



# Sex differences in long-term outcomes following surgery for acute type A aortic dissection: a systematic review and meta-analysis

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**Background:** Recent reports on sex differences in long-term outcomes after surgery for acute type A aortic dissection (ATAAD) are conflicting. We aimed to aggregate updated data on long-term survival and reoperation stratified by sex.

**Methods:** A literature search was conducted using Medline, Embase, and Cochrane Central. Studies reporting sex-stratified long-term survival and/or reoperation following surgery for ATAAD between January 1, 2000, to March 15, 2023 were included. Preoperative characteristics, intraoperative variables, and early perioperative outcomes were meta-analyzed using a random effects model and pooled risk ratio (RR) with men as the reference group. Individual patient-level data for long-term outcomes was reconstructed to generate sex-specific pooled Kaplan-Meier curves to assess long-term survival and freedom from reoperation.

**Results:** A total of 15 studies with 7,608 male and 3,989 female patients were included in this analysis. Female patients were older, had higher rates of hypertension, and had less previous cardiac surgery. Intraoperatively, women received less extensive repairs with lower rates of aortic valve replacement and total arch replacement, and higher rates of hemiarch replacement. There were no sex differences for in-hospital/30-day mortality [risk ratio (RR), 1.18; 95% confidence interval (CI): 0.96, 1.45; P=0.12], stroke (RR, 1.07; 95% CI: 0.90, 1.28; P=0.46), and early reoperation (RR, 0.90; 95% CI: 0.75, 1.09; P=0.28). Female patients had lower long-term survival overall (P<0.001) and amongst survivors at 1-year (P=0.014). Overall survival at 5-year was 82.4% in men and 78.1% in women, and at 10-year was 68.1% for men and 63.4% in women. Male patients had higher rates of long-term reoperation (P<0.001). Freedom for reoperation at 5-year was 88.4% in men *vs.* 93.1% in women.

**Conclusions:** Though perioperative early outcomes have equalized between the sexes following surgery for ATAAD, differences remain in long-term survival and reoperation.

**Keywords:** Sex differences; acute type A aortic dissection (ATAAD); long-term outcomes



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## Introduction

Acute type A aortic dissection (ATAAD) is a life-threatening condition with a 50% mortality rate before reaching a specialist center (1), where emergency life-saving surgery then carries an additional 9–26% mortality rate (2–6). Important sex-related differences in presentation and management of ATAAD have been described (7,8). Whether this then translated into in-hospital outcome differences was unclear as there was conflicting data from international registries, multi-center, and single-center studies (9–13). Recent updated analyses from the Canadian Thoracic Aortic Collaborative (CTAC) have demonstrated that while historically women had worse outcomes than men following aortic arch surgery, including surgery for ATAAD, this outcome gap has decreased and been eliminated over time (14). Furthermore, updated data from the International Registry for Aortic Dissections (IRAD) also showed reduction of sex differences in operative mortality amongst surgically treated ATAAD patients (9). In fact, recent systematic reviews and meta-analyses corroborate that early outcomes between the sexes have now become comparable (15,16).

Questions remain as to whether long-term outcomes differ between men and women following surgery for ATAAD. Sex-stratified analyses of patients receiving surgery for ATAAD have shown conflicting evidence (9–11,17), with some showing female sex as an independent predictor of worse long-term mortality (10), while other reports show that, among hospital survivors, women have better long-term outcomes than men (18,19). Aggregation of these studies through meta-analysis may provide clarity.

The first meta-analysis of long-term sex differences in patients undergoing surgery for ATAAD reported comparable overall survival between the sexes and higher rates of reoperation in male ATAAD patients (15). However, this analysis included a limited number of studies (five for long-term mortality and two studies for long-term reoperation). Another meta-analysis reported worse long-term survival in women, but several studies were not included, and long-term reoperation was not assessed (20). Therefore, sex differences in long-term outcomes after ATAAD remain controversial. In this systematic review and meta-analysis, we aim to definitively aggregate updated evidence on sex differences in long-term mortality and reoperation.

## Methods

### Literature search strategy

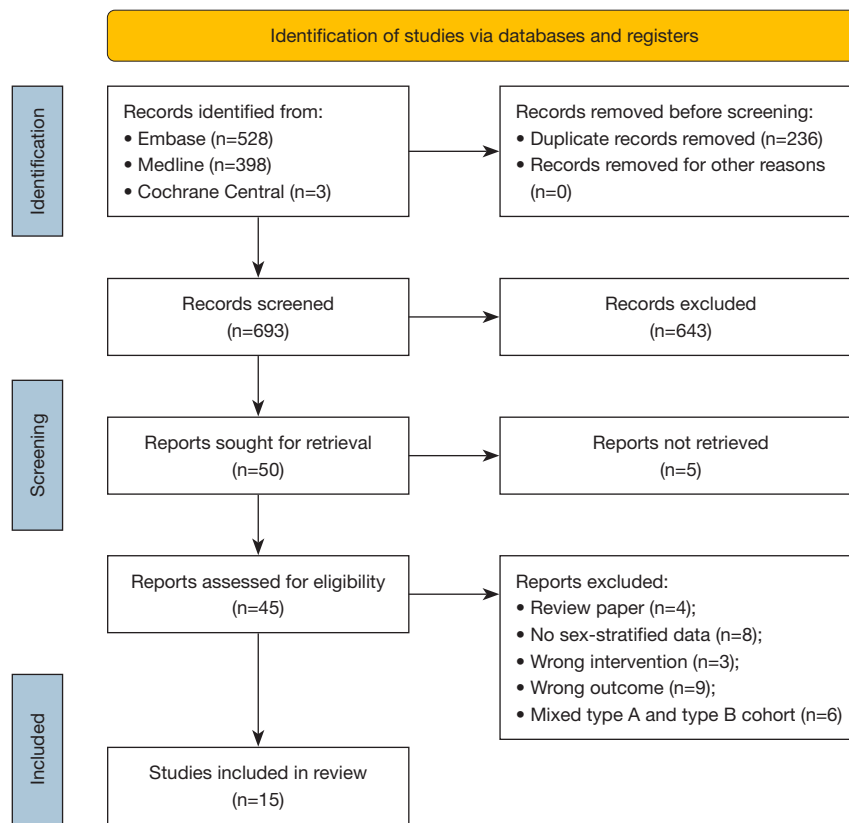
A systematic review and meta-analysis were conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*Figure 1*) (21). A systematic review was initiated by searching Medline, Embase, and Cochrane Central from January 1, 2000, to March 15, 2023. Articles prior to 2000 were excluded due to changing cardiac surgery practice including the widespread combined use of contemporary perfusion techniques and systemic hypothermic circulatory arrest which have improved safety. A professional research librarian from our institution was consulted to review and optimize search terms. Both Medical Subject Heading (MeSH) and title, abstract, subject heading, and keyword were used to create search terms. A complete list of search terms for each database is provided in [Appendix 1, Table S1](#).

### Eligibility criteria

Relevant studies that met the inclusion criteria were those that included patients who underwent aortic surgery for the diagnosis of ATAAD, performed long-term follow-up of mortality or reoperation outcomes, and reported outcomes stratified by sex. Exclusion criteria included studies with data limited to a specific patient population (e.g., young patients, older patients, Marfan's patients), acute aortic dissection without differentiation of type A *vs.* type B, chronic dissection, no stratification of outcomes by sex, and no long-term follow-up. Moreover, review articles without original data and conference abstracts were excluded. Title and abstract screening of articles from the systematic literature search was performed independently by two authors (Bhatt N and Rocha RV) in Covidence (Melbourne, Australia). Full-text review was also independently performed by Bhatt N and Rocha RV. Discrepancies in assessment were resolved by discussion and consensus.

### Data extraction and critical appraisal

Data was extracted independently from text, tables, and figures. The primary data variables of interest were long-term mortality and reoperation. For studies with published



**Figure 1** PRISMA flow diagram summarizing systematic review search strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Kaplan-Meier curves comparing outcomes between the sexes, all graphs were saved digitally and the data from the number at risk table was extracted. From published Kaplan-Meier curves, we used a validated algorithm to reconstruct individual patient-level survival data (22). Additionally, preoperative baseline characteristics and intraoperative variables were extracted from included studies. Continuous variables that were reported as median and interquartile range (IQR) were converted to mean  $\pm$  standard deviation (SD) using a validated estimation method (23). A full list of extracted data variables is provided in [Appendix 2, Table S2](#).

The validated Newcastle-Ottawa Scale (NOS) was used for quality and risk of bias assessment for nonrandomized cohort studies (24). NOS scores graded participant selection (maximum four stars), comparability between studied groups (maximum two stars), and assessment of outcome and follow-up (maximum three stars), for a maximum score of nine stars.

### Statistical analysis

Continuous variables were reported as mean  $\pm$  SD and categorical variables were reported as frequency (percentages). Extracted preoperative and intraoperative variables were aggregated using random effects models in Review Manager (RevMan) (version 5.4). Sex differences were assessed using pooled risk ratio (RR) (categorical variables) or mean difference (continuous variables), with men being the reference group. Heterogeneity across studies was assessed by calculating  $I^2$ , with values of <25%, 25–75%, and >75% being interpreted as low, moderate, and high heterogeneity, respectively. Publication bias for preoperative characteristics, intraoperative variables, and early post-operative outcomes was assessed for analyses where at least 10 studies were included by plotting funnel plots in RevMan and performing Egger's test in R statistical software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) using the 'metafor' package

**Table 1** Characteristics of included studies

Studies	Type	Country/region	Matched	Time	Male, n	Female, n
Gasser <i>et al.</i>	Single-center	Austria	No	2000–2020	268	126
Huckaby <i>et al.</i>	Multi-center, IRAD	Multi-national	No	1996–2018	1,854	969
Liu <i>et al.</i>	Single-center	China	No	2002–2016	167	68
Li <i>et al.</i>	Single-center	China	Yes	2009–2014	451	302
Norton <i>et al.</i>	Single-center	United States	No	1996–2018	444	206
Rios <i>et al.</i>	Single-center	Brazil	No	2006–2016	63	24
Sabashnikov <i>et al.</i>	Single-center	United States	Yes	2006–2015	153	87
Suzuki <i>et al.</i>	Single-center	Japan	No	2004–2016	156	147
Yousef <i>et al.</i>	Single-center	United States	No	2007–2021	361	240
Conway <i>et al.</i>	Multi-center, STS database	United States	No	2000–2010	172	79
Friedrich <i>et al.</i>	Single-center	Germany	No	2001–2016	242	126
Fukui <i>et al.</i>	Single-center	Japan	No	2006–2013	259	245
Chen <i>et al.</i>	Multi-center, Taiwan NHIRD	Taiwan	No	2004–2013	2,883	1,286
Santamaria <i>et al.</i>	Single-center	Italy	No	2009–2016	98	36
Hirata <i>et al.</i>	Single-center	Japan	No	2009–2013	37	48

IRAD, International Registry of Acute Aortic Dissections; STS, Society of Thoracic Surgeons; NHIRD, National Health Insurance Research Database.

(version 4.2.0).

Sex differences in long-term outcomes were analyzed by reconstructing individual patient-level data for survival and reoperation outcomes, which was then aggregated to generate pooled Kaplan-Meier curves and obtain overall estimates of sex-specific survival and freedom from reoperation. We also performed a landmark analysis starting at 1-year following surgery, to exclude the influence of perioperative outcomes and the early patient course, and to assess sex differences in long-term outcomes in patients who were alive at 1-year.

Life expectancy for males and females in the general Canadian population were retrieved from data published by Statistics Canada (25). This data represented life expectancy for all male and female Canadians at a specific age. After adjusting for the average age of male and female patients receiving surgery for ATAAD, yearly life expectancies were plotted against the pooled Kaplan-Meier curve for both sexes.

Two separate sensitivity analyses were performed by excluding studies that performed propensity score matching, and including only studies rated as moderate to good

quality according to our NOS assessment (overall score  $\geq 6$ ). All analysis of long-term outcomes was performed using R statistical software and Prism 9 (version 9.4.1; GraphPad, Boston, MA, USA). Significance level was taken as  $P < 0.05$ .

## Results

### Quantity and quality of evidence

Our initial systematic search produced 929 studies of which 236 were duplicates and excluded prior to screening. Title and abstract screening resulted in 50 articles which were sought for full text review. The full text for five articles could not be retrieved via institutional library access. The remaining 45 articles underwent full-text review and 15 articles met inclusion criteria and were included in the qualitative synthesis and quantitative analysis. *Table 1* outlines the characteristics of included studies. Across the 15 included studies, there were 7,608 male and 3,989 female patients. Of these, 12 reported single-center retrospective data (10,11,19,26–34), one reported multi-center data 35, and two reported on large multi-center national or

**Table 2** NOS for risk of bias assessment in included studies

Studies	Selection (maximum four stars)	Comparability (maximum two stars)	Outcome (maximum three stars)	Total
Gasser <i>et al.</i>	***	–	**	5
Huckaby <i>et al.</i>	***	**	***	8
Liu <i>et al.</i>	**	**	*	5
Li <i>et al.</i>	***	**	***	8
Norton <i>et al.</i>	***	**	***	8
Rios <i>et al.</i>	**	–	*	3
Sabashnikov <i>et al.</i>	**	**	**	6
Suzuki <i>et al.</i>	***	**	***	8
Yousef <i>et al.</i>	***	**	***	8
Conway <i>et al.</i>	***	–	***	6
Friedrich <i>et al.</i>	***	**	***	8
Fukui <i>et al.</i>	****	**	***	9
Chen <i>et al.</i>	***	**	***	8
Santamaria <i>et al.</i>	***	**	***	8
Hirata <i>et al.</i>	**	*	**	5

Total scores greater or equal to six were considered moderate to good quality. NOS, Newcastle-Ottawa Scale.

international datasets (9,17). A total of 13 studies published Kaplan-Meier curves for survival (9-11,19,26-28,30-35) and four studies published curves for reoperation (9,17,19,28) and were subsequently included in the respective pooled Kaplan-Meier analyses. Two studies included cohorts starting from the earliest timepoint and followed patients over the longest time span from 1996–2018 (9,32).

The NOS evaluation is displayed in *Table 2*. Nine of 16 studies included were scored eight or nine points suggesting they have good quality (9,11,17,19,26-29,32). Three studies scored less than six points which was due to no description of comparability of cohorts, or lack of information about the method for outcomes ascertainment and assessment (10,30,33). The 12 studies scored as having moderate to good quality (NOS scores  $\geq 6$ ) included a total of 6,947 men and 3,707 women.

### Patient and operative characteristics

*Table 3* summarizes pooled number of studies and patients analyzed as well as results for preoperative patient characteristics, intraoperative variables, and perioperative outcomes from the included studies (see [Appendix 3](#),

[Figures S1-S24](#)). Women were older than men [mean difference, 8.07 years; 95% confidence interval (CI): 7.05, 9.10;  $P < 0.001$ ; ten studies included (10,303 patients)] and had a lower body mass index [mean difference,  $-1.09$ ; 95% CI:  $-1.56$ ,  $-0.62$ ;  $P < 0.001$ ; seven studies (5,379 patients)]; these analyses showed moderate heterogeneity ( $I^2 = 62\%$  and  $I^2 = 54\%$ , respectively). Women had higher rates of hypertension [risk ratio (RR), 1.06; 95% CI: 1.03, 1.09;  $P < 0.001$ ; ten studies (10,303 patients)] and lower rates of chronic kidney disease [RR, 0.74; 95% CI: 0.59, 0.93;  $P = 0.01$ ; seven studies (9,154 patients)]; these analyses showed moderate heterogeneity ( $I^2 = 26\%$  and  $I^2 = 38\%$ , respectively). Women were less likely to be currently smoking [RR, 0.47; 95% CI: 0.25, 0.88;  $P = 0.02$ ; five studies (4,144 patients)]; though this analysis showed high heterogeneity ( $I^2 = 94\%$ ). Women were also less likely to have undergone previous cardiovascular surgery [RR, 0.70; 95% CI: 0.59, 0.84;  $P < 0.001$ ; six studies (9,005 patients)]; this analysis showed low heterogeneity ( $I^2 = 0\%$ ).

Intraoperatively, females had shorter cardiopulmonary bypass times [mean difference,  $-11.51$  minutes; 95% CI:  $-20.58$ ,  $-2.44$ ;  $P = 0.01$ ; nine studies (5,903 patients)]; however, this analysis showed high heterogeneity ( $I^2 = 86\%$ ).

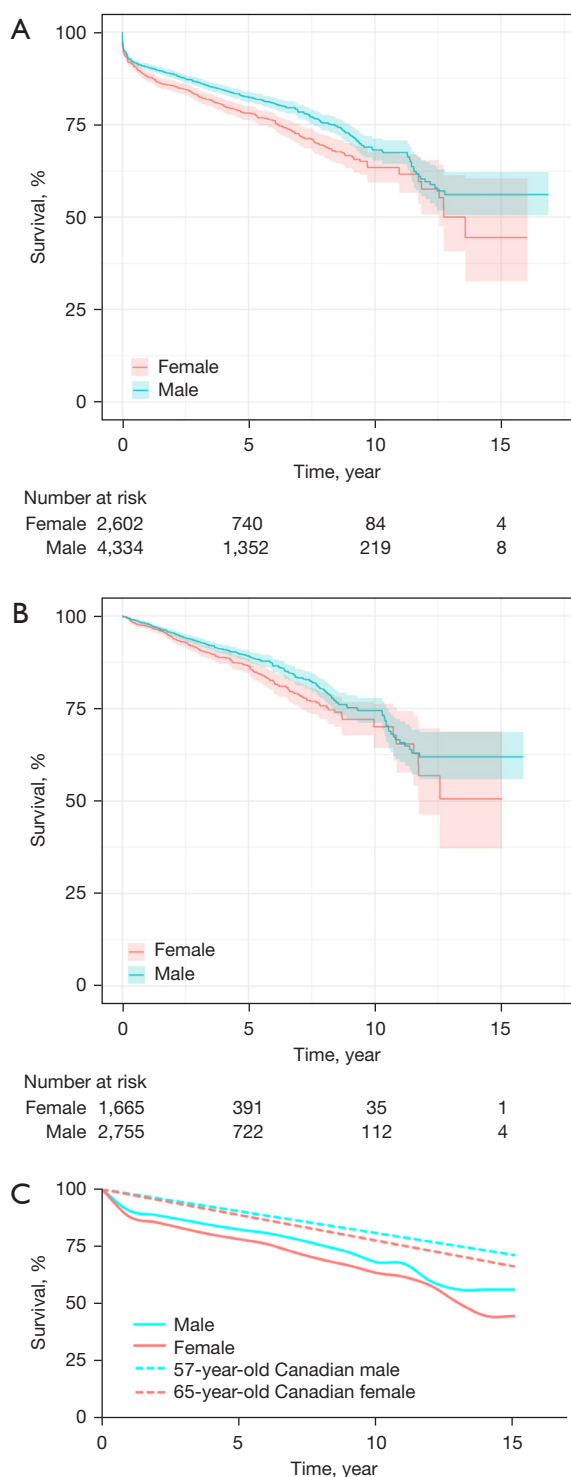
**Table 3** Pooled estimates of preoperative patient characteristics, intraoperative variables, and perioperative outcomes

Variables	Number studies	Male, n	Female, n	RR/MD	95% CI	P value	I <sup>2</sup> (%)
<b>Preoperative variables<sup>†</sup></b>							
Age	10	6,792	3,511	8.07	7.05, 9.10	<0.001*	62
BMI	7	3,478	1,901	-1.09	-1.56, -0.62	<0.001*	54
Hypertension	10	6,792	3,511	1.06	1.03, 1.09	<0.001*	26
Prior CVA	4	3,767	1,697	1.78	1.01, 3.15	0.05	76
Prior CKD	7	6,093	3,061	0.74	0.59, 0.93	0.01*	38
CTD	7	6,106	3,105	1.17	0.91, 1.50	0.23	0
CAD	5	1,468	785	0.94	0.77, 1.15	0.57	0
COPD	6	4,165	1,970	1.05	0.82, 1.34	0.71	20
Diabetes mellitus	9	6,524	3,385	1.22	0.94, 1.59	0.13	62
Current smoker	5	2,696	1,448	0.47	0.25, 0.88	0.02*	94
Prior cardiac surgery	6	6,052	2,953	0.70	0.59, 0.84	<0.001*	0
Shock	5	2,955	1,693	1.13	0.99, 1.29	0.07	0
Malperfusion	5	1,382	806	0.94	0.81, 1.10	0.46	21
<b>Intraoperative variables<sup>‡</sup></b>							
CPB time	9	3,740	2,163	-11.51	-20.58, -2.44	0.01*	86
Nadir temperature	3	2,566	1,301	0.27	-0.05, 0.59	0.10	0
AVR	6	3,335	1,882	0.80	0.70, 0.90	<0.001*	0
Total arch	9	4,018	2,400	0.73	0.58, 0.93	0.01*	85
Hemiarch	5	2,987	1,641	1.06	1.01, 1.11	0.01*	11
<b>Cannulation</b>							
Aortic	4	2,610	1,422	1.17	0.93, 1.48	0.18	73
Axillary/subclavian	6	3,050	1,627	0.83	0.77, 0.91	<0.001*	0
Femoral	6	3,050	1,627	0.98	0.89, 1.08	0.68	1
<b>Perioperative outcomes</b>							
In-hospital/30-day mortality	11	6,972	3,757	1.18	0.96, 1.45	0.12	46
Stroke	10	6,901	3,686	1.07	0.90, 1.28	0.46	12
Reoperation for bleeding	8	3,588	2,100	0.90	0.75, 1.09	0.28	0

<sup>†</sup>, analysis of preoperative variables used unmatched data from Sabashnikov *et al.* (34) and Li *et al.* (11); <sup>‡</sup>, analysis of intraoperative variables used unmatched data from Sabashnikov *et al.* (34); \*, P<0.05. RR, risk ratio; MD, mean difference; CI, confidence interval; BMI, body mass index; CVA, cerebrovascular accident; CKD, chronic kidney disease; CTD, connective tissue disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; AVR, aortic valve replacement.

Furthermore, women had less extensive surgery with lower rates of total arch replacements [RR, 0.73; 95% CI: 0.58, 0.93; P=0.01; nine studies (6,418 patients)]; though this analysis showed high heterogeneity (I<sup>2</sup>=85%). Women

received more hemiarch replacements [RR, 1.06; 95% CI: 1.01, 1.11; P=0.01; five studies (4,628 patients)] and less aortic valve replacements [RR, 0.80; 95% CI: 0.70, 0.90; P<0.001; six studies (5,217 patients)]; these analyses showed



**Figure 2** Pooled Kaplan-Meier curve of long-term survival with 95% CI for (A) all patients, (B) patients who survived 1-year post-surgery, and (C) all patients plotted against yearly life expectancy of age- and sex-matched general Canadian population, data retrieved from Statistics Canada (25). CI, confidence interval.

low heterogeneity ( $I^2=11\%$  and  $I^2=0\%$ , respectively). Cannulation strategy was also different between the sexes with women receiving axillary cannulation less frequently than men [RR, 0.83; 95% CI: 0.77, 0.91;  $P<0.001$ ; six studies (4,677 patients)], though rates of femoral cannulation did not differ significantly [RR, 0.98; 95% CI: 0.89, 1.08;  $P=0.68$ ; six studies (4,677 patients)]; these analyses showed low heterogeneity ( $I^2=0\%$  and  $I^2=1\%$ , respectively). No other sex differences in preoperative and intraoperative variables were noted.

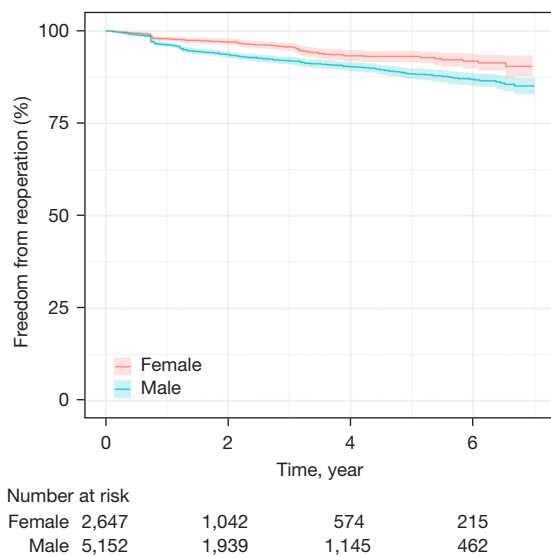
For perioperative outcomes, the aggregate studies showed no differences in in-hospital/30-day mortality, perioperative stroke, or early reoperation for bleeding.

In analyses where  $\geq 10$  studies were included (i.e., age, hypertension, in-hospital/30-day mortality, and perioperative stroke) we did not note any large asymmetry in funnel plots (Appendix 4, Figures S25-S28) and detected no significant asymmetry in funnel plots by Egger's test for age ( $P=0.92$ ), hypertension ( $P=0.35$ ), in-hospital/30-day mortality ( $P=0.84$ ), and perioperative stroke ( $P=0.20$ ).

### Long-term survival

Overall survival (Figure 2A) was significantly worse in women in comparison to men ( $P<0.001$ ). Using the pooled Kaplan-Meier curves, estimates for 5-year survival were 82.4% in men and 78.1% in women, and for 10-year survival were 68.1% in men and 63.4% in women. Sensitivity analysis showed long-term survival remained poorer for women after removing studies with propensity-matched cohorts ( $P=0.0004$ ) and studies graded as poor quality ( $P=0.002$ ). Landmark analysis of patients surviving 1-year post-surgery (Figure 2B) also showed poorer survival for women in the long-term ( $P=0.014$ ), though the difference between the sexes was less with 5-year survival of 90.9% in males vs. 88.9% in females and a 10-year survival of 75.1% in males vs. 72.0% in females. For reference, the long-term survival curves were superimposed with the expected survival of age- and sex-matched Canadians (Figure 2C).

Of the two studies that did not publish Kaplan-Meier curves for survival, Chen and colleagues reported no significant differences between male and female patients in all-cause mortality [35.3% vs. 34.7%; odds ratio (OR), 0.99; 95% CI: 0.88, 1.10] across a mean follow up of  $2.8\pm 2.7$  years (17). Meanwhile, Santamaria and colleagues reported worse long-term survival in female patients (47% vs. 24%,  $P=0.005$ ) across a mean follow-up of  $3.25\pm 3$  years (29).



**Figure 3** Pooled Kaplan-Meier curve with 95% CI of long-term reoperation for all patients. CI, confidence interval.

### Long-term reoperation

Long-term freedom from reoperation (Figure 3) was lower in men compared to women ( $P < 0.001$ ). Freedom from reoperation at 5-year was estimated to be 88.4% in men *vs.* 93.1% in women. Sensitivity analysis was not performed for this outcome, as none of the included studies had propensity-matched cohorts and all studies received scores  $\geq 6$  on NOS assessment. Although Gasser and colleagues did not publish a Kaplan-Meier curve for freedom from reoperation, they reported higher rates of reoperation during follow-up for men (8.6% *vs.* 4.0%) and this difference was not statistically significant ( $P = 0.08$ ) (10).

### Discussion

This meta-analysis evaluated the influence of sex on long-term death and reoperation following surgical treatment of ATAAD using all available updated sex-stratified data. Our literature search identified 15 studies reporting sex-specific data for long-term survival and/or reoperation which included over 11,000 ATAAD patients undergoing surgical repair. We found that men and women now have comparable perioperative outcomes. However, women had worse long-term survival, and men had higher rates of long-term reoperation.

Our study found that women presented on average

~8 years older than men, which is similar to the results reported by two previous meta-analyses (15,20). Furthermore, we found that men received more extensive surgical repair for ATAAD which could potentially be due to more extensive distal disease involving the descending thoracic and abdominal aorta in men (36). Despite similar rates of preoperative malperfusion syndrome, there was a trend towards women presenting with shock, which may have influenced the surgeon's decision to perform a more conservative intervention.

Our study was the first to meta-analyze sex differences in total arch and hemiarch replacements, and arterial cannulation. We found that women received less total arch replacements and more hemiarch replacements. Furthermore, women were less likely to receive axillary cannulation, though there were no sex differences in rates of direct aortic and femoral cannulation. Ohira and colleagues also found that female sex was an independent predictor of axillary non-cannulation and hypothesized this could be due to a combination of lower vessel caliber, increased age, and increased urgency of surgery which prohibited against the typically longer times required to establish axillary cannulation (37). While some studies have found comparable outcomes across all three cannulation strategies (38), two meta-analyses showed axillary cannulation is superior to femoral cannulation for in-hospital mortality and stroke (39,40).

The finding that there were no sex differences in the rates of in-hospital/30-day mortality and perioperative stroke in our analysis was similar to recent reports and meta-analyses (15,16,20). Previously, there was a gender gap reported in perioperative outcomes which has been eliminated over time. Contemporary data from IRAD shows female in-hospital mortality following ATAAD surgery decreased from 27% to 16% (trend  $P = 0.114$ ), and female sex was eliminated as an independent predictor of mortality when considering patients enrolled in the last decade of the study [2006–2017] (9). Moreover, CTAC data also shows equalization between the sexes driven largely by significant improvements for women undergoing urgent aortic arch surgery (30% to 11%, trend  $P = 0.01$ ) (14). This era effect may be due to advances in surgical techniques and improving safety of aortic surgery, which could drive large improvements in outcomes for female patients due to the initial disparities between the sexes. Our updated meta-analysis of all available data, including more contemporary results, can make this effect more definitive.



Despite having comparable in-hospital/30-day mortality, long-term survival was worse in women. One important factor influencing this could be the older age at presentation of women compared to men. Across included studies, the average age at presentation was 65 years for women compared to 57 years for men. In Canada, the general population life expectancy was 22.2 years for women aged 65 and 26.1 years for men aged 57 years (25). Similarly, in the United States, life expectancy was 20.8 years for women aged 65 and 24.2 years for men aged 57 (41). However, the differences in yearly survival between the average Canadian 65-year-old woman and 57-year-old man were smaller than the differences in survival between the sexes following surgery for ATAAD (shown in *Figure 2C*). This suggests that older age at presentation for female patients is an important factor though may not fully account for the sex-based differences in long-term survival.

Furthermore, in our pooled Kaplan-Meier plot, the sex-specific survival curves demonstrated the greatest separation within the first-year post-surgery. Given the dynamic changes in the outcome gap between men and women within the early perioperative period over the past 10–20 years, we sought to neutralize this confounding effect. Therefore, we carried out a landmark analysis of patients alive at 1 year, which showed a smaller difference between men and women, though survival remained significantly poorer in women. In their meta-analysis, Carbone and colleagues found higher risk of mortality at 5- and 10-year for women, though their study did not estimate pooled survival rates at 5- and 10-year (20). Our findings are in contrast to the meta-analysis by Meccanici and colleagues who reported comparable long-term survival between men and women, however their analysis only included five studies and did not analyze differences beyond 5-year post-surgery (15). Overall, the sum of the data suggests that a difference in long-term survival between the sexes after surgery for ATAAD does exist but is not large. Encouragingly, our analysis suggests that this difference is at least partially accounted for by the expected differences in long-term survival of age- and sex-matched cohorts in the general population.

Despite men having more extensive surgery, there was a higher rate of reoperation among them. It has been suggested that this could be due to lower age at presentation, as advanced age may be a reason against performing late reoperation (19,28). Other confounders could be the higher long-term mortality in females, which

is a competing risk. Geirsson and colleagues reported more extensive distal dissection and younger age, both more common in men, to be independent predictors of distal reoperations in surgically treated ATAAD patients (42), while An and colleagues also reported advanced age and female sex as protective factors against reoperation amongst patients who survived at least 90 days post-surgery (18). The only previous study to perform meta-analysis of long-term reoperation is Meccanici and colleagues, which included only two studies (15). Nonetheless, they also reported higher rates of reoperation in men.

### Limitations

There are several limitations to our current study. Firstly, this is a systematic review of retrospective, observational studies. The majority of included studies have provided data regarding sex differences in unmatched cohorts. However, two included studies provided outcomes data from propensity-matched cohorts (11,34); we performed sensitivity analysis on the effect of including these two propensity-matched cohorts in our meta-analysis and found no significant changes to our results. Secondly, our inclusion criteria limited our analysis to studies providing long-term sex-specific outcomes in surgically treated ATAAD patients. As such, several studies included in previous meta-analyses were excluded from the present analysis. Of these, the most significant exclusion is sex-stratified data from the large, multicenter, international German Registry for Acute Aortic Dissection Type A (GERAADA) which has reported on sex differences in preoperative characteristics, intraoperative variables, and perioperative outcomes, however has not yet published data on long-term follow-up (36). Thirdly, some variables showed high heterogeneity (*Table 3*), including prior cerebrovascular accident and current smoking, which may be due to challenges in the classification and reporting of these variables, as well as total arch and aortic cannulation, which may be due to differences in standard practice between institutions. Finally, there are limitations to the algorithm used to reconstruct individual patient-level data and generate pooled Kaplan-Meier curves. The algorithm assumes a constant rate of censoring over time (22), and some individual studies included in our analysis capture mortality as a censored event when the outcome of interest is reoperation, as such the cumulative probability of reported reoperation may be susceptible to inaccuracy. Nonetheless, our estimated 5- and

10-year reoperation rates were similar to those reported in individual studies.

## Conclusions

In this updated meta-analysis of surgically treated ATAAD patients, sex differences in preoperative characteristics and intraoperative management were apparent. Women had worse long-term survival compared to men. This difference remains even amongst patients who survive the first-year post-surgery, though the difference is smaller. Male sex was associated with higher rates of reoperation. Future work is needed to understand if there are any associations between specific preoperative and intraoperative variables and long-term outcomes.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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