Sex-based Outcomes after Surgery for Acute Type A Aortic Dissection

Sarah Yousef[1], Forozan Navid[1], Jianhui Zhu[2], James Brown[1], Derek Serna-Gallegos[1], Edgar Aranda-Michel[1], Valentino Bianco[1], Danny Chu[1], and Ibrahim Sultan[1]

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Abstract

Background: While prior data have suggested worse outcomes in women after acute type A aortic dissection (ATAAD) repair when compared to men, results have been inconsistent across studies over time. This study sought to evaluate the impact of sex on short- and long-term outcomes after ATAAD repair. *Methods:* This was a retrospective study utilizing an institutional database of ATAAD repairs from 2007 to 2021. Patients were stratified according to sex. Kaplan-Meier survival estimation and multivariable Cox regression were performed. Supplementary analysis using propensity score matching was also performed. *Results:* Of the 601 patients who underwent ATAAD repair, 361 were males (60.1%) and 240 (39.9%) were females. Females were significantly older, more likely to have hypertension, and more likely to have chronic lung disease. Females were also significantly more likely than males to undergo hemiarch replacement, while males were significantly more likely than females to undergo total arch replacement and frozen elephant trunk. Operative mortality was 9.4% among males and 13.8% among females, though this was not a statistically significant difference (p=0.098). Postoperative complications were comparable between groups. Kaplan-Meier survival estimates were similar for men and women, and, on multivariable Cox regression, sex was not significantly associated with long-term survival (HR 1.00, 95% CI: 0.73, 1.37, p=0.986). Outcomes remained comparable after supplementary propensity score matched analysis. *Conclusion:* ATAAD repair can be performed with comparable short-term and long-term outcomes in both men and women.

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ABSTRACT

Background: While prior data have suggested worse outcomes in women after acute type A aortic dissection (ATAAD) repair when compared to men, results have been inconsistent across studies over time. This study sought to evaluate the impact of sex on short- and long-term outcomes after ATAAD repair.

Methods: This was a retrospective study utilizing an institutional database of ATAAD repairs from 2007 to 2021. Patients were stratified according to sex. Kaplan-Meier survival estimation and multivariable Cox regression were performed. Supplementary analysis using propensity score matching was also performed.

Results: Of the 601 patients who underwent ATAAD repair, 361 were males (60.1%) and 240 (39.9%) were females. Females were significantly older, more likely to have hypertension, and more likely to have chronic lung disease. Females were also significantly more likely than males to undergo hemiarch replacement, while males were significantly more likely than females to undergo total arch replacement and frozen elephant trunk. Operative mortality was 9.4% among males and 13.8% among females, though this was not a statistically significant difference (p=0.098). Postoperative complications were comparable between groups. Kaplan-Meier survival estimates were similar for men and women, and, on multivariable Cox regression, sex was not significantly associated with long-term survival (HR 1.00, 95% CI: 0.73, 1.37, p=0.986). Outcomes remained comparable after supplementary propensity score matched analysis.

Conclusion: ATAAD repair can be performed with comparable short-term and long-term outcomes in both men and women.

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INTRODUCTION

Several sex-based differences in the pathophysiology of aortic diseases have been established, such as later presentation of women with acute type A aortic dissection (ATAAD) [1] and faster growth rate of thoracic aortic aneurysms in women when compared to men [2]. In light of these differences, studies have also been conducted to investigate potential differences in sex-based outcomes after ATAAD repair. Some data have suggested worse outcomes in women, though there have been conflicting findings and inconclusive results among these studies over time [3,4,5]. Moreover, it is unclear whether findings of worse outcomes in women were actually attributable to sex-based differences in pathophysiology and initial presentation. Some hypothesize that women have had worse outcomes and higher mortality because of more frequent atypical clinical presentations, leading to considerable delays in diagnosis and management [6]. Over the past decade, outcomes of ATAAD repair have improved significantly, due to advancements in diagnostic methods, cerebral perfusion strategies, spinal cord protection, surgical techniques, and endovascular technologies [7]. Whether sex-related disparities in outcomes of ATAAD repair persist in the modern era is not yet well-established.

To help clarify these questions, we present sex-based outcomes from our experience of ATAAD repair, with additional propensity score matched analysis to eliminate the effects of age, type of repair, and other confounding variables on outcomes.

METHODS

Patient Population and Study Design

We conducted a retrospective study using an institutional database of aortic surgeries performed at our center from January 2007 to April 2021. Definitions and terminology were consistent with the Society of Thoracic Surgeons database. All patients undergoing open repair for acute type A aortic dissection were included. Those undergoing concomitant operations such as coronary artery bypass grafting (CABG) or carotid artery replacement were also included. Patients undergoing aortic surgery for other pathologies were excluded.

The primary aims of this study were to compare short-term postoperative outcomes and long-term survival between males and females undergoing ATAAD repair. Follow-up data was obtained from the clinical warehouse that contains all long-term survival data for patients undergoing cardiac and aortic surgery at the University of Pittsburgh Medical Center. This study was approved by the Institutional Review Board of the University of Pittsburgh on 4/17/2019 (STUDY18120143), with written consent being waived.

Operative technique

All patients who presented with ATAAD underwent emergent repair. Central aortic cannulation, the preferred approach at our institution, was performed utilizing a modified Seldinger technique, with transesophageal echocardiographic (TEE) guidance to ensure cannulation of the true lumen. Peripheral cannulation was performed if any of the following contraindications to central cannulation were present: arch rupture, complex primary or secondary arch tear, or complete circumferential arch dissection [8]. When peripheral cannulation was required, right subclavian artery cannulation through a silo graft was preferred over femoral cannulation. Hypothermic circulatory arrest was employed routinely, and patients were cooled to electroencephalogram (EEG) silence [9]. The default repair strategy involved hemiarch replacement with retrograde cerebral perfusion (RCP). Total arch replacement with antegrade cerebral perfusion (ACP) was performed if any of the following pathologies were present: 1) primary or secondary arch tear, 2) circumferential arch dissection, 3) arch aneurysm, or 4) carotid dissection resulting in cerebral malperfusion. Finally, a frozen elephant trunk was performed in any cases of distal arch tear at or beyond the origin of the left subclavian, severe pseudocoarctation, and/or significant dilation of the proximal descending aorta with concern for disruption [10,11,12].

Statistical Methods and Analysis

Primary stratification was between males and females who underwent ATAAD repair. Continuous variables were presented as mean ± standard deviation for normally distributed data, or median and interquartile range (IQR) for non-normally distributed data. Categorical data were reported by frequency and percentage. Normally distributed continuous variables were analyzed using the student's t-test, while non-normally distributed continuous variables were analyzed with the nonparametric Mann-Whitney U test. The Chi-squared or Fisher's exact test was used to compare categorical variables between groups, as appropriate. Unadjusted survival estimates were generated using Kaplan-Meier methods and compared using log-rank statistics. A Cox proportional hazards regression model was used for the multivariable analysis of mortality. The assumption of proportional hazards was validated using Schoenfeld residuals, and, for covariates other than sex in the model, the method of stepwise selection was employed with a threshold of inclusion in the model of $p<0.020$.

Supplementary propensity score matched analyses were performed using greedy nearest neighbor caliper matching, with calipers of width setting at 0.2 of standard deviation. Propensity score matching incorporated the following variables: patient age, history of hypertension, history of chronic lung disease, performance of hemiarch replacement, and performance of total arch replacement. All statistical analyses were performed using SAS/STAT Version 15.2 (SAS Institute Inc., Cary, NC, USA). All tests were 2-sided with an alpha level of 0.05 designated to indicate statistical significance.

RESULTS

Baseline demographic, clinical, and operative variables

Of the 601 patients who underwent ATAAD repair, 361 were males (60.1%) and 240 (39.9%) were females. Baseline characteristics were reported and compared between the two groups (Table 1). Females were significantly older, more likely to have hypertension, and more likely to have chronic lung disease when compared to males. Other baseline variables, including race, BMI, previous sternotomy, ejection fraction, history of diabetes, peripheral vascular disease, or coronary artery disease, and presence of tamponade, rupture, shock, or any malperfusion syndrome on presentation were comparable between the two groups.

Operative variables were also reported and compared between groups (Table 2). Females were significantly more likely than males to undergo hemiarch replacement, while males were significantly more likely than females to undergo total arch replacement and frozen elephant trunk. Females were more likely than males to undergo bilateral carotid artery replacement.

Postoperative outcomes

Postoperative outcomes are summarized in Table 3. Operative mortality was 9.4% among males and 13.8% among females, though this was not a statistically significant difference (p=0.098). Males had a significantly higher rate of [?] moderate residual aortic insufficiency and lower 1-month follow-up ejection fraction than females. Females had a longer duration of postoperative mechanical ventilation than males did. Rates of pneumonia, stroke, new-onset renal failure requiring dialysis, and re-exploration for bleeding were comparable between groups. Postoperative length of stay was also comparable between groups.

Long-term survival

Total median follow-up for males was 4.7 [1.82-7.8] years and for females was 4.5 [1.06-7.9] years (p=0.453). Kaplan-Meier survival estimates were comparable between the two groups (Figure 1, p=0.315, log-rank). On multivariable Cox proportional hazards regression, sex was not significantly associated with long-term survival (HR 1.00, 95% CI: 0.73, 1.37, p=0.986, Table 4). Age, African American race, diabetes, and presence of any malperfusion syndrome were all significantly associated with an increased hazard of death (HR >1, p<0.05).

Supplementary Propensity-Matched Analysis

Given differences in baseline characteristics including age and type of operation performed, propensity score matching was also performed as a supplementary analysis. Samples were matched based on propensity score corresponding to patient age, history of hypertension, history of chronic lung disease, performance of hemiarch replacement, and performance of total arch replacement. Postoperative outcomes and long-term survival still did not differ between groups when analyzed in matched samples (Supplementary Tables 1 and 2; Supplementary Figure 1).

DISCUSSION

This single-center study compares sex-based outcomes of ATAAD repair. There were no significant differences in operative mortality or long-term survival between men and women. Rates of postoperative stroke, renal failure requiring dialysis, and re-exploration for bleeding were also comparable between groups. Because of the differences in baseline characteristics and operative variables between the two groups, we also performed supplementary propensity-score matched analyses, which yielded comparable results.

Our findings differ from those of many prior studies which suggest worse outcomes in women. A single-center study of 400 patients in China demonstrated higher in-hospital mortality and higher rates of in-hospital complications such as myocardial ischemia, hypoxemia, and tamponade in women with ATAAD when compared to men [13]. Another study from the International Registry of Acute Aortic Dissection (IRAD) database in 2004 demonstrated that women, while less likely than men to develop ATAAD, were more likely to present later in life, to have complications such as rupture and tamponade, to have worse surgical outcomes, and to have higher in-hospital mortality than men with ATAAD [5].

Placing our findings in the context of prior studies, perhaps the differences can be explained by a reduction of sex-related disparities in outcomes over time. Indeed, a more recent query of the IRAD database demonstrated significantly higher in-hospital mortality for women with ATAAD when compared to men overall, but not within the last decade of enrollment, suggesting that disparity in sex-based outcomes may be improving with time [14]. Like ours, this study also demonstrated that females with ATAAD presented later in life than males did, and that males were more likely overall to undergo total arch and elephant trunk procedures. Consistent with our study's findings, a meta-analysis published in 2022 demonstrates comparable short-term mortality and postoperative outcomes between men and women after ATAAD repair [15], and another 2022 study using the Taiwan National Health Insurance Research database found no significant sex-related differences in in-hospital mortality or all-cause mortality between men and women undergoing ATAAD repair [16].

Our study did find a significant association with African American race and risk of mortality (Table 4), with a higher hazard ratio than any other variable in the model, including presence of malperfusion. This suggests that, while we may have come a long way with improving sex-related disparities in outcomes, we still have considerable work to do in mitigating race-related disparities.

Limitations

This study is inherently limited by its retrospective, observational design with potential for selection bias. Additionally, the study analyzed longitudinal data with varying follow-up times, with some patients being lost to follow-up. Finally, the data is from a single, high-volume center, which may limit generalizability to other institutions.

Conclusion

ATAAD repair can be performed with comparable short-term and long-term outcomes in both men and women.

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Table 1. Baseline Characteristics

Variable	Male (n=361)	Female (n=240)	p-value
Age (years)	58.6 ± 13.2	65.5 ± 12.7	<0.001
Race Caucasian African American Other	292 (80.9) 51 (14.1) 18 (5.0)	201 (83.4) 32 (13.3) 7 (2.9)	0.429
Body mass index (kg/m^2)	30.1 ± 6.51	29.9 ± 6.97	0.795
Hypertension	264 (73.13)	193 (80.42)	0.040
Diabetes mellitus	37 (10.25)	26 (10.83)	0.819
Chronic lung disease	40 (11.08)	46 (19.17)	0.006
Chronic kidney disease	11 (3.05)	2 (0.83)	0.087
Peripheral vascular disease	119 (32.96)	88 (36.67)	0.350
Atrial fibrillation	34 (9.42)	27 (11.25)	0.466
Coronary artery disease	57 (15.79)	29 (12.08)	0.204
Redo sternotomy	50 (13.85)	22 (9.17)	0.083
Bicuspid aortic valve	21 (5.82)	6 (2.50)	0.055

Variable	Male (n=361)	Female (n=240)	p-value
Preoperative hematocrit	39.6 ± 6.06	36.8 ± 5.79	<0.001
Aortic insufficiency [?] moderate	159 (44.04)	93 (38.75)	0.198
Ejection fraction	54.8 ± 9.56	56.1 ± 9.47	0.097
Tamponade, rupture, or shock	111 (30.75)	76 (31.67)	0.812
Any malperfusion syndrome	121 (33.52)	69 (28.75)	0.218
Type of malperfusion syndrome Cerebral Coronary Visceral Renal Iliofemoral	45 (12.5) 26 (7.2) 23 (6.4) 25 (6.9) 61 (16.9)	29 (12.1) 16 (6.7) 12 (5.0) 11 (4.6) 24 (10.0)	0.889 0.801 0.482 0.236 0.018

Table 2. Intraoperative Variables

Variable	Male (n=361)	Female (n=240)	p-value
Primary tear location Non coronary sinus Left coronary sinus Right coronary sinus Sinotubular junction Ascending aorta Aortic arch	60 (16.6) 14 (3.9) 13 (3.6) 61 (16.9) 157 (43.5) 39 (10.8)	37 (15.4) 12 (5.0) 15 (6.3) 30 (12.5) 125 (52.1) 15 (6.3)	0.062
Secondary arch tear (y/n)	75 (20.8)	29 (12.1)	0.006
Cannulation strategy Aortic Subclavian Femoral	291 (80.6) 31 (8.6) 21 (5.8)	199 (82.9) 23 (9.6) 12 (5.0)	0.447
Distal aorta Hemiarch replacement Total arch replacement Elephant trunk Frozen elephant trunk	208 (57.6) 141 (39.1) 29 (8.0) 47 (13.0)	165 (68.8) 70 (29.2) 10 (4.2) 18 (7.5)	0.006 0.013 0.060 0.033
Carotid artery replacement Both carotid arteries Left carotid artery only Right carotid artery only	9 (2.5) 17 (4.7) 13 (3.6)	18 (7.5) 2 (0.8) 10 (4.2)	0.004 0.008 0.723
Concomitant coronary artery bypass graft	51 (14.13)	34 (14.17)	0.989
Cardiopulmonary bypass time (min)	207 ± 74.0	197 ± 73.5	0.094
Ischemic time (min)	141 ± 63.4	135 ± 58.3	0.188
Antegrade cerebral perfusion time (min)	15.0 ± 21.8	12.7 ± 20.7	0.223
Retrograde cerebral perfusion time (min)	16.6 ± 15.4	17.9 ± 14.0	0.315

Variable	Male (n=361)	Female (n=240)	p-value
Proximal reconstruction Aortic valve resuspension Aortic valve replacement Valve-sparing root replacement Complete aortic root replacement Mechanical valve implant Bioprosthetic valve implant	203 (56.2) 22 (6.1) 82 (22.7) 66 (18.3) 31 (8.6) 34 (9.4)	156 (65.0) 15 (6.2) 40 (16.7) 45 (18.7) 14 (5.8) 30 (12.5)	0.032 0.938 0.071 0.885 0.209 0.230

Table 3. Postoperative Outcomes

Variable	Male (n=361)	Female (n=240)	p-value
Operative mortality (STS definition)	34 (9.4)	33 (13.8)	0.098
Total postoperative length of stay (days)	12.0 ± 13.0	12.7 ± 12.5	0.565
Pneumonia	33 (9.1)	29 (12.1)	0.246
New-onset cerebrovascular accident	14 (3.9)	12 (5.0)	0.508
Mechanical ventilation time (hours)			
Mean ± SD	35.0 ± 90.2	55.7 ± 122	0.022
Median (IQR)	9.2 (5.4 -20.8)	13.9 (7.1-51.6)	<0.001
New-onset renal failure requiring hemodialysis	38 (10.5)	30 (12.5)	0.456
Re-exploration for excessive bleeding	32 (8.9)	22 (9.2)	0.899
Residual aortic insufficiency ([?] moderate)	7 (1.9)	0 (0.00)	0.046
1-month follow-up ejection fraction	54.9 ± 11.3	58.1 ± 7.3	<0.001

Table 4. Multivariable Cox proportional-hazards regression model for mortality in the entire cohort (n=601)

Variable	Hazard Ratio	95% CI	p-value
Gender (female)	1.00	0.73, 1.37	0.986
Age (years)	1.02	1.01, 1.04	0.001
Race (ref: Caucasian) African American Other	2.19 0.75	1.44, 3.32 0.30, 1.89	<0.001 0.540
Body mass index (kg/m^2)	0.97	0.95, 1.00	0.022
Hypertension	1.53	0.99, 2.37	0.054
Diabetes mellitus	1.89	1.25, 2.84	0.002

Variable	Hazard Ratio	95% CI	p-value
COPD	1.43	0.99, 2.08	0.058
Bicuspid aortic valve	0.32	0.08, 1.31	0.112
Ejection fraction	0.98	0.96, 0.99	<0.001
Tamponade, rupture, or shock	1.32	0.96, 1.81	0.091
Any malperfusion syndrome	1.92	1.41, 2.61	<0.001
Atrial fibrillation	1.40	0.89, 2.21	0.143

***Harrell's C-index = 0.71**

Figure Legends:

Figure 1. Kaplan-Meier survival estimates for males (n=361) and females (n=240).

Survival probability (95% confidence limit) estimate

	Male	Female
1st year	85.5 (81.7 – 89.0)	78.7 (73.3 – 83.7)
5th year	76.0 (71.2 - 80.5)	71.2 (65.1 - 77.0)
10th year	62.5 (55.1 – 69.7)	63.1 (55.4 – 70.5)

Supplementary Table 1. PSM analysis: Baseline characteristics in the matched samples

Variable	Male (n=222)	Female (n=222)	p-value
Age (years)	63.5 ± 11.9	64.6 ± 12.6	0.351
Race Caucasian African American Other	189 (85.1) 24 (10.8) 9 (4.1)	184 (82.9) 32 (14.4) 6 (2.7)	0.405
Body mass index (kg/m^2)	29.8 ± 6.34	30.1 ± 7.12	0.560
Hypertension	182 (81.98)	176 (79.28)	0.471
Diabetes mellitus	26 (11.71)	24 (10.81)	0.764
Chronic lung disease	36 (16.22)	41 (18.47)	0.531
Chronic kidney disease	7 (3.15)	2 (0.90)	0.175
Peripheral vascular disease	81 (36.49)	80 (36.04)	0.921
Atrial fibrillation	23 (10.36)	25 (11.26)	0.760
Coronary artery disease	43 (19.37)	24 (10.81)	0.012
Redo sternotomy	38 (17.12)	20 (9.01)	0.011
Root replacement	80 (36.04)	76 (34.23)	0.691
Bicuspid aortic valve	11 (4.95)	6 (2.70)	0.216
Preoperative hematocrit	39.4 ± 6.20	36.9 ± 5.81	0.000
Aortic insufficiency [?] moderate	98 (44.14)	91 (40.99)	0.502
Ejection fraction	55.0 ± 9.17	56.0 ± 9.71	0.260
Tamponade, rupture, or shock	64 (28.83)	73 (32.88)	0.355
Any malperfusion syndrome	76 (34.23)	65 (29.28)	0.262

Variable	Male (n=222)	Female (n=222)	p-value
Type of malperfusion syndrome Cerebral Coronary Visceral Renal Iliofemoral	27 (12.2) 16 (7.2) 13 (5.9) 12 (5.4) 39 (17.6)	28 (12.6) 14 (6.3) 12 (5.4) 10 (4.5) 24 (10.8)	0.886 0.705 0.837 0.662 0.041

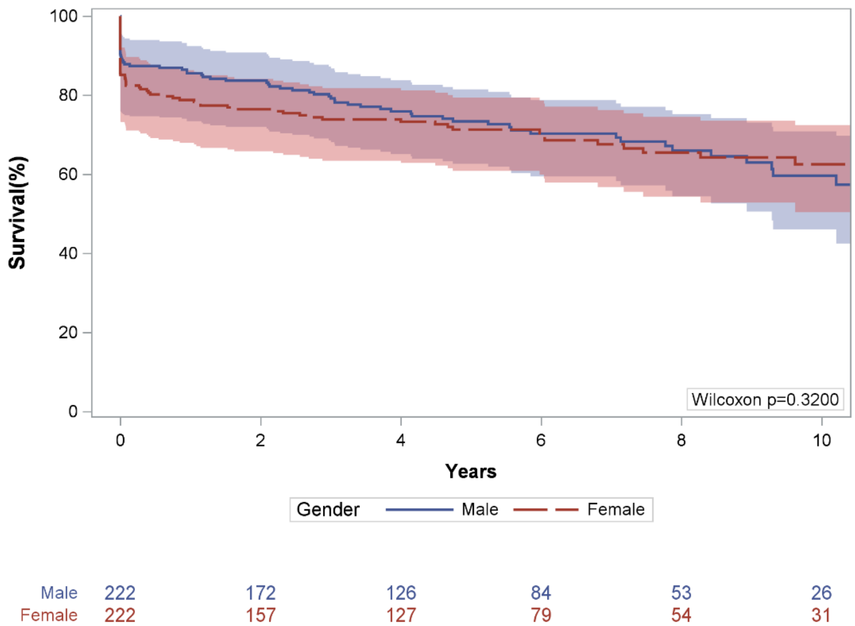
Supplementary Table 2. PSM analysis: Postoperative Outcomes in the matched samples

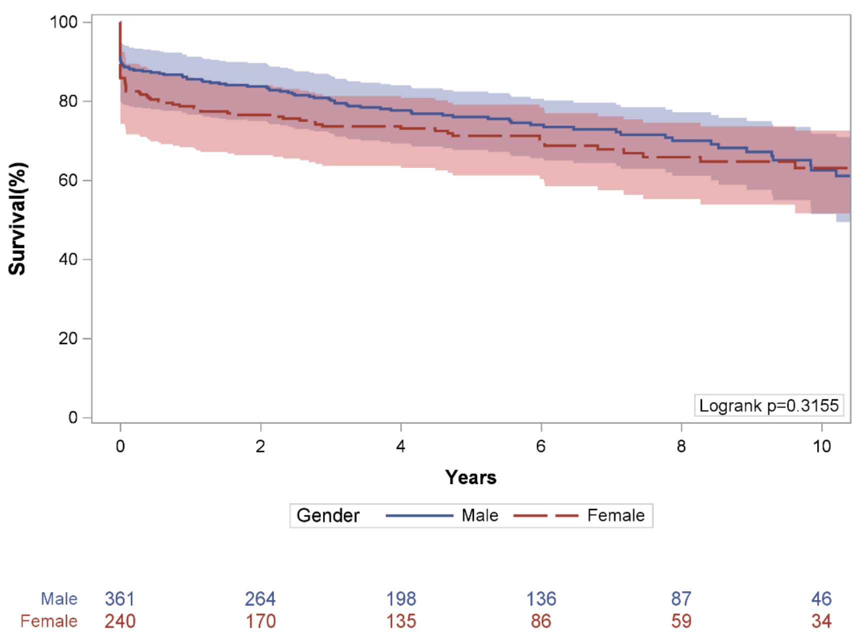
Variable	Male (n=222)	Female (n=222)	p-value
Operative mortality	21 (9.5)	32 (14.4)	0.107
Total postoperative length of stay (days)	12.2 ± 12.1	12.9 ± 12.9	0.577
Pneumonia	23 (10.4)	28 (12.6)	0.457
New-onset cerebrovascular accident	10 (4.5)	12 (5.4)	0.662
Mechanical ventilation time (hours)			
Mean ± SD	34.2 ± 71.5	57.2 ± 126	0.024
Median (IQR)	9.6 (5.5 -23.4)	13.9 (6.8-52.6)	<0.001
New-onset renal failure requiring hemodialysis	26 (11.7)	29 (13.1)	0.666
Re-exploration for excessive bleeding	23 (10.4)	21 (9.5)	0.751
Residual aortic insufficiency ([?] moderate)	5 (2.3)	0 (0.0)	0.061
1-month follow-up ejection fraction	55.2 ± 10.2	58.0 ± 7.5	0.005

Supplementary Figure 1. PSM analysis: Kaplan-Meier survival estimates for the matched samples (n=222 in each group)

Survival probability (95% confidence limit) estimate

	Male	Female
1st year	85.5 (80.6 – 89.9)	78.8 (73.2 – 83.9)
5th year	73.4 (67.1 – 79.3)	71.3 (65.0 - 77.3)
10th year	59.7 (50.6 – 68.4)	62.5 (54.4 – 70.3)


Survival(%)
100
80
60
40
20
0
0
2
4
6
8
10
Years
Wilcoxon p=0.3200
Gender
Male
Female
Male 222 172 126 84 53 26
Female 222 157 127 79 54 31


Survival(%)
100
80
60
40
20
0
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6
8
10
Years
Logrank p=0.3155
Gender
Male
Female
Male 361 264 198 136 87 46
Female 240 170 135 86 59 34