Table 4a and Table 4b). Please see Table 3 for other independent predictors of MVR.

Discussion

Our results confirm that significant sex-based discrepancies exist in patients undergoing surgery for degenerative MV disease in the UK. Women make up only 35% of patients referred for surgery, despite recently published data showing that women in the general population have a significantly higher burden of degenerative MV disease compared to men across all age categories [14]. Women seem more likely to present for surgery urgently, older and more breathless. They have higher rates of atrial fibrillation (AF) and concomitant TV disease, both indicators of advanced disease. They are more likely to receive a mitral valve re-

Table 2. Intra and postoperative characteristics of men and women undergoing mitral valve surgery for degenerative mitral valve disease in a UK population (2000–2019).

Variable	Women (n = 7977)	Men (n = 14,681)	*p*-value	Missing
MV Procedure			<**0.001**	0 (0%)
Repair	5264 (66%)	11,104 (76%)		
Replacement	2713 (34%)	3577 (24%)		
MVR: Mitral prosthesis			**0.006**	288 (1%)
Biological	1732 (67%)	2185 (64%)		
Mechanical	845 (33%)	1240 (36%)		
Concomitant CABG	1302 (16%)	3771 (26%)	<**0.001**	6786 (30%)
Concomitant TV surgery	1680 (21%)	2267 (15%)	<**0.001**	13,780 (61%)
Concomitant ablation[1]	491 (16%)	893 (18%)	0.111	5651 (25%)
Cardiopulmonary bypass time, minutes [Mean (SD)]	117.6 (±46.6)	130.6 (±51.6)	<**0.001**	604 (3%)
Cross clamp time, minutes [Mean (SD)]	87.0 (±36.1)	97.0 (±38.2)	<**0.001**	606 (3%)
Mortality	263 (3%)	286 (2%)	<**0.001**	227 (1%)
Re-exploration for bleeding	381 (5%)	889 (6%)	<**0.001**	1112 (5%)
Stroke	122 (2%)	183 (1%)	0.078	2778 (12%)
Postoperative dialysis	225 (3%)	382 (3%)	0.330	2028 (9%)
Deep sternal wound infection	18 (0%)	46 (0%)	0.235	9696 (57%)
Length of stay, days	9 (7–13)	8 (6–11)	<**0.001**	233(1%)
Admitted ≥10 days	3779 (48%)	5756 (40%)	<**0.001**	233 (1%)

Numbers are n (%) unless otherwise indicated. The denominators used to calculate the percentages take into account the missing values for each variable. Bold indicates statistical significance. Abbreviations: MV, mitral valve; MVR, mitral valve replacement; CABG, coronary artery bypass graft; TV, tricuspid valve; BMI, body mass index. Normal continuous variables: mean ± SE. Non-normal variables: median (IQR) [1]. Ablation rates calculated as proportion of patients with preoperative AF, rather than whole population.

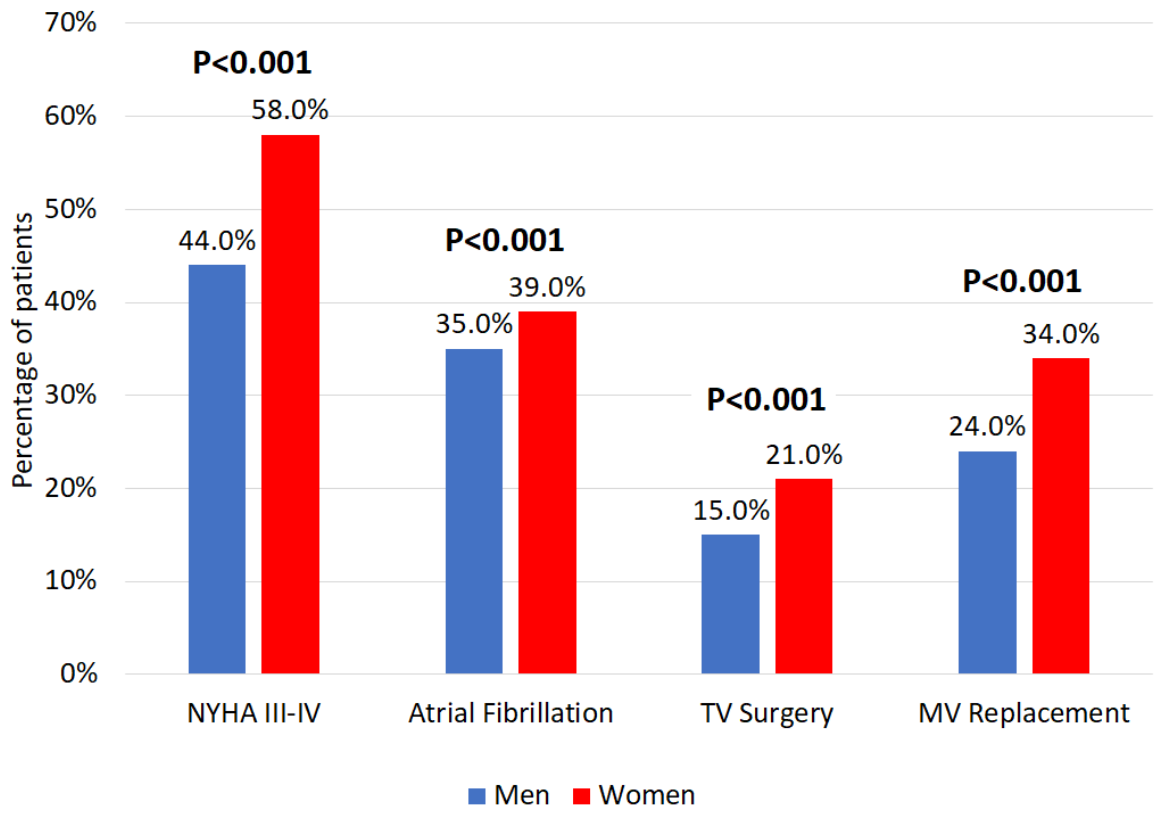

Fig. 2. Characteristics associated with advanced disease by sex.

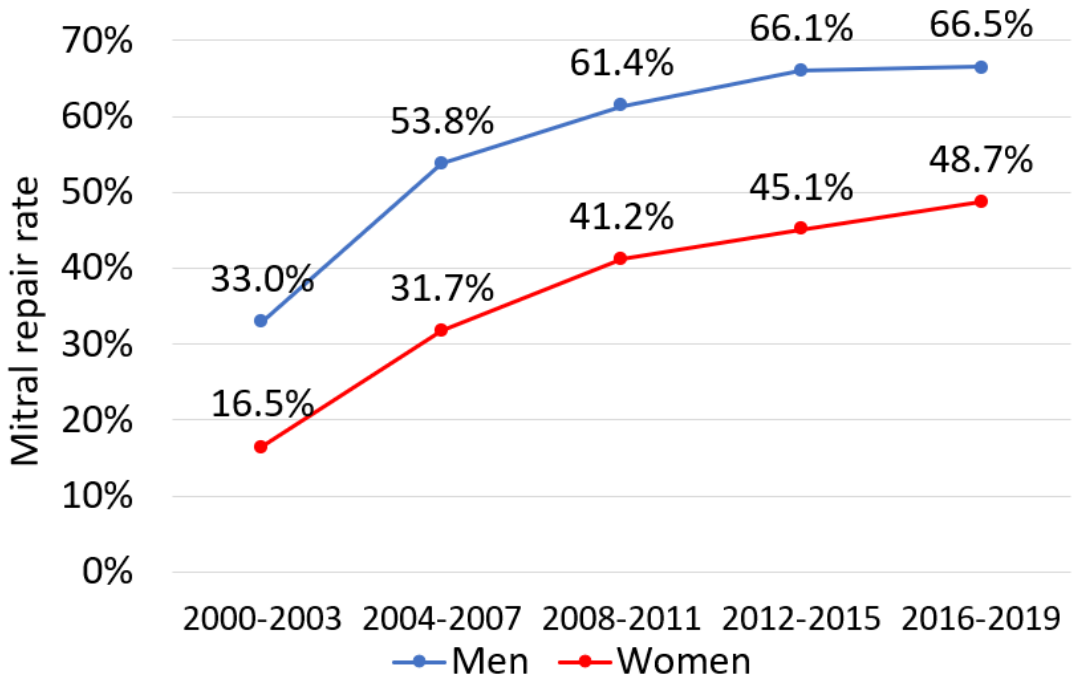

Fig. 3. Repair rates over time stratified by sex.

placement, have higher mortality rates and longer hospital admissions. Regression analysis showed female sex to be an independent predictor of mortality, receiving a replacement and of prolonged admission. Men were more likely to present with higher BMIs, coronary disease and underwent higher rates of concomitant CABG. This is in keeping with the higher prevalence of coronary disease amongst men in the general population [15]. Male sex seems to be independently associated with re-exploration for bleeding.

According to our results, the relationship between female sex and postoperative mortality was modified by age and CCS score. The relationship between advanced age (85 and above) and mortality appears to be more pronounced in women than men (see Table 4b), with women being more sensitive to the impact of advancing age on early postoperative mortality. In terms of CCS scores, we see that advanced CCS scores (III–IV) independently predict female mortality following surgery for degenerative MV disease. The same is not true for men. This may be caused by sex-differences in symptom reporting, as women who qualify as CCS III–IV may actually have worse symptoms than men with the same scores. Alternatively, it may be that sex-differences in exertional behaviour as people age result in women developing CCS class III–IV symptoms further along in their disease course. This would explain why the same CCS scores in appear to have different prognostic implications for men and women.

These findings from a large UK database suggest that women undergo delayed surgery for degenerative mitral disease compared to men. This was also the conclusion of a large retrospective US study looking at 183,792 patients undergoing MV surgery between 2000–2009, which noted that sex-based outcome differences were driven largely by women presenting for surgery later in the disease process [16]. This suggests that current referral criteria and thresholds for MV surgery in women remain sub-optimal at earlier detection of MV disease compared to men, and these criteria may be missing a considerable number of patients who would benefit from earlier surgical intervention. The latest European and American guidelines both use left ventricular end-systolic diameter (LVESD) ≥40 mm as a class I indication for MV surgery in asymptomatic patients [17,18]. This may contribute to the discrepancy, as a large US study showed that women with severe MR are less likely to have LVESD >40 mm than men, and that after correction for body surface area, they had significant left ventricular and left atrial changes than men [19,20]. This is a clear target for improvement within clinical practice, as this cut-off for early intervention appears to serves men better than women. Surgical decision-making for early intervention should be guided either by sex-stratified LVESD measurements, with different thresholds for men and women, or by LVESD measurements adjusted for body surface area. Asymptomatic women with severe primary mitral regurgitation (MR) and LVESD measurements approaching 40mm should be counselled regarding this and offered further measurements adjusted for body surface area to help guide optimal decision-making. This will likely improve access to surgical intervention earlier in the disease process for women, and provide better long-term outcomes.

Our results confirm that sex-differences exist in mortality and repair rates after mitral valve surgery, with

Table 3. Odds ratios and 95% confidence intervals for mortality, re-exploration and prolonged admission patients undergoing mitral valve surgery in a UK populations (2000–2019).

Variable	Outcome			
	Mortality	Re-exploration	Admission ≥10 days	MV replacement
Female sex	1.52 (1.21–1.90)	0.68 (0.59–0.8)	1.21 (1.12–1.30)	1.35 (1.25–1.47)
Mitral replacement	1.82 (1.44–2.30)	1.29 (1.1–1.51)	1.69 (1.55–1.84)	-
NYHA score III–IV	1.39 (1.09–1.76)	0.95 (0.83–1.1)	1.33 (1.23–1.43)	1.26 (1.16–1.36)
CCS score				
I (reference)				
II	1.02 (0.79–1.32)	1.35 (1.15–1.58)	1.13 (1.04–1.23)	1.42 (1.30–1.56)
III	1.22 (0.84–1.77)	1.21 (0.91–1.62)	1.06 (0.90–1.24)	1.11 (0.93–1.31)
Hypertension	1.39 (1.10–1.75)	1.19 (1.04–1.37)	1.03 (0.96–1.10)	1.04 (0.96–1.13)
Coronary disease	1.65 (1.14–2.39)	1.05 (0.79–1.39)	0.93 (0.79–1.08)	1.22 (1.10–1.35)
Active smoker	0.73 (0.37–1.43)	0.61 (0.40–0.93)	0.95 (0.80–1.14)	1.28 (1.06–1.55)
Year of admission				
2000–2003 reference				
2004–2007	0.87 (0.56–1.36)	0.80 (0.60–1.06)	0.94 (0.79–1.12)	0.36 (0.30–0.42)
2008–2011	0.73 (0.47–1.14)	0.80 (0.61–1.06)	0.69 (0.59–0.82)	0.19 (0.17–0.23)
2012–2015	0.55 (0.33–0.89)	0.75 (0.56–1.01)	0.71 (0.60–0.85)	0.15 (0.13–0.18)
2016–2019	0.50 (0.29–0.84)	0.65 (0.45–0.94)	0.52 (0.42–0.64)	0.13 (0.10–0.16)
IMD quintile				
I–II	0.95 (0.64–1.41)	0.90 (0.70–1.16)	1.05 (0.92–1.20)	0.81 (0.7–0.93)
III–IV	0.95 (0.65–1.38)	0.93 (0.73–1.18)	0.90 (0.79–1.02)	0.80 (0.70–0.92)
V–VI	0.87 (0.60–1.25)	0.93 (0.74–1.17)	0.85 (0.76–0.96)	0.76 (0.67–0.87)
VII–VIII	1.15 (0.81–1.63)	0.99 (0.79–1.24)	0.93 (0.82–1.04)	0.67 (0.59–0.77)
IX–XI (reference)				
Urgency				
Elective (reference)				
Urgent	1.43 (1.09–1.86)	0.97 (0.8–1.19)	4.62 (4.1–5.21)	1.05 (0.93–1.18)
Previous MI	1.40 (1.02–1.90)	0.88 (0.69–1.13)	1.34 (1.17–1.54)	1.22 (1.05–1.40)
Redo sternotomy	2.25 (1.64–3.08)	0.81 (0.61–1.07)	1.24 (1.07–1.43)	5.75 (5.01–6.59)
Previous stroke/TIA	1.25 (0.88–1.77)	1.29 (1.01–1.65)	1.21 (1.05–1.40)	1.36 (1.16–1.59)
PVD	1.80 (1.26–2.55)	0.72 (0.51–1.01)	1.32 (1.10–1.58)	0.94 (0.78–1.14)
Preoperative AF	1.20 (0.96–1.50)	1.20 (1.04–1.38)	1.15 (1.06–1.23)	1.22 (1.12–1.32)
EF range				
Good (reference)				
Moderate	1.49 (1.15–1.94)	0.96 (0.81–1.14)	1.14 (1.04–1.25)	0.94 (0.85–1.04)
Poor	1.48 (0.98–2.23)	0.81 (0.61–1.10)	0.99 (0.84–1.16)	0.94 (0.79–1.12)
Mitral stenosis	0.49 (0.24–0.99)	0.82 (0.46–1.48)	0.90 (0.66–1.24)	1.49 (0.99–2.25)
Concomitant CABG	2.18 (1.48–3.20)	1.10 (0.83–1.47)	1.06 (0.91–1.24)	-
Concomitant TVS	1.11 (0.85–1.45)	1.03 (0.86–1.24)	1.72 (1.56–1.89)	-
Age	1.07 (1.06–1.09)	1.01 (1.00–1.01)	1.04 (1.04–1.04)	1.01 (1.01–1.02)
BMI	1.00 (0.97–1.02)	0.97 (0.96–0.99)	1.00 (1.00–1.01)	1.02 (1.01–1.03)
CPB time	1.01 (1.01–1.01)	1.00 (1.00–1.00)	1.00(1.00–1.01)	-
Cross clamp time	0.99 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.00)	-
Length of admission	1.01 (1.01–1.02)	1.03 (1.03–1.04)	-	-

Abbreviations: MV, mitral valve; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; IMD, index of multiple deprivation; MI, myocardial infarction; TIA, transient ischaemic attack; PVD, peripheral vascular disease; AF, atrial fibrillation; EF, ejection fraction; CABG, coronary artery bypass graft; TVS, tricuspid valve surgery; BMI, body mass index; CPB, cardiopulmonary bypass.

women experiencing higher mortality and lower repair rates than men [10,21,22]. Whilst this would be in keeping with the hypothesis that they present further along in their disease course, it does not explain female sex emerging as an independent predictor for mortality, MVR, and prolonged admission in the multivariable models. This sug-

Table 4a. Modifying effect of sex on post-operative outcomes.

Variable	Adjusted odds ratio for women (95% CI)		Interaction *p*-value
	Presence of characteristic	Absence of characteristic	
	Mortality		
Age		-	0.010
<64 (n = 7906)	1.80 (0.83–3.92)		
64–74 (n = 8127)	2.34 (1.57–3.50)		
75–85 (n = 6239)	1.08 (0.79–1.47)		
>85 (n = 384)	7.62 (0.80–72.83)		
CCS score		-	0.036
0 (n = 16067)	1.30 (0.97–1.73)		
I–II (n = 5119)	1.73 (1.12–2.67)		
III–IV (n = 1186)	2.49 (1.20–5.20)		
	Re-exploration for bleeding		
Year of admission		-	<0.001
2000–2003 (n = 1297)	0.88 (0.51–1.53)		
2004–2007 (n = 3800)	0.61 (0.43–0.86)		
2008–2011 (n = 5442)	0.49 (0.36–0.66)		
2012–2015 (n = 5824)	1.03 (0.73–1.45)		
2016–2019 (n = 6038)	0.81 (0.61–1.09)		
Concomitant TVS (n = 3947)	0.52 (0.38–0.73)	0.76 (0.64–0.90)	0.038
	Prolonged admission		
Age	-	-	0.043
<64 (n = 7906)	1.38 (1.19–1.60)		
64–74 (n = 8127)	1.10 (0.98–1.25)		
75–85 (n = 6239)	1.13 (0.99–1.28)		
>85 (n = 384)	0.70 (0.36–1.36)		
BMI		-	0.017
<18.5 (n = 458)	0.80 (0.46–1.37)		
18.5–24.9 (n = 9212)	1.14 (1.02–1.27)		
25–29.9 (n = 8649)	1.19 (1.05–1.36)		
30–39.9 (n = 3660)	1.28 (1.06–1.55)		
>40 (n = 189)	3.22 (0.71–14.52)		
Concomitant TVS (n = 3947)	1.02 (0.86–1.21)	1.21 (1.11–1.32)	0.045
	Mitral replacement		
Mitral stenosis	3.38 (1.73–6.61)	1.27 (1.17–1.38)	<0.001

Abbreviations: CI, confidence interval; CCS, Canadian Cardiovascular Society; TVS, tricuspid valve surgery; BMI, body mass index.

gests there are either sex-specific factors, physician behaviour factors or other unmeasured confounders not included in our data. An explanation which has been described in the literature is that women experience a more aggressive form of mitral valve disease [21]. A single-centre study looking at 3671 patients receiving minimally invasive MVS between 1999–2011 described significant differences in both the degenerative mitral pathologies seen and the repair techniques performed in men and women. They found that women are more likely to present with anterior mitral valve leaflet (AMVL) and bileaflet prolapse, pathologies considered more challenging to surgically repair than isolated posterior mitral valve leaflet (PMVL) prolapse. They also found that women are more likely to suffer associated PMVL calcification (20.1% *vs.* 6.5%). These differences naturally translate into differences in repair techniques; in the same study, PMVL resection was performed in 17.9% of men versus 10.1% of women, and PMVL neochord insertion was performed in 39.3% of men compared with 20.4% of women. Different morphological patterns of mitral prolapse have also been identified, with women being more likely to present with thickened leaflets and less likely to have posterior leaflet prolapse [10]. Whilst sex-differences in the morphology and severity of MV disease have been previously demonstrated, knowledge of the role of sex hormones in the development of degenerative mitral disease is limited.

A range of potential confounding variables may contribute to the observed differences in outcomes between men and women including surgical experience, surgeon-

Table 4b. Sex-stratified odds ratios for variables with positive interaction term.

Variable	Sex-stratified odds ratio (95% CI)		Interaction *p*-value
	Women	Men	
	Mortality		
Age			0.010
<64 (n = 7906) [REF]	-	-	
64–74 (n = 8127)	2.92 (1.61–5.39)	1.75 (1.07–2.87)	
75–85 (n = 6239)	3.86 (2.12–7.03)	5.00 (3.12–8.02)	
>85 (n = 384)	8.51 (3.39–21.36)	5.16 (2.08–12.81)	
CCS score			0.036
0 (n = 16067) [REF]	-	-	
I–II (n = 5119)	1.27 (0.87–1.85)	0.88 (0.62–1.25)	
III–IV (n = 1186)	1.68 (1.02–2.78)	0.79 (0.44–1.42)	
	Re-exploration for bleeding		
Year of admission			<0.001
2000–2003 (n = 1297) [REF]	-	-	
2004–2007 (n = 3800)	0.61 (0.37–1.00)	0.90 (0.64–1.27)	
2008–2011 (n = 5442)	0.50 (0.30–0.82)	0.89 (0.63–1.25)	
2012–2015 (n = 5824)	0.83 (0.50–1.36)	0.64 (0.44–0.92)	
2016–2019 (n = 6038)	0.70 (0.36–1.35)	0.59 (0.38–0.91)	
Concomitant TVS (n = 3947)	0.75 (0.54–1.05)	1.33 (1.07–1.65)	0.038
	Prolonged admission		
Age			0.043
<64 (n = 7906) [REF]	-	-	
64–74 (n = 8127)	1.38 (1.18–1.60)	1.72 (1.55–1.91)	
75–85 (n = 6239)	2.37 (2.02–2.79)	2.90 (2.57–3.27)	
>85 (n = 384)	3.20 (2.09–4.92)	5.28 (3.65–7.63)	
BMI			0.017
<18.5 (n = 458) [REF]	-	-	
18.5–24.9 (n = 9212)	1.07 (0.79–1.46)	1.81 (1.20–2.73)	
25–29.9 (n = 8649)	0.87 (0.76–1.00)	0.89 (0.80–0.98)	
30–39.9 (n = 3660)	1.12 (0.95–1.32)	1.06 (0.93–1.21)	
>40 (n = 189)	3.10 (1.76–5.44)	1.20 (0.71–2.03)	
Concomitant TVS (n = 3947)	1.50 (1.29–1.75)	1.21 (1.11–1.32)	0.045
	Mitral replacement		
Mitral stenosis	17.27 (11.41–26.12)	8.69 (5.90–12.78)	<0.001

Abbreviations: REF, reference; CI, confidence interval; CCS, Canadian Cardiovascular Society; BMI, body mass index; TVS, tricuspid valve surgery.

specific factors and hospital-level factors. Whilst it remains to be shown specifically in the field of cardiac surgery, it has been suggested that female patients operated on by female surgeons experience better outcomes [23]. Given that the proportion of women presenting for MV surgery is significantly lower than men, less exposure to female patients overall may also contribute to slightly poorer outcomes.

The uniquely large UK sample size based on prospectively collected data provides strength to our study. Multivariable analyses allowed us to account for the impact of covariates. It is important to acknowledge the limitations of our study design when drawing conclusions from our findings. All nonrandomized retrospective database research suffers from a degree of inherent limitations. Whilst the NICOR database undergoes regular maintenance and validation, we cannot rule out the possibility of some data being recorded incorrectly. A lack of granularity in the data limits the conclusions we were able to make; data on the different types of repairs performed, as well as information on why surgeons chose not to repair in MVR cases, would have allowed us to comment further on the reasons behind the observed sex-discrepancies in MV surgery. Lack of long-term follow up data limited out study to looking at early post-operative outcomes. The size of the dataset and low levels of missingness in the data limit the impact of these factors. Whilst recognising these limitations, our study appears to confirm the relationship between sex and post-operative outcomes for patients with degenerative mitral disease.

Conclusions

(1) Sex-based differences in preoperative profiles and clinical outcomes exist in the field of degenerative MV disease.

(2) Sex differences in pathology may explain these findings; further research into the differences in progression of degenerative MV disease between men and women is required.

(3) Further prospective research into differences in healthcare access, surgical technique and referral patterns are required to determine the role physician bias may play.

(4) Sex-stratified recommendations should be considered when MV surgical guidelines are next reviewed.

Availability of Data and Materials

The data underlying this article were provided by NICOR by permission. Data will be shared on request to the corresponding author with permission of NICOR.

Author Contributions

FA, MP, HV, GA and MS designed the research study. FA analyzed the data and wrote the initial manuscript draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The register-based cohort study is part of a research approved by the Health Research Authority (HRA) and Health and Care Research Wales and a need for patients' consent was waived, as all patients in the database were anonymised (HCRW) (IRAS ID: 257758,23.7.2019).

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.6741.

References

[1] Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet (London, England). 2009; 373: 1382–1394.

[2] Chivasso P, Bruno VD, Farid S, Malvindi PG, Modi A, Benedetto U, *et al*. Predictors of survival in octogenarians after mitral valve surgery for degenerative disease: The Mitral Surgery in Octogenarians study. The Journal of Thoracic and Cardiovascular Surgery. 2018; 155: 1474–1482.e2.

[3] Filsoufi F, Carpentier A. Principles of reconstructive surgery in degenerative mitral valve disease. Seminars in Thoracic and Cardiovascular Surgery. 2007; 19: 103–110.

[4] Suri RM, Schaff HV, Dearani JA, Sundt TM, 3rd, Daly RC, Mullany CJ, *et al*. Survival advantage and improved durability of mitral repair for leaflet prolapse subsets in the current era. The Annals of Thoracic Surgery. 2006; 82: 819–826.

[5] Enriquez-Sarano M, Schaff HV, Orszulak TA, Tajik AJ, Bailey KR, Frye RL. Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. Circulation. 1995; 91: 1022–1028.

[6] Braunberger E, Deloche A, Berrebi A, Abdallah F, Celestin JA, Meimoun P, *et al*. Very long-term results (more than 20 years) of valve repair with carpentier's techniques in nonrheumatic mitral valve insufficiency. Circulation. 2001; 104: I8–I11.

[7] Piazza N, Onuma Y, de Jaegere P, Serruys PW. Guidelines for reporting mortality and morbidity after cardiac valve interventions–need for a reappraisal? The Annals of Thoracic Surgery. 2009; 87: 357–358; discussion 359–360.

[8] Anyanwu AC, Itagaki S, Chikwe J, El-Eshmawi A, Adams DH. A complexity scoring system for degenerative mitral valve repair. The Journal of Thoracic and Cardiovascular Surgery. 2016; 151: 1661–1670.

[9] Gillinov AM, Cosgrove DM, Blackstone EH, Diaz R, Arnold JH, Lytle BW, *et al*. Durability of mitral valve repair for degenerative disease. The Journal of Thoracic and Cardiovascular Surgery. 1998; 116: 734–743.

[10] Seeburger J, Eifert S, Pfannmüller B, Garbade J, Vollroth M, Misfeld M, *et al*. Gender differences in mitral valve surgery. The Thoracic and Cardiovascular Surgeon. 2013; 61: 42–46.

[11] Kaczmarek I, Meiser B, Beiras-Fernandez A, Guethoff S, Überfuhr P, Angele M, *et al*. Gender does matter: gender-specific outcome analysis of 67,855 heart transplants. The Thoracic and Cardiovascular Surgeon. 2013; 61: 29–36.

[12] Beller CJ, Farag M, Wannaku S, Seppelt P, Arif R, Ruhparwar A, *et al*. Gender-specific differences in outcome of ascending aortic aneurysm surgery. PLoS ONE. 2015; 10: e0124461.

[13] El-Andari R, Bozso SJ, Fialka NM, Kang JJH, Nagendran J. Does sex impact outcomes after mitral valve surgery? A systematic review and meta-analysis. Scandinavian Journal of Surgery: SJS: Official Organ for the Finnish Surgical Society and the Scandinavian Surgical Society. 2022; 111: 99–109.

[14] DesJardin JT, Chikwe J, Hahn RT, Hung JW, Delling FN. Sex Differences and Similarities in Valvular Heart Disease. Circulation Research. 2022; 130: 455–473.
[15] Weidner G. Why do men get more heart disease than women? An international perspective. Journal of American College Health. 2000; 48: 291–294.
[16] Vassileva CM, McNeely C, Mishkel G, Boley T, Markwell S, Hazelrigg S. Gender differences in long-term survival of Medicare beneficiaries undergoing mitral valve operations. The Annals of Thoracic Surgery. 2013; 96: 1367–1373.
[17] Corrigendum to: 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2022; 43: 2022.
[18] Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, 3rd, Gentile F, *et al*. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021; 143: e72–e227.
[19] McNeely C, Vassileva C. Mitral Valve Surgery in Women: Another Target for Eradicating Sex Inequality. Circulation. Cardiovascular Quality and Outcomes. 2016; 9: S94–S96.
[20] Avierinos JF, Inamo J, Grigioni F, Gersh B, Shub C, Enriquez-Sarano M. Sex differences in morphology and outcomes of mitral valve prolapse. Annals of Internal Medicine. 2008; 149: 787–795.
[21] Kislitsina ON, Zareba KM, Bonow RO, Andrei AC, Kruse J, Puthumana J, *et al*. Is mitral valve disease treated differently in men and women? European Journal of Preventive Cardiology. 2019; 26: 1433–1443.
[22] Al-Zubaidi F, Pufulete M, Sinha S, Kendall S, Moorjani N, Caputo M, *et al.* Mitral repair versus replacement: 20-year outcome trends in the UK (2000–2019). Interdisciplinary CardioVascular and Thoracic Surgery. 2023; 36: ivad086.
[23] Wallis CJD, Jerath A, Coburn N, Klaassen Z, Luckenbaugh AN, Magee DE, *et al*. Association of Surgeon-Patient Sex Concordance With Postoperative Outcomes. JAMA Surgery. 2022; 157: 146–156.