

1 **Title:** Effect of sex and surgical incision on survival after isolated primary mitral valve operations

2 **Running title:** Mitral valve surgery and sex differences

3 Maciej Dębski^{1,2}, Rebecca Taylor¹, Amr Abdelrahman¹, Karolina Dębska², Omar Assaf¹, Syed Qadri¹,

4 Kenneth Y-K Wong^{1,3}, Vassilios Vassiliou², Joseph Zacharias¹

5 1. Lancashire Cardiac Centre, Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool,
6 United Kingdom

7 2. Norfolk and Norwich University Hospital, University of East Anglia, Norwich, United Kingdom

8 3. Liverpool Centre for Cardiovascular Science, Liverpool, United Kingdom

9 **Corresponding author:** Maciej Dębski, MD, PhD

10 Research&Development Department, Blackpool Victoria Hospital

11 Whinney Heys Rd, FY3 8NR, Blackpool, United Kingdom

12 e-mail: maciej.debski@nhs.net

13 The abstract was presented at the American Heart Association's Scientific Sessions 2019

14 **Manuscript:** 5099 words

15

16

17

18

19

20

21

22

23

24 **Key question:**

25 Does minimally-invasive mitral valve surgery (MIMVS) have impact on improving sex-specific
26 survival compared to conventional mitral valve surgery (CS)?

27 **Key findings:**

28 A Cox model was fitted on 342 propensity score-matched pairs of MIMVS and CS patients and
29 adjusted for propensity score. It showed no survival difference with surgical approach, sex or the
30 interaction.

31 **Take-home message:**

32 MIMVS appears not to impact long-term survival either in women or men. However, it might aid the
33 acceptance of earlier intervention with mitral surgery with its better cosmetic results.

34
35
36
37
38
39
40
41
42
43
44
45
46
47

ACCEPTED MANUSCRIPT

48 **Abstract**

49 Objective: Multiple studies have suggested that women have worse outcomes than men following
50 mitral valve surgery—most of those studies reported on conventional sternotomy mitral valve surgery
51 (CS). Therefore, we aimed to explore whether or not the minimally invasive mitral valve surgery
52 (MIMVS) approach might mitigate a worse survival in women following CS.

53 Methods: We identified patients with isolated primary mitral valve operations with or without
54 tricuspid valve repair performed between 2007 and 2019. Patients were propensity score-matched
55 across the MIMVS and CS surgical approaches. Sex was excluded from the matching process to
56 discern whether female patients have a different likelihood of receiving minimally invasive surgery
57 than males. A Cox proportional hazards model was fitted in the matched cohort and adjusted for the
58 imbalance in baseline characteristics using the propensity score.

59 Results: Of 956 patients (417 MIMVS, 539 CS; 424 females), the matched set comprised 342 pairs
60 (684 patients; 296 females) of patients who were well balanced across MIMVS and CS groups with
61 regard to preoperative clinical characteristics. We observed a 47/53% female/male ratio in the CS and
62 a 39/61% in the MIMVS group, $p=0.054$. In both matched groups, women were older than males. A
63 Cox model adjusted for propensity scores showed no survival difference with sex, surgical type, or
64 interaction.

65 Conclusions: Women present to the surgical team at an older age. They appear less likely to be
66 considered for a MIMVS approach than men. Neither sex nor surgical approach was associated with
67 survival in a matched sample.

68 **Keywords:** Gender; Minimally invasive surgery; Mitral valve; Outcomes; Techniques

69 **Introduction:**

70 Women are considered to have a greater risk for postoperative morbidity and mortality in cardiac
71 surgery. Female sex remains an independent risk factor even after accounting for baseline imbalances
72 in the risk profile.^{1,2} This is recognized by most perioperative, short-term risk cardiac surgery risk
73 models, which give a higher score for the female sex. The original European System for Cardiac
74 Operative Risk Evaluation (EuroSCORE) and the updated EuroSCORE II were predominantly based
75 on patients undergoing coronary artery bypass grafting (CABG) and aortic valve surgery. Patients
76 undergoing isolated mitral valve (MV) repair or replacement accounted for 9% and 18% of the
77 databases,³⁻⁵ thus rendering the predictive performance less precise for the MV population.⁶ The
78 Society of Thoracic Surgeons recently released updated recalibrated short-term risk calculators,
79 including stand-alone risk calculators for isolated mitral valve replacement and repair where female
80 sex remained an independent risk factor for operative mortality.^{7,8} On the other hand, numerous
81 reports show that the outcomes of sternotomy approach MV surgery are similar for women and men
82 after risk adjustment.^{9,10}

83 The reasons which could explain the sex-based differences in MV operative risk are still elusive.^{11,12}
84 Women tend to have smaller atria and ventricles than men, however more prominent when indexed to
85 body surface area. Consequently, fewer women than men reach the classic surgical threshold of left
86 ventricular diameter, which is an absolute rather than an indexed value.^{13,14} Women referred for MV
87 surgery are older than men, with more advanced disease and more comorbidities.^{15,16} Women have
88 markedly higher rates of rheumatic valve disease than men,¹⁷ and are more likely to undergo mitral
89 valve replacement as opposed to repair, which has been shown to produce superior outcomes.^{9,15,18-20}
90 Finally, women are less likely to experience postoperative left ventricular remodeling than men.²¹
91 Notably, there is a paucity of data regarding the sex-based outcomes of minimally invasive mitral
92 valve surgery (MIMVS). Therefore, it is unclear whether it provides females with a long-term
93 survival advantage or not over the sternotomy approach. Furthermore, a recent report suggested that
94 MIMVS did not offer any benefits over sternotomy in terms of in-hospital deaths or postoperative
95 complications.²² We aimed to explore whether the effect of the surgical approach on long-term

96 survival varies by sex and to discern whether female patients had a different likelihood of receiving
97 MIMVS than males with similar preoperative characteristics.

98

99 **Methods**

100 ETHICS STATEMENT

101 The study was approved by the Research Ethics Committee - Health Research Authority (HRA), and
102 in line with other retrospective studies, the need for informed consent was waived (study ID 278325;
103 reference number 20/HRA/3772). The database was anonymized before analysis.

104 STUDY POPULATION AND STUDY DESIGN

105 We conducted a longitudinal, observational, retrospective cohort study in a tertiary care
106 cardiothoracic center in North West England, UK, of all consecutive patients undergoing mitral valve
107 surgery between January 2007 and December 2019 who met the following criteria: first mitral valve
108 surgery, either conventional (via sternotomy) (CS) or minimally invasive (MIMVS) with or without
109 tricuspid valve surgery or procedures for atrial fibrillation. Patients with previous mitral valve
110 surgery, concomitant coronary artery bypass graft surgery, simultaneous aortic valve
111 repair/replacement or surgery on ascending aorta, emergency (operation before the beginning of the
112 next working day after the decision to operate) or salvage procedure (patients requiring
113 cardiopulmonary resuscitation en route to the operating theatre or prior to induction of anaesthesia),
114 and those younger than 18 were excluded. Demographic and preoperative information, operative data,
115 and in-hospital postoperative outcomes for all patients were retrieved from the institutional database
116 maintained and validated for the purpose of outcome reporting to The National Adult Cardiac Surgery
117 Audit managed by the National Institute for Cardiovascular Outcomes Research (NICOR). The study
118 outcome measure was time to all-cause mortality. Information on vital status and date of death was
119 obtained from our Institution's Patient Administration System linked to the UK's Office for National
120 Statistics. It was up-to-date as of May 14, 2020.

121

122 STATISTICAL ANALYSIS

123 For all analyses, a 2-sided $p < 0.05$ was considered statistically significant. All data were processed
124 using R v. 4.1.2. The normality assumption for continuous variables was evaluated with the Shapiro–
125 Wilk test. Continuous variables are presented as median [interquartile range (IQR)] and compared
126 using the Kruskal–Wallis H test. Categorical variables are presented as counts and percentages and
127 compared with Fisher's exact test.

128 The sample of patients was propensity-matched across MIMVS and CS surgical types, using a logistic
129 model to derive propensity scores with the following predictor variables: age, body mass index
130 (BMI), arterial hypertension, pulmonary hypertension (defined as systolic pulmonary artery pressure
131 > 60 mmHg), diabetes mellitus, New York Heart Association (NYHA) functional class 3 or 4, chronic
132 pulmonary disease, recent myocardial infarction (within 90 days), left ventricular ejection fraction
133 category (poor 30% or less, fair 31-50% or good $> 50\%$), poor mobility, serum creatinine > 200
134 $\mu\text{mol/L}$, operative urgency (elective vs urgent), previous cardiac surgery, critical preoperative status
135 as per the EuroSCORE definition (ventricular tachycardia or ventricular fibrillation or aborted sudden
136 death, preoperative cardiac massage, preoperative ventilation before anaesthetic room, preoperative
137 inotropes or intra-aortic balloon pump, preoperative acute renal failure), concomitant tricuspid valve
138 surgery, and underlying mitral valve pathology (categorized as degenerative, functional, rheumatic,
139 infective endocarditis or other).

140 Sex was excluded from the matching process to discern whether female patients have a different
141 likelihood of receiving minimally invasive surgery than males with similar preoperative
142 characteristics. We did not use EuroSCORE itself as a predictor variable as the majority of its
143 components were individually used in the matching process.

144 Propensity score matching was conducted using the MatchIt package with a greedy "nearest
145 neighbour" algorithm and a caliper 0.2 times the standard deviation of propensity scores.²³ MIMVS
146 and CS patients were paired 1:1 and without replacement.

147 Survival for the matched set was visualized using a plot of Kaplan–Meier estimates. A Cox
148 proportional hazards model was fitted to explore whether the effect of surgical type varies by sex

149 using an interaction between surgery and sex while adjusting for the imbalance in baseline
150 characteristics between sexes using the propensity score.

151

152 **Results**

153 **BASELINE CHARACTERISTICS**

154 We included 956 patients undergoing their first mitral valve surgery, 539 (56.4 %) had surgery via
155 a conventional approach (sternotomy), and 417 (43.6 %) via a minimally invasive approach
156 (Supplementary Figure S1). Twelve patients (2.9%) had surgical access intraoperatively converted
157 from minimally invasive to conventional. There were 275 females and 287 males in the CS approach
158 and 158 females and 259 males in the MIMVS approach, whose baseline characteristics are presented
159 in Table 1. At first mitral valve surgery, the median age was 68 years (IQR 58-75), range 19-92, and
160 424 (44.4%) were females. The median survival for the whole sample was 4.9 years (IQR 2.3 – 8.2);
161 197 (20.1%) patients died during the study period.

162 The matched set comprised 342 pairs (684 patients) of patients who are well balanced across MIMVS
163 and CS groups (Figures 1 & 2 & 3, Table 2). Balance was assessed using standardized mean
164 differences (SMD) between surgical groups, with an SMD lower than 0.1 deemed satisfactory
165 balance; Figure 2 shows the between-group SMD of preoperative characteristics in the whole sample
166 and in the matched sub-sample.

167 The matched set described a subset of the observed cohort: the group of patients with a small
168 probability of receiving MIMVS given their baseline characteristics, shown by the first local mode
169 coloured pink in Figure 1, were largely discarded during the matching process. Table 2 suggests that
170 patients in the whole sample receiving conventional surgery were much more likely to be tricuspid
171 valve surgery patients and showed higher rates of hypertension, diabetes and dyspnoea than the
172 conventional sternotomy patients remaining in the matched sample. Therefore, conclusions drawn
173 from this analysis relate to those patients described in the matched sample for whom both operative
174 approaches were viable options for their surgery.

175 The 342-pair matched sample showed some imbalance in the mitral valve pathology category;
176 however, this was much improved from the whole, unmatched sample and was likely due to small
177 numbers split across many (five) categories. In addition, the Fisher's exact test of independence for
178 the mitral valve pathology variable in the matched sample was non-significant with $p=0.45$, which
179 gives some confidence that the remaining imbalance should not significantly affect conclusions.

180 The matched set described a set of patients with very similar preoperative clinical characteristics. A
181 substantially higher proportion of the MIMVS group were male than in the CS group (61% vs 53%
182 male, $p=0.054$, SMD 0.154), suggesting that females were under-represented in the MIMVS group
183 despite the two surgical groups being clinically similar in all other relevant preoperative
184 characteristics.

185 When exploring matching in more detail, we observed that males had much higher propensity scores
186 (likelihood of MIMVS) than females, regardless of whether they received MIMVS or CS (Figure 3).
187 In the matched cohort across MIMVS and CS, we showed that in the CS group, women were older
188 (66.7 vs 63.6 years, SMD=0.227) and sicker than men (NYHA 3 or 4: 58.4% vs 43.1%, SMD=0.309),
189 in MIMVS women were older (67.4 vs 62.0 years, pairwise SMD=0.417) but comparably sick
190 (NYHA 3 or 4: 51.1% vs 45.9%, pairwise SMD=0.105) (Supplementary Table S1).

191 Kaplan–Meier survival estimates of the matched set showed no difference in survival between the
192 treatment groups (Figure 4, log-rank test $p=0.72$). Also, Kaplan–Meier curves in a four-way
193 sex/treatment variable showed no significant difference in survival (Supplementary Figure S2, log-
194 rank test $p=0.21$).

195 A Cox proportional hazard model adjusted for surgical type, sex, the interaction of surgical type and
196 sex, and the propensity score (as a measure of preoperative imbalance) showed no survival difference
197 with any covariate once sex baseline imbalance is accounted for (Table 3). This model satisfied the
198 assumption of proportional hazards (global $p=0.63$).

199

200

201 Discussion

202 We present for the first time results on long-term sex-based differences in survival after isolated
203 mitral valve surgery relative to the surgical approach. Of 956 patients included, 44% were women.
204 Several notable baseline differences were discovered based on sample division by sex and surgical
205 approach. First, there were significant differences in age at the time of surgery; females were older
206 than men in CS, and MIMVS approaches. While our observations corroborate evidence concerning
207 age discrepancy in conventional MVR, the differences in MIMVS have not been shown before.^{15,16} In
208 terms of the NYHA class, women undergoing sternotomy had a higher degree of dyspnoea than those
209 with MIMVS. In our population, females had a higher incidence of rheumatic valve disease, whereas
210 males had more degenerative valve disease. That may explain why females were more likely to
211 receive a replacement than males.^{9,14,15,18-20,24}

212 MIMVS is perceived to cause less pain to the patient and superior cosmetic results. There is evidence
213 in aortic valve surgery that leaving the pericardium intact in minimally invasive surgery as opposed to
214 leaving it open in sternotomy results in the right ventricular (RV) function being less affected.²⁵
215 Previous studies also showed that there is less need for blood transfusion in MIMVS vs CS and
216 MIMVS results in shorter postoperative stay compared to CS. In contrast, the cumulative bypass and
217 cross-clamp times are longer in MIMVS.²⁶ However, the long-term effects of MIMVS appear to be on
218 par with CS.^{26,27} The debate between these two approaches is still ongoing as a UK-based randomized
219 trial of minimally invasive techniques versus sternotomy for mitral valve surgery is currently
220 underway with a primary outcome of functional recovery after surgery.²⁸ Noteworthy, the UK's mini-
221 mitral trial excludes patients with previous cardiac surgery and those who required mitral valve
222 replacement. Our data show that patients meeting the above criteria constituted approximately one-
223 third of all comers, of whom one-third had MIMVR and two-thirds had a sternotomy. We also
224 showed that unmatched patients receiving the conventional surgery were much more likely to need
225 tricuspid valve surgery and had higher rates of hypertension, diabetes, and NYHA class than the
226 conventional surgery patients remaining in the matched sample. Notably, the inference based on the

227 matched sub-cohort only goes as far as the patient types included in the matched population, and a
228 randomized controlled trial is warranted to exclude the bias inherent to observational data.

229 In agreement with our findings, previous studies have demonstrated that short and long-term results of
230 MIMVS and CS are equivalent if experienced surgeons undertake minimally invasive surgery in large
231 volumes like in our center.²⁶ After adjusting for propensity scores, no difference in survival was noted
232 between sex, surgical approach and their interaction term. Our long-term findings are concordant with
233 the recent study looking at in-hospital mortality following minimally invasive and sternotomy isolated
234 aortic and mitral valve operations where no significant interaction was found between sex and
235 surgical approach in neither aortic nor mitral valve subgroups after adjusting for confounders. The
236 advantage of our analysis was the robust and complete data for post-discharge survival. Additionally,
237 in the matched samples across surgical types, we have shown that females were less likely than males
238 to receive MIMVS, and we found no apparent reason for this since survival appeared unrelated to
239 treatment type or sex. This potential discrepancy in access to minimally invasive mitral valve surgery
240 warrants further exploration, emphasizing referral pathways and a broader decision-making process.
241 We found that women are older than males and with higher NYHA class at the surgery. Further
242 studies are needed to evaluate the psychological impact of the scar that may be in play when women
243 consider sternotomy surgery.²⁹ We hope that our results will highlight the sex gap in minimally
244 invasive mitral surgery and help persuade women to consider heart surgery earlier in the course of the
245 mitral valve disease.^{29, 30}

246 LIMITATIONS

247 This study is a retrospective review of patients with all inherent limitations. We have only analyzed
248 data that were available for all the subjects; we did not include information on atrial fibrillation
249 history, relevant echocardiographic parameters, or the degree of mitral annular calcification due to
250 missing data. A single-center setting limits the generalisability of study findings. In addition, the
251 treatment allocation was likely confounded by the surgical risk profile and patient and surgeon
252 preference. However, to counterbalance the non-experimental study design, we propensity score-
253 matched patients across the two types of surgical approaches. The matched set is matched entirely,

254 but the subgroups of male and female patients are not directly matched. A four-way matched solution
255 was not able to be found. Deriving propensity scores for sex is not clinically useful (sex is pre-
256 determined and cannot be randomly assigned pre-operatively). While propensity scores for treatment
257 allocation could then be used to match males and females within each surgical type separately, these
258 groups were no longer matched across treatment allocation.

259 This may mean we still do not have all the answers as to whether there is a sex-by-surgery difference.
260 However, we can conclude this far that given all relevant baseline covariates (of which sex is just one)
261 for this matched sub-cohort, there appears to be no difference in survival by surgery type, by sex or by
262 the interaction of both.

263 In contrast to using Cox models without matching first, the present method adds (a) description of the
264 cohort who are viable and comparable MIMVS candidates and (b) the result that females appear to be
265 disadvantaged with respect to access to MIMVS without apparent cause.

266

267 **Conclusions**

268 In a matched sub-cohort across conventional and minimally invasive mitral valve surgery without
269 using sex as a predictor variable, we show that females are less likely to be offered minimally
270 invasive mitral valve surgery in our centre. After adjusting for surgical access, sex, the interaction of
271 surgical access and sex, and the propensity score (as a measure of preoperative imbalance), there
272 appears to be no difference in survival by surgery type, by sex or by the interaction of both.

273

274

275 **Funding:** MD is an NIHR Academic Clinical Fellow and is supported by National Institute for Health
276 Research (award number ACF-2020-15-001). No other funding was obtained.

277 **Conflict of interest:** JZ receives Proctoring Fees from Edwards Lifesciences, Abbott, Cryolife and
278 Medtronic. VV receives payment or honoraria for lectures, presentations, speakers bureaus or

279 educational events from Medtronic, Novartis and Astra Zeneca. Other authors declare no conflict of
280 interest.

281 **Author contributions:** MD, RT, and JZ had full access to all the data in the study. RT conducted a
282 formal analysis. MD and RT wrote the manuscript draft and take responsibility for the data integrity
283 and the accuracy of the results. JZ provided mentorship and oversight over the administration and
284 management of the research project. VV provided supervision and assisted in the study design. All
285 authors critically revised the manuscript and approved the final version.

286 **Acknowledgements:** We thank Mrs Catherine Malpas for her assistance in data curation.

287 **Data availability statement:** The data underlying this article will be shared on reasonable request to
288 the corresponding author.

289

290 **Figure legends:**

291 Central Image. Key messages, the standardized mean difference of preoperative characteristics in the
292 whole and matched samples and a Cox proportional hazards model on the matched set.

293 Figure 1. Distributional balance of propensity scores.

294 Figure 2. A standardized mean difference of preoperative characteristics in the whole and matched
295 samples.

296 Figure 3. Propensity scores for males and females.

297 Figure 4. Kaplan–Meier survival curves for the matched set, split by surgery type. CS=conventional
298 sternotomy, MI=minimally invasive mitral valve surgery. A log-rank p-value is given.

299

300 Table 1: Treatment by sex differences in preoperative and operative clinical characteristics for all data, n=956. Global differences between the four
 301 groups are tested using the Kruskal–Wallis H test (continuous variables) or Fisher's exact test (categorical variables). SMD=standardised mean
 302 difference; mean-averaged across all pairwise SMD. IE=infective endocarditis; NYHA=New York Heart Association. Previous cardiac surgery was
 303 coronary artery bypass grafting (CABG) in 26 pts, CABG and aortic valve surgery (AVS) in 13 pts, AVS in 40 pts, and other heart surgery,
 304 including congenital heart disease correction in 7 pts.

Characteristic		Conventional		Minimally Invasive		Global test of group difference	Average SMD
		Female, n=266	Male, n=273	Female, n=158	Male, n=259		
Age, years		71 [63-76]	67 [58-75]	70 [61-76]	64 [52-71]	<0.001	0.273
Hypertension	Yes	155 (58.3)	39 (50.9)	81 (51.3)	111 (42.9)	0.006	0.157
Pulmonary hypertension	Severe	71 (26.7)	66 (24.2)	36 (22.8)	49 (18.9)	0.200	0.098
Poor mobility	Yes	31 (11.7)	16 (5.9)	19 (12.0)	17 (6.6)	0.024	0.138
Diabetes	Yes	34 (12.8)	19 (7.0)	7 (4.4)	14 (5.4)	0.003	0.162
Dyspnoea	NYHA class 3 or 4	166 (62.4)	136 (49.8)	82 (51.9)	115 (44.4)	<0.001	0.190
Previous cardiac surgery	Yes	22 (8.3)	18 (6.6)	19 (12.0)	27 (10.4)	0.211	0.106
Chronic lung disease	Yes	38 (14.3)	28 (10.3)	18 (11.4)	33 (12.7)	0.531	0.068
Creatinine	>200 µmol/L	1 (0.4)	7 (2.6)	0	5 (1.9)	0.053	0.148
Recent myocardial infarction	Yes	5 (1.9)	3 (1.1)	0	0	0.065	0.126
Left ventricular ejection fraction	Poor (≤30%)	5 (1.9)	8 (2.9)	3 (1.9)	6 (2.3)	0.401	0.137
	Fair (31-50%)	44 (16.5)	41 (15.0)	15 (9.5)	45 (17.4)		
	Good (>50%)	217 (81.6)	224 (82.1)	140 (88.6)	208 (80.3)		
Operative priority	Urgent	35 (13.2)	35 (12.8)	9 (5.7)	17 (6.6)	0.008	0.164

Critical pre-operative state	Yes	3 (1.1)	3 (1.1)	0	1 (0.4)	0.445	0.093
Body mass index, kg/m²		26.4 [23.7-30.0]	25.9 [23.6-28.7]	24.9 [21.9-28.8]	26.4 [23.7-28.9]	0.024	0.150
Mitral valve pathology	Degenerative	152 (57.1)	202 (74.0)	97 (61.4)	181 (69.9)	<0.001	0.473
	Functional	28 (10.5)	36 (13.2)	27 (17.1)	55 (21.2)		
	IE	4 (1.5)	7 (2.6)	0	1 (0.4)		
	Rheumatic	70 (26.3)	14 (5.1)	26 (16.5)	10 (3.9)		
	Other	12 (4.5)	14 (5.1)	8 (5.1)	12 (4.6)		
Tricuspid valve surgery	Yes	128 (48.1)	111 (40.7)	39 (24.7)	26 (10.0)	<0.001	0.511

305

306

307

308

309

310

311

ACCEPTED MANUSCRIPT

312 Table 2: Preoperative patient characteristics, before and after propensity matching. Age and body mass index are given as mean and standard
 313 deviation, all others as frequency and percentage. SMD = standardized mean difference. IE = infective endocarditis; NYHA = New York Heart
 314 Association.

Characteristic	Whole sample, n=956			Matched sample, n=684			
	Conventional, n=539	Minimally invasive, n=417	SMD	Conventional, n=342	Minimally invasive, n=342	SMD	
<i>Matching covariates:</i>							
Age, years	70 [60-76]	66 [55-74]	0.249	68 [58-75]	67 [56-74]	0.081	
Hypertension	Yes	294 (55)	192 (46)	0.171	169 (49)	162 (47)	0.041
Pulmonary hypertension	Severe	137 (25)	85 (20)	0.120	75 (22)	70 (21)	0.036
Poor mobility	Yes	47 (9)	36 (9)	0.003	29 (9)	33 (10)	0.041
Diabetes	Yes	53 (10)	21 (5)	0.184	23 (7)	18 (5)	0.062
Dyspnoea	NYHA class 3 or 4	302 (56)	197 (47)	0.177	172 (50)	164 (48)	0.047
Previous cardiac surgery	Yes	40 (7)	46 (11)	0.125	30 (9)	33 (10)	0.030
Chronic lung disease	Yes	66 (12)	51 (12)	<0.001	42 (12)	44 (13)	0.009
Creatinine	>200 µmol/L	8 (2)	5 (1)	0.025	6 (2)	3 (1)	0.077
Recent myocardial infarction	Yes	8 (2)	0	0.174	0	0	<0.001
Left ventricular ejection fraction	Poor (≤30%)	13 (2)	9 (2)	0.043	6 (2)	8 (2)	0.075
	Fair (31-50%)	85 (16)	60 (14)		42 (12)	49 (14)	
	Good (>50%)	441 (82)	348 (84)		294 (86)	285 (83)	
Operative priority	Urgent	70 (13)	26 (6)	0.231	24 (7)	25 (7)	0.011
Critical pre-operative state	Yes	6 (1)	1 (0.2)	0.107	0	1 (0.3)	0.077
Body mass index, kg/m²	26.1 [23.6-29.4]	25.8 [22.8-28.9]	0.090	26.0 [23.8-29.4]	25.8 [22.7-28.9]	0.086	

Mitral valve pathology	Degenerative	354 (66)	278 (67)	0.332	240 (70)	236 (69)	0.143
	Functional	64 (12)	82 (20)		44 (13)	59 (17)	
	IE	11 (2)	1 (0.2)		1 (0.3)	1 (0.3)	
	Rheumatic	84 (16)	36 (9)		41 (12)	32 (9)	
	Other	26 (5)	20 (5)		16 (5)	14 (4)	
Tricuspid valve surgery	Yes	239 (44)	65 (16%)	0.661	75 (22)	70 (21)	0.030
<i>Covariates not matched for:</i>							
Sex	Male	273 (51)	259 (62)	0.233	181 (53)	207 (61)	0.154
Type of mitral valve surgery	Replacement	185 (34.3)	93 (22.3)	0.269	115 (33.6)	75 (21.9)	0.263
Need for blood transfusion	Yes	109 (20.2)	28 (6.7)	0.404	62 (18.1)	24 (7.0)	0.340
Postprocedural length of stay, days		9 [7-14]	6 [5-8]	0.480	8 [6-13]	6 [5-9]	0.350
Cumulative bypass time, min		132 [110-166]	164 [141-195]	0.606	125 [103-154]	162 [141-194]	0.767
Cumulative cross-clamp time, min		98 [80-125]	110 [91-131]	0.139	91 [73-114]	110 [93-129]	0.324
Logistic EuroSCORE		5.8 [3.3-10.2]	4.4 [2.2-8.1]	0.129	5.18 [2.44-8.72]	4.46 [2.27-8.14]	0.010
Additive EuroSCORE		6 [5-8]	5 [3-7]	0.278	6 [4-8]	5 [3-7]	0.107

315

316

317

318 Table 3: Cox model on matched set, n=684. HR=hazard ratio. CI=confidence interval.

Covariate	HR (95% CI)	p-value
MIMVS	1.15 (0.70, 1.88)	0.58
Male sex	0.75 (0.47, 1.20)	0.23
MIMVS and male sex (interaction)	0.95 (0.47, 1.92)	0.89
Propensity score	0.54 (0.17, 1.67)	0.28

319

320

321

322

323

324

325

326

327

ACCEPTED MANUSCRIPT

328 **References**

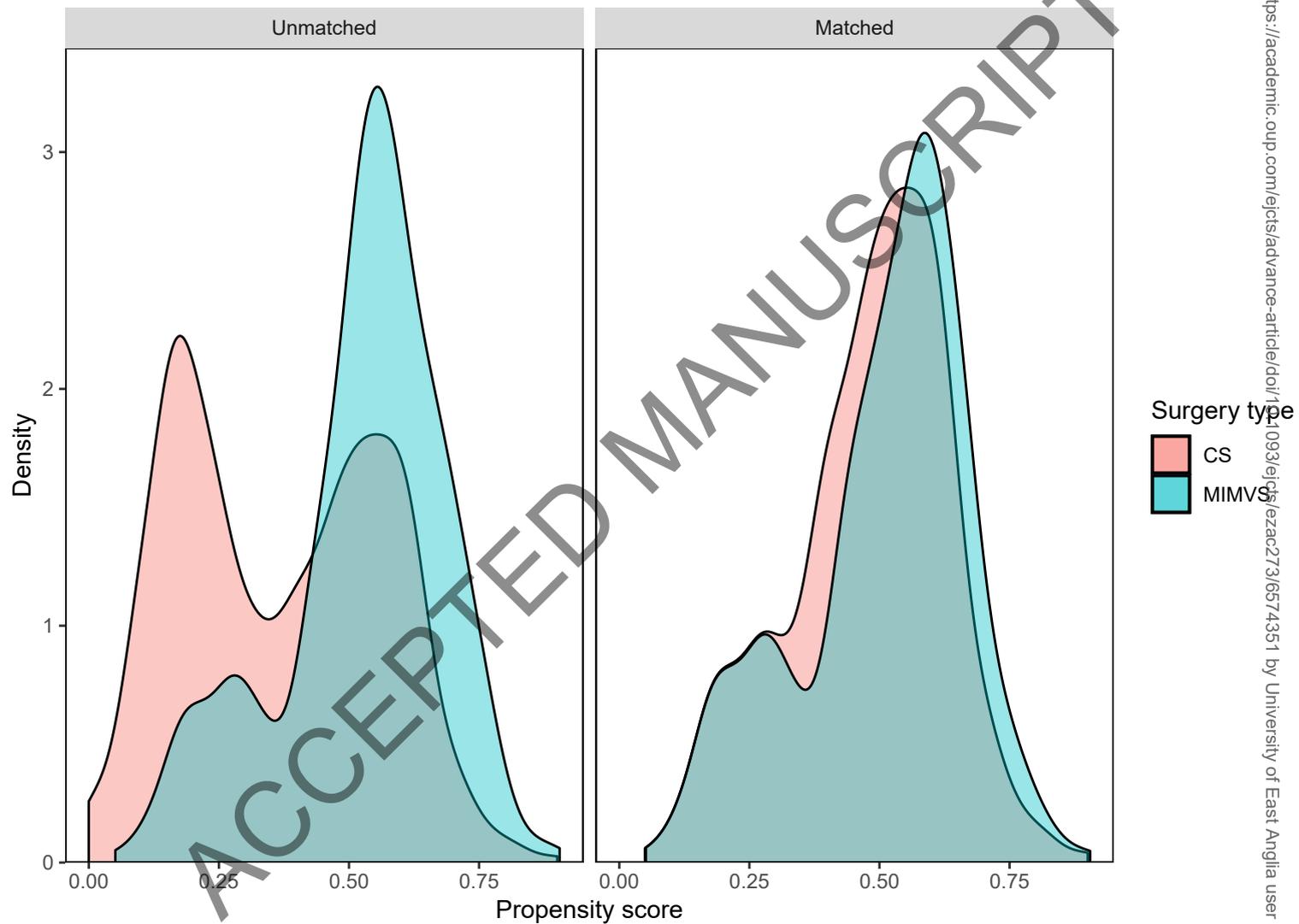
- 329 1. Singh A, Musa TA, Treibel TA, Vassiliou VS, Captur G, Chin C, et al. Sex differences in left ventricular remodelling, myocardial fibrosis and
330 mortality after aortic valve replacement. *Heart*. 2019;105:1818-1824.
- 331 2. Johnston A, Mesana TG, Lee DS, Eddeen AB, Sun LY. Sex Differences in Long-Term Survival After Major Cardiac Surgery: A Population-Based
332 Cohort Study. *J Am Heart Assoc*. 2019;8:e013260.
- 333 3. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, et al. Risk factors and outcome in European cardiac surgery: analysis of
334 the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg*. 1999;15:816-22.
- 335 4. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur*
336 *J Cardiothorac Surg*. 1999;16:9-13.
- 337 5. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012;41:734-744.
- 338 6. Carino D, Denti P, Ascione G, Del Forno B, Lapenna E, Ruggeri S, et al. Is the EuroSCORE II reliable in surgical mitral valve repair? A single-centre
339 validation study. *Eur J Cardiothorac Surg*. 2021;59:863-868.
- 340 7. Shahian DM, Jacobs JP, Badhwar V, Kurlansky PA, Furnary AP, Cleveland JC, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery
341 Risk Models: Part 1-Background, Design Considerations, and Model Development. *Ann Thorac Surg*. 2018;105:1411-1418.
- 342 8. O'Brien SM, Feng L, He X, Xian Y, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 2-
343 Statistical Methods and Results. *Ann Thorac Surg*. 2018;105:1419-1428.
- 344 9. Vassileva CM, McNeely C, Mishkel G, Boley T, Markwell S, Hazelrigg S. Gender differences in long-term survival of Medicare beneficiaries
345 undergoing mitral valve operations. *Ann Thorac Surg*. 2013;96:1367-1373.

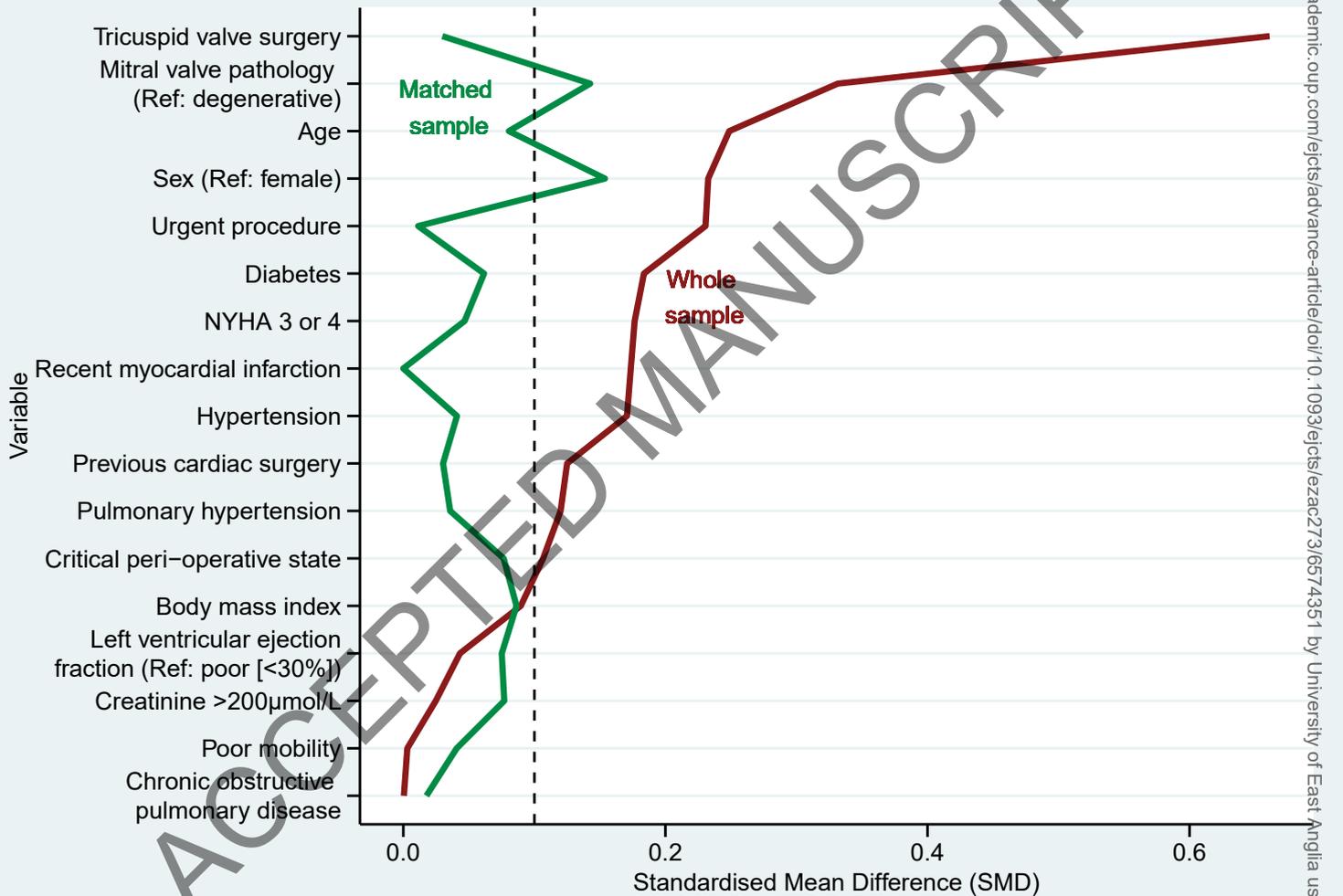
- 346 10. Kandula V, Kislitsina ON, Rigolin VH, Thomas JD, Malaisrie SC, Andrei AC, et al. Does gender bias affect outcomes in mitral valve surgery for
347 degenerative mitral regurgitation? *Interact Cardiovasc Thorac Surg.* 2021;33:325-332.
- 348 11. Lampert BC, Lindenfeld J, Abraham WT. Too Different or Too Late?: Gender Differences in Outcomes After Mitral Valve Surgery. *JACC Heart*
349 *Fail.* 2019;7:491-492.
- 350 12. McNeely C, Vassileva C. Mitral Valve Surgery in Women: Another Target for Eradicating Sex Inequality. *Circ Cardiovasc Qual Outcomes.*
351 2016;9:S94-S96.
- 352 13. Avierinos JF, Inamo J, Grigioni F, Gersh B, Shub C, Enriquez-Sarano M. Sex differences in morphology and outcomes of mitral valve prolapse. *Ann*
353 *Intern Med.* 2008;149:787-795.
- 354 14. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart
355 disease. *Eur J Cardiothorac Surg.* 2021;60:727–800.
- 356 15. Kislitsina ON, Zareba KM, Bonow RO, Andrei AC, Kruse J, Puthumana J, et al. Is mitral valve disease treated differently in men and women? *Eur J*
357 *Prev Cardiol.* 2019;26:1433-1443.
- 358 16. Mokhles MM, Siregar S, Versteegh MI, Noyez L, van Putte B, Vonk AB, et al. Male-female differences and survival in patients undergoing isolated
359 mitral valve surgery: a nationwide cohort study in the Netherlands. *Eur J Cardiothorac Surg.* 2016;50:482-487.
- 360 17. Vakamudi S, Jellis C, Mick S, Wu Y, Gillinov AM, Mihaljevic T, et al. Sex Differences in the Etiology of Surgical Mitral Valve Disease.
361 *Circulation.* 2018;138:1749-1751.
- 362 18. Seeburger J, Eifert S, Pfannmüller B, Garbade J, Völlroth M, Misfeld M, et al. Gender differences in mitral valve surgery. *Thorac Cardiovasc Surg.*
363 2013;61:42-46.

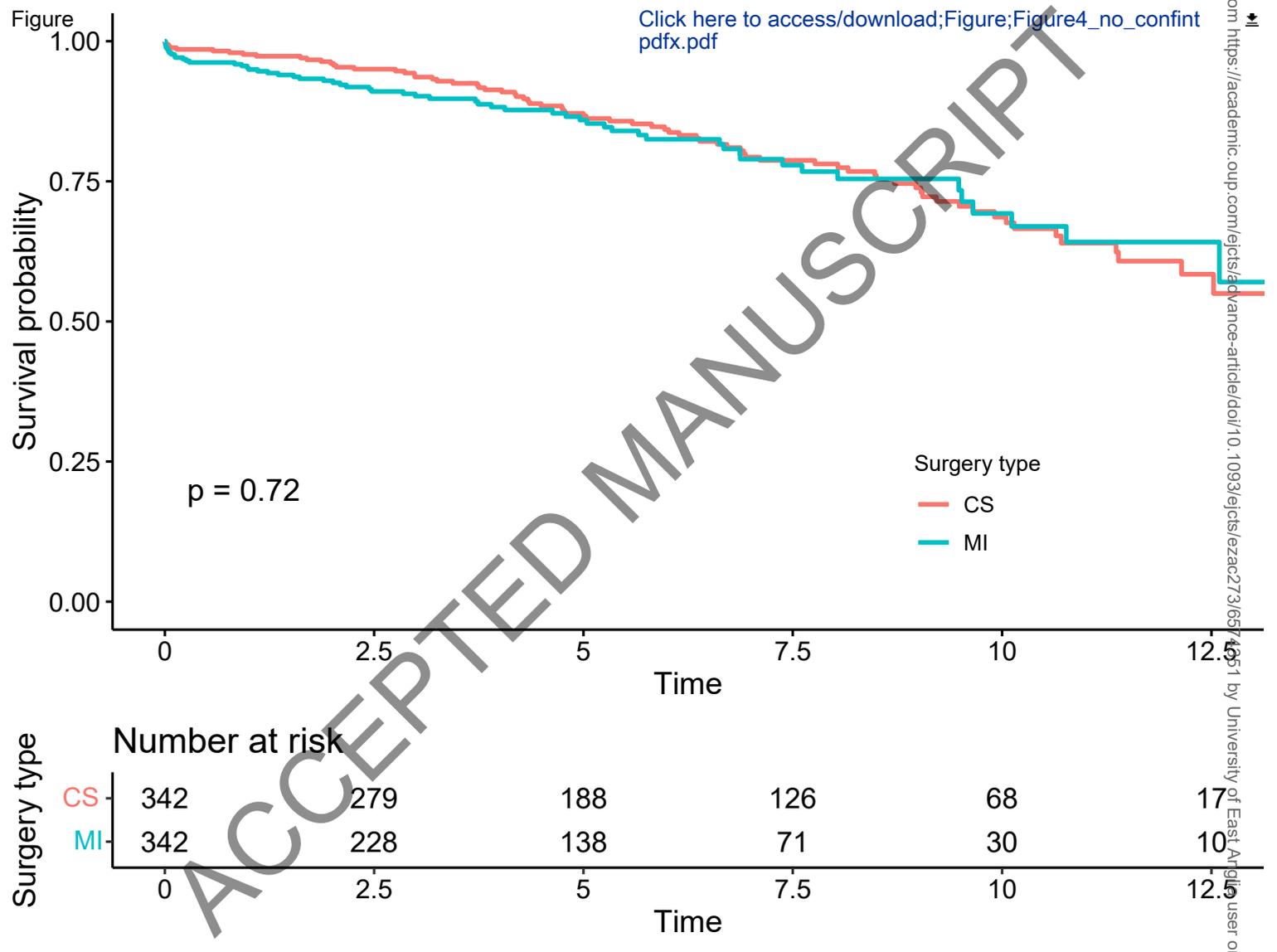
- 364 19. Vassileva CM, Mishkel G, McNeely C, Boley T, Markwell S, Scaife S et al. Long-term survival of patients undergoing mitral valve repair and
365 replacement: a longitudinal analysis of Medicare fee-for-service beneficiaries. *Circulation*. 2013;127:1870-1876.
- 366 20. Yun-Dan D, Wen-Jing D, Xi-Jun X. Comparison of Outcomes following Mitral Valve Repair versus Replacement for Chronic Ischemic Mitral
367 Regurgitation: A Meta-Analysis. *Thorac Cardiovasc Surg*. 2017;65:432-441.
- 368 21. Chan V, Chen L, Messika-Zeitoun D, Elmistekawy E, Ruel M, Mesana T. Is Late Left Ventricle Remodeling After Repair of Degenerative Mitral
369 Regurgitation Worse in Women? *Ann Thorac Surg*. 2019;108:1189-1193.
- 370 22. Moscarelli M, Lorusso R, Angelini GD, Di Bari N, Paparella D, Fattouch K, et al. Sex-specific differences and postoperative outcomes of minimally
371 invasive and sternotomy valve surgery. *Eur J Cardiothorac Surg*. 2022;61:695-702.
- 372 23. Ho D, Imai K, King G, Stuart EA. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. *Journal of Statistical Software*. 2011;42:1-
373 28.
- 374 24 Gammie JS, Chikwe J, Badhwar V, Thibault DP, Vemulapalli S, Thourani VH, et al. Isolated Mitral Valve Surgery: The Society of Thoracic
375 Surgeons Adult Cardiac Surgery Database Analysis. *Ann Thorac Surg*. 2018;106:716-727.
- 376 25. Hashemi N, Johnson J, Brodin LÅ, Gomes-Bernardes A, Sartipy U, Svenarud P, et al. Right ventricular mechanics and contractility after aortic valve
377 replacement surgery: a randomized study comparing minimally invasive versus conventional approach. *Open Heart*. 2018;5:e000842.
- 378 26 Grant SW, Hickey GL, Modi P, Hunter S, Akowuah E, Zacharias J. Propensity-matched analysis of minimally invasive approach versus sternotomy
379 for mitral valve surgery. *Heart*. 2019;105:783-789.
- 380 27 Abdelrahman A, Debski M, Qadri S, Guella E, Tay J, Wong KYK, et al. Association between preoperative right ventricular impairment on
381 transthoracic echocardiography and outcomes after conventional and minimally invasive mitral valve surgery. *Acta Cardiol*. 2021;76:895-903.

- 382 28 Maier RH, Kasim AS, Zacharias J, Vale L, Graham R, Walker A, et al. Minimally invasive versus conventional sternotomy for Mitral valve repair:
383 protocol for a multicentre randomized controlled trial (UK Mini Mitral). *BMJ Open*. 2021;11:e047676.
- 384 29 Piarulli A, Chiariello GA, Bruno P, Cammertoni F, Rabini A, Pavone N, et al. Psychological Effects of Skin Incision Size in Minimally Invasive
385 Valve Surgery Patients. *Innovations (Phila)*. 2020;15:532-540.
- 386 30. Vohra HA, Salmasi MY, Chien L, Baghai M, Deshpande R, Akowuah E, et al; British and Irish Society for Minimally Invasive Cardiac Surgery.
387 BISMICS consensus statement: implementing a safe minimally invasive mitral programme in the UK healthcare setting. *Open Heart*. 2020;7:e001259.

ACCEPTED MANUSCRIPT







Key question

- Does minimally-invasive mitral valve surgery (MIMVS) have impact on improving sex-specific survival compared to conventional mitral valve surgery (CS)?

Key findings

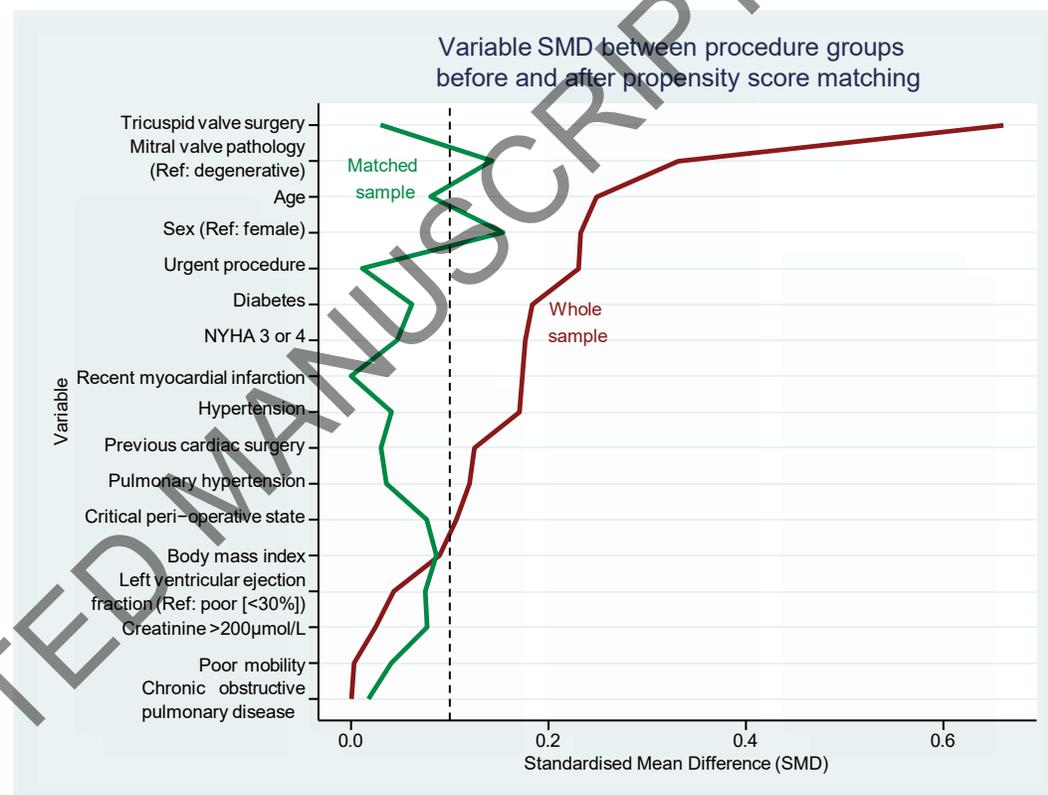
- A Cox model was fitted on 342 propensity score-matched pairs of MIMVS and CS patients and adjusted for propensity score. It showed no survival difference with surgical approach, sex or the interaction.

Take-home message

- MIMVS appears not to impact long-term survival either in women or men. However, it might aid the acceptance of earlier intervention with mitral surgery with its better cosmetic results.

956 patients with de novo mitral valve surgery ± tricuspid valve surgery: 417 MIMVS, 539 CS; 424 females

MIMVS and CS patients were propensity score-matched using 16 predictor variables except sex resulting in 342 pairs



Covariate	HR (95% CI)	p-value
MIMVS	1.15 (0.70, 1.88)	0.58
Male sex	0.75 (0.47, 1.20)	0.23
MIMVS and male sex (interaction)	0.95 (0.47, 1.92)	0.89
Propensity score	0.54 (0.17, 1.67)	0.28