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ORIGINAL RESEARCH

CRITICAL CARE CARDIOLOGY

Operative Mortality After Type A Aortic Dissection Surgery

Differences Based on Sex and Age

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ABSTRACT

BACKGROUND There is controversy regarding sex differences in short-term mortality in acute type A aortic dissection (ATAAD).

OBJECTIVES This study aimed to investigate the impact of sex differences on 30-day operative mortality after ATAAD surgery and to determine if other covariates modify the association.

METHODS Consecutive patients (N = 5670) with surgically repaired ATAAD were identified from the multicenter China 5A study. The primary outcome was operative mortality. The age dependency was modeled using a cubic spline curve.

RESULTS There were 1,503 females (26.5%) and 4,167 males (73.5%). Females were older and had a lower percentage of comorbidities compared with males. Females had higher mortality compared to males (10.2% vs 8.2%, $P = 0.019$); however, there was no difference after propensity analyses (adjusted OR: 1.334 [95% CI: 0.918-1.938]). There was an interaction with sex and age ($P_{\text{interaction}} = 0.035$): older age was associated with higher odds of operative mortality among females (OR: 1.045 [95% CI: 1.029-1.061]) compared with males (OR: 1.025 [95% CI: 1.016-1.035]). The risk of mortality for males and females appears to diverge at 55 years of age ($P_{\text{interaction}} = 0.019$): females under 55 years of age had similar odds to males (OR: 0.852 [95% CI: 0.603-1.205]) but higher odds when over 55 years (OR: 1.420 [95% CI: 1.096-1.839]) compared to males.

CONCLUSIONS Under the age of 55 years, females have similar odds of operative mortality compared with males; however, over the age of 55 years females have higher odds than males. Understanding differences in risk allows for individualized treatment strategies. (Additive Anti-inflammatory Action for Aortopathy & Arteriopathy; NCT04398992) (JACC Adv 2024;3:100909) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ATAAD = acute type A aortic dissection

NNH = number needed to harm

Acute type A aortic dissection (ATAAD) is a major cardiovascular emergency both for female and male patients.[1] Sex differences in mortality among aortic dissection patients have gained attention,[2] however, data pertaining to disparities in outcomes between males and females are conflicting.[3] While some studies have demonstrated that surgically treated females with ATAAD have a higher odds of in-hospital mortality compared with males,[4-8] other studies have found no significant differences in in-hospital mortality between males and females after surgical repair of ATAAD.[9-12] A systematic review and meta-analysis reported no difference in early mortality between sexes after surgical repair of ATAAD.[3,13-16] However, published literature is fragmented and heterogenous, which limits tour ability to understand sex differences among ATAAD patients. We hypothesized that other confounders modified the association between sex with early mortality in ATAAD and contributed to contradictory results. Therefore, using the China 5A study, a large multicenter observational cohort study of patients with ATAAD, we sought to investigate the impact of sex differences on early mortality and to determine if other covariates modified the association between the variables.

METHODS

STUDY DESIGN. The China 5A (Additive Anti-inflammatory Action for Aortopathy & Arteriopathy) registry study is an ongoing prospective, multicenter cohort registry (14 hospitals in the regions of China) designed to collect data on clinical baseline variables and outcomes of patients hospitalized for aortic dissection. The study began in January 2016, was conducted in accordance with the Declaration of Helsinki, and registered in ClinicalTrials.gov as NCT04398992. The Institutional Review Board of each institution approved this study (2021-SR-381). Patient written consent for the publication of the study data was waived due to this retrospectively observational study. Patient selection, data collection, and data analysis were performed in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[17]

PATIENT SELECTION. From January 2016 to May 2022, consecutive patients with ATAAD hospitalized through the emergency department at participating hospitals were retrospectively identified from China 5A study at the time of their first admission and then followed after discharge (Supplemental Figure 1). Patients 18 years of age or older were included if they underwent aortic surgery within 14 days from symptom onset to hospital arrival. Key criteria for exclusion included type B aortic dissection, recurrent aortic dissection, traumatic aortic dissection, iatrogenic aortic dissection, and chronic aortic aneurysm.[18] Surgical procedures have been described previously.[19,20] Importantly, standardized antegrade or retrograde cerebral protection techniques were used at all facilities according to the Dr Sun's procedure.[19,20]

DATA COLLECTION. Patient information obtained included demographic data, medical history and risk factors, baseline characteristics, and surgical procedures as well as postoperative outcomes. Specifically, we collected data on demographic variables (body mass index), clinical risk factors and comorbidity (smoking, coronary heart disease, hypertension, alcohol drinking, diabetes mellitus, stroke, hyperlipidemia, chronic lung diseases, and ventricular arrhythmia), and laboratory parameters (leukocyte, hemoglobin, creatinine, platelet, urea nitrogen, aspartate aminotransferase, and alanine aminotransferase). All central laboratories at participating sites have been recognized and certified by the China National Accreditation Service for Conformity Assessment of Laboratory.

CLINICAL OUTCOMES. The primary outcome was operative mortality defined as any death, regardless of cause, occurring within 30 days after surgery in or out of the hospital, and after 30 days during the same hospitalization subsequent to the operation according to Society of Thoracic Surgeons criterion.[21] Secondary outcomes were 30-day mortality, mechanical ventilation time, intensive care unit duration, and hospital duration.

STATISTICAL ANALYSIS. Because of covariates that were potentially missing, not-completely at-random, covariates were imputed for the multivariable analysis by means of a single imputation with 10 iterations with all the covariates, using the 'MICE' package for R.[22] Summary of missing data and missing pattern was shown in Supplemental Figure 2. We conducted complete case analysis, imputation analysis, and propensity matching analysis.

Propensity score matching was used to reduce bias from confounding and balance characteristics between groups that were highlighted in the univariable analysis (preoperative characteristics that showed statistically significant differences between the 2 groups) or that were considered clinically significant based on the previous research. In brief, a propensity score for each patient was estimated using the logistic

TABLE 1 **Baseline, Clinical, and Procedural Characteristics of Study Population by Sex**

	Overall (N = 5,670)	Female (n = 1,503)	Male (n = 4,167)	*P* Value
Demography				
Age (y)	52 (43-60)	55 (46-64)	51 (42-59)	<0.001
Height (cm)	170 (165-175)	162 (158-168)	173 (170-177)	<0.001
Weight (kg)	75 (65-83)	65 (58-72)	77 (70-85)	<0.001
Body mass index (kg/m^2)	25.4 (22.9-27.8)	24.4 (22.0-26.9)	25.7 (23.5-28.3)	<0.001
Clinical characteristics				
Smoking (%)	2,429 (42.8%)	87 (5.7%)	2,342 (56.2%)	<0.001
Alcohol drinking (%)	1,429 (25.2%)	41 (2.7%)	1,388 (33.3%)	<0.001
Hypertension (%)	4,188 (74.3%)	1,044 (69.8%)	3,144 (75.8%)	<0.001
Diabetes mellitus (%)	310 (5.5%)	84 (5.6%)	226 (5.4%)	0.820
Hyperlipemia (%)	484 (8.5%)	88 (5.9%)	396 (9.5%)	<0.001
Chronic lung diseases (%)	171 (3.0%)	33 (2.2%)	138 (3.3%)	0.030
Stroke (%)	298 (5.3%)	80 (5.3%)	218 (5.2%)	0.900
Coronary heart disease (%)	545 (9.6%)	120 (8.0%)	425 (10.2%)	0.038
Ventricular arrhythmia (%)	254 (4.5%)	63 (4.2%)	191 (4.6%)	0.526
Clinical characteristics				
Leukocyte (×10^9/L)	9.9 (7.0-13.3)	9.3 (6.4-12.6)	10.2 (7.2-13.4)	<0.001
Hemoglobin (g/L)	133 (118-146)	121 (108-131)	138 (124-149)	<0.001
Creatinine (μmol/L)	79 (65-102)	62 (51-82)	83 (71-107)	<0.001
Platelet (×10^9/L)	181 (142-227)	187 (143-234)	179 (142-224)	0.003
Blood urea nitrogen (mmol/L)	6.4 (5.0-8.2)	5.8 (4.4-7.9)	6.5 (5.2-8.3)	<0.001
Aspartate aminotransferase (μ/L)	22 (17-34)	22 (17-35)	22 (17-34)	0.462
Alanine aminotransferase (μ/L)	21 (14-35)	19 (13-34)	22 (15-36)	<0.001
Albumin (g/L)	40 (37-43)	39 (36-42)	40 (37-43)	<0.001
eGFR (ml/min/1.73 m^2)	101 (75-131)	90 (64-117)	105 (80-134)	<0.001
Surgical procedure				
Root procedure (%)				<0.001
Aortic valve replacement	240 (4.2%)	69 (4.6%)	171 (4.1%)	
Bentall	1,710 (30.2%)	371 (24.7%)	1,339 (32.1%)	
David	70 (1.2%)	18 (1.2%)	52 (1.2%)	
Cabrol	4 (0.1%)	1 (0.1%)	3 (0.1%)	
Arch procedure (%)				<0.001
Hemi-arch replacement	547 (9.6%)	208 (13.8%)	339 (8.1%)	
Total arch replacement	3,540 (62.4%)	892 (59.3%)	2,648 (63.5%)	
CABG (%)	393 (6.9%)	89 (5.9%)	304 (7.3%)	0.072
Other surgery (%)	205 (3.6%)	54 (3.6%)	151 (3.6%)	0.956
Inclusion technique (%)	2,769 (48.8%)	701 (46.6%)	2,068 (49.6%)	0.047
Total arch replacement and FET implantation (%)	3,482 (61.4%)	872 (58.0%)	2,610 (62.6%)	0.002
Outcomes				
Operative mortality	494 (8.7%)	153 (10.2%)	341 (8.2%)	0.019
30-d mortality	434 (7.7%)	130 (8.6%)	304 (7.3%)	0.091
ICU stay (d)	2 (1-6)	3 (1-7)	2 (1-6)	<0.001
Mechanical ventilation time (h)	21 (15-62)	24 (16-70)	21 (15-58)	<0.001
Hospital stay (d)	16 (12-23)	17 (12-25)	16 (12-23)	<0.001

Values are median (IQR) or n (%).
CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; FET = frozen elephant trunk; ICU = intensive care unit.

regression model of R software flowed by a 1:1 nearest-neighbor matching method with a tolerance level on the maximum propensity score distance (calipers of width 0.2 standard deviations of the logit of the propensity score).[23-26] After matching, we used the *t*-test for paired samples to evaluate the balance between the matched cohorts for continuous variables and the McNamar test for dichotomous variables. A standardized mean difference <0.20 was used for each of the matching variables.

To examine the potential factors that modify the association of sex with operative mortality, we further assessed the interaction effect of sex with covariates using interaction terms in a multivariable

TABLE 2 Sensitivity Analysis of Association of Sex and Age With Operative Mortality

	Reference	Comparator	OR (95% CI)	*P* Value
Complete case analysis				
Overall	Male	Female	1.246 (0.988-1.570)	0.06290
Overall	Age ≤55 y	Age >55 y	1.854 (1.513-2.273)	<0.0001
By sex stratification				
Female	Age ≤55 y	Age >55 y	1.564 (1.241-1.972)	0.0002
Male	Age ≤55 y	Age >55 y	2.618 (1.784-3.842)	<0.0001
By age stratification				
Age ≤55 y	Male	Female	0.956 (0.657-1.391)	0.815
Age >55 y	Male	Female	1.370 (1.039-1.806)	0.029
Crude before imputations				
Overall	Male	Female	1.271 (1.021-1.582)	0.031
Overall	Age ≤55 y	Age >55 y	1.772 (1.449-2.166)	<0.001
By sex stratification				
Female	Age ≤55 y	Age >55 y	2.529 (1.729-3.698)	<0.001
Male	Age ≤55 y	Age >55 y	1.491 (1.189-1.869)	0.0005
By age stratification				
Age ≤55 y	Male	Female	0.818 (0.574-1.165)	0.265
Age >55 y	Male	Female	1.390 (1.066-1.812)	0.015
Crude after imputations				
Overall	Male	Female	1.272 (1.041-1.554)	0.019
Overall	Age ≤55 y	Age >55 y	1.791 (1.487-2.156)	<0.001
By sex stratification				
Female	Age ≤55 y	Age >55 y	2.539 (1.752-3.678)	<0.001
Male	Age ≤55 y	Age >55 y	1.524 (1.220-1.904)	0.0002
By age stratification				
Age ≤55 y	Male	Female	0.852 (0.603-1.205)	0.366
Age >55 y	Male	Female	1.420 (1.096-1.839)	0.008
Propensity score matching				
Overall	Male	Female	1.334 (0.918-1.938)	0.131
Overall	Age <55 y	Age >55 y	2.448 (1.634-3.669)	<0.001
By sex stratification				
Female	Age ≤55 y	Age >55 y	1.775 (1.044-3.018)	0.034
Male	Age ≤55 y	Age >55 y	3.544 (1.882-6.674)	<0.001
By age stratification				
Age ≤55 y	Male	Female	1.017 (0.647-1.600)	0.942
Age >55 y	Male	Female	2.030 (1.018-4.051)	0.045

model,[27] where heterogeneity was evaluated using the likelihood ratio test.[28] The age dependency was modeled using a cubic spline curve. In female vs male patients with ATAAD, we further tested the 3-way interaction terms between age and procedural factors (arch procedure, inclusion technique and hypothermia and circulatory arrest).[29,30]

Logistic regression was used to estimate the OR and 95% CI of primary outcome. In addition, we calculated the number needed to harm (NNH), a measure that indicates how many patients on average need to be exposed to a risk factor to cause harm in an average of 1 patient who would not otherwise have been harmed.[31,32]

Continuous data were presented as mean ± SD compared by *t*-test or median (IQR) compared by Mann-Whitney test, and categorical data were reported as percentages (%) compared by chi-square test or Fisher exact test. Because this was an exploratory analysis, all *P* values are of a descriptive nature only, and *P* values <0.05 were considered statistically significant only in a descriptive manner. Statistical analysis was performed with R software.

RESULTS

PATIENT CHARACTERISTICS. We identified 5,670 ATAAD patients, with 1,503 females (26.5%). Females tended to be older, had lower weight height, and lower body mass index. Males had higher rates of smoking, alcohol drinking, chronic pulmonary disease, hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease (Table 1). Males were more likely to undergo extensive procedures in terms of aortic root replacement, total arch replacement, and inclusion technique (Table 1). There were significant differences in laboratory biochemical profiles between females and males (all $P < 0.05$).

After propensity score matching, a total of 1,002 patients (501 pairs) remained for the analysis, whereas both groups were comparable and well matched for most patient characteristics regarding demographic features, the prevalence of significant comorbidities, and laboratory parameters in Supplemental Table 1.

ASSOCIATION BETWEEN SEX AND OUTCOMES. In parsimonious model, the odds of operative mortality were higher in female than male (153/1,503 [10.2%] vs 341/4,167 [8.2%]; crude OR: 1.272 [95% CI 1.041, 1.554], $P = 0.019$). In the adjusted model, this estimated association was rendered statistically insignificant (adjusted OR: 1.334 [95% CI: 0.918-1.938], $P = 0.157$) (Table 2). In addition, the perioperative outcomes were apparently worse in females than males, that is, longer mechanical ventilation time, longer intensive care unit length of stay, and longer hospital length of stay (Table 1).

INTERACTION ANALYSIS OF SEX AND COVARIATES. Analysis for interaction effect of sex with covariates was showed in Supplemental Table 2. We found a significant interaction between sex and continuous age ($P_{\text{interaction}} = 0.035$): older age associated with higher odds of operative mortality among females (OR: 1.045 [95% CI: 1.029-1.061] per 1-year increase; $P < 0.001$) than among males (OR: 1.025 [95% CI: 1.016-1.035] per 1-year increase, $P < 0.001$). Subsequently, we fitted the functional relationship between age as continuous scale and operative mortality by cubic splines and found that operative mortality significantly increased with increased age

(OR: 1.032 [95% CI: 1.024-1.040] per 1-year increase; $P < 0.001$). Spline curves of continuous age with operative mortality for females and males cross at age of 55 years, with a significant interaction between sex and 2 age categories ($P_{\text{interaction}} = 0.019$): females associated with similar odds of operative mortality under 55 years (OR: 0.852 [95% CI: 0.603-1.205], $P = 0.366$) but higher odds over 55 years (OR: 1.420 [95% CI: 1.096-1.839]; $P = 0.008$) compared to males (Figure 1). Analogously, a significant interaction was found ($P_{\text{interaction}} = 0.019$): age >55 years associated with higher odds of operative mortality among females (OR: 2.539 [95% CI: 1.752-3.678]; $P < 0.001$) than among males (OR: 1.524 [95% CI: 1.220-1.904], $P = 0.002$) compared to age ≤55 years (Table 2). Results were similar in complete case analysis and propensity score-matched patients (Table 2). Alluvial plot showed distribution of age on a categorical scale (#55 years vs >55 years) across sex (female vs male) and operative mortality (Figure 2).

NUMBER NEEDED TO HARM ANALYSIS. Regarding sex, the NNH was 50 patients (95% CI: 27-333) among females for 1 patient to cause operative death compared with males (Figure 3). In terms of age, the NNH was 22 patients (95% CI: 19-32) over 55 years of age for 1 patient to cause operative death compared with those under 55 years of age (Figure 3). Stratified by sex differences, the NNH increased to 17 (95% CI: 14-24) patients over 55 years compared with those under 55 years among males, while the NNH was 13 patients (95% CI: 9-21) over 55 years compared with those under 55 years among males (Figure 3). Stratified by age categories, the NNH increased to 104 (not significant) patients among females compared with males under 55 years, while the NNH was 13 patients (95% CI: 10-20) among females compared with males over 55 years (Figure 3).

3-WAY INTERACTIONS ANALYSIS. Categorical age (age of ≤55 years vs > 55 years) in the association between sex (male vs female) and operative mortality were further accentuated in procedural differences with regard to total arch replacement and frozen elephant trunk implantation (absence vs presence), inclusion technique (absence vs presence), and hypothermic circulatory arrest (absence vs presence) (Figure 4).

DISCUSSION

Based on this large Chinese database of ATAAD patients, we found no difference in operative mortality between females and males after adjustment for potential confounding factors. A significant interaction was observed between sex and age of patients on operative mortality: older age was associated with a greater odds of operative mortality among females when compared to males. We also found that females and males had similar odds under age of 55 years but that females had a higher odds over age of 55 years. These patterns of differences in operative mortality based on sex and age will aid clinicians to formulate individualized treatment strategies for ATAAD patients, which also highlight the important role of age and sex in the perioperative outcomes in ATAAD patients.

In this present study, no differences were observed regarding operative mortality following ATAAD surgery between women and men after adjusting for possible confounding factors, such as demographic variables, clinical risk factors and comorbidity, and laboratory parameters. Despite our best efforts to adjust for the confounders, some confounders that were not included in this study might generate a threat of biases to some extent. Therefore, we cannot determine the observed association resulting from either sex itself or other confounders beyond our currently available knowledge.[14,16] Further investigations need to investigate the conclusive association between sex and short-term mortality (Central Illustration).

Age has been shown to be a strong critical factor of outcomes in ATAAD, while treatment strategies and surgical methods differentiate according to age stratification.[1,33,34] Catalano et al[35] reported that patients aged 71 to 80 years had a 5.3-fold increased risk of in-hospital mortality compared with patients ≤40 years old ($P < 0.001$), and patients aged

FIGURE 1 Spline Curve of Age With Risk Probability of Operative Mortality

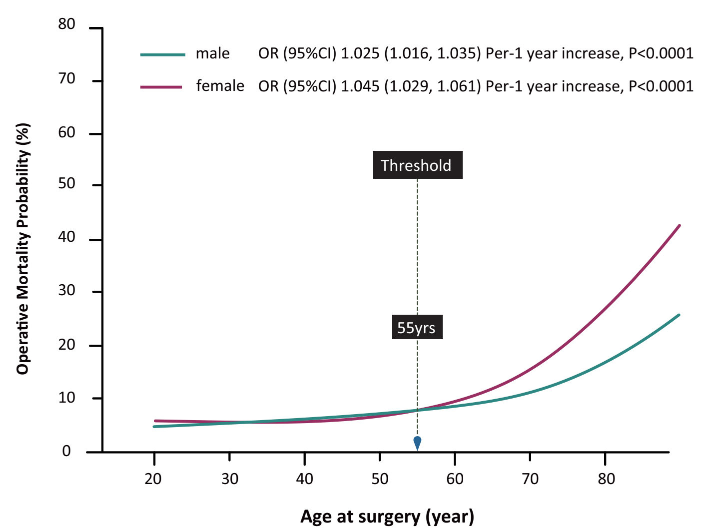

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FIGURE 2 Alluvial Plot of Distribution of Age Across Sex and Outcome

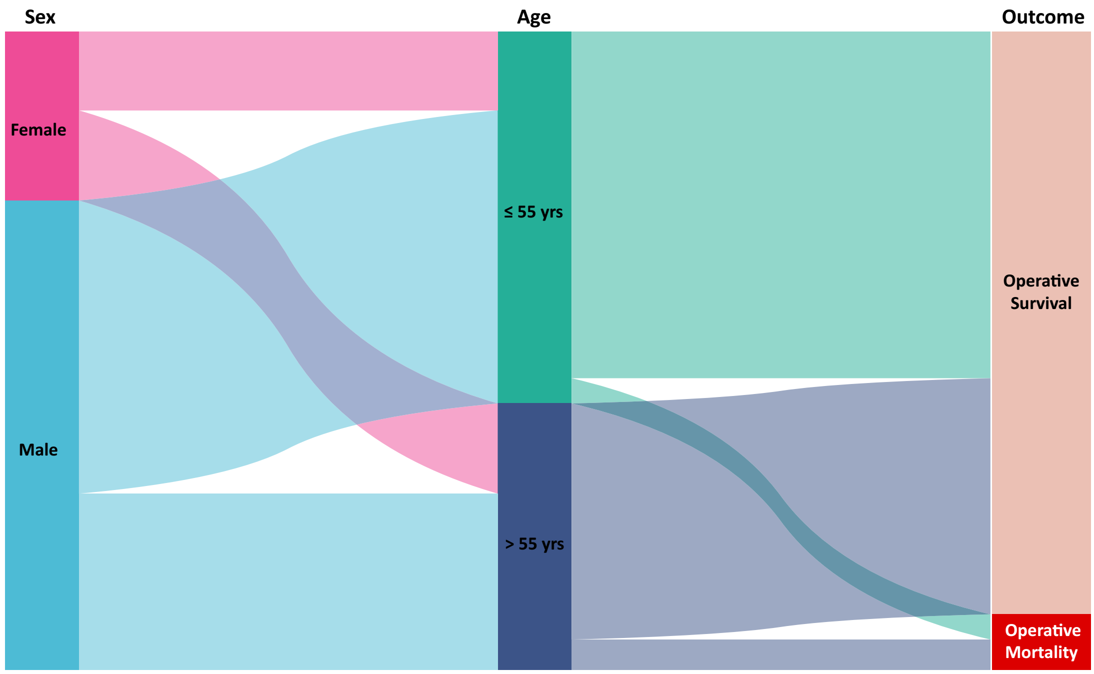


FIGURE 3 Number Needed to Harm: Sex and Age Differences With Operative Mortality

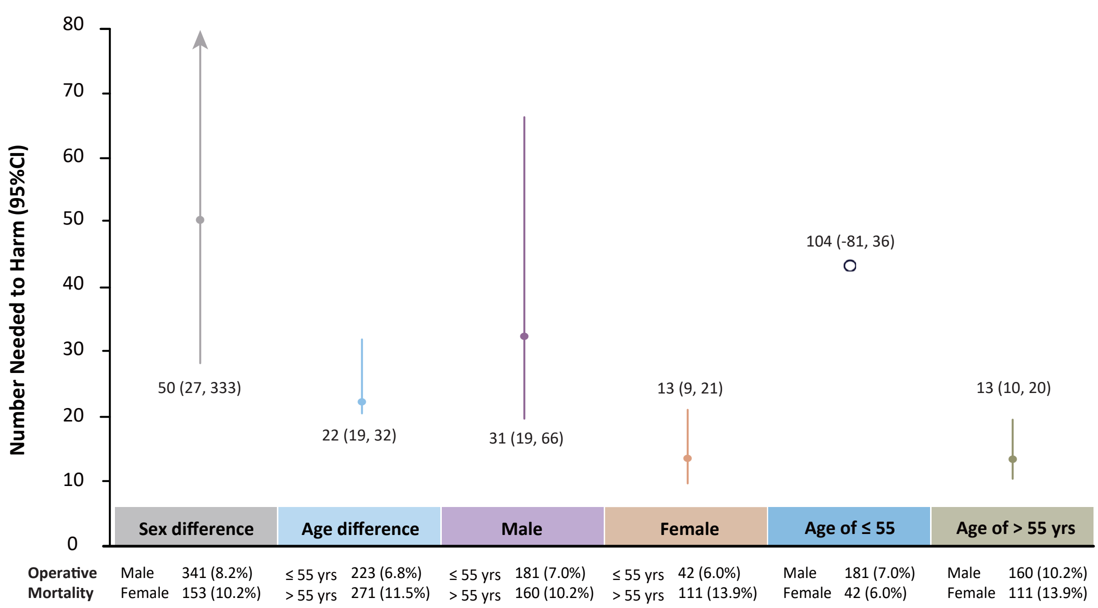
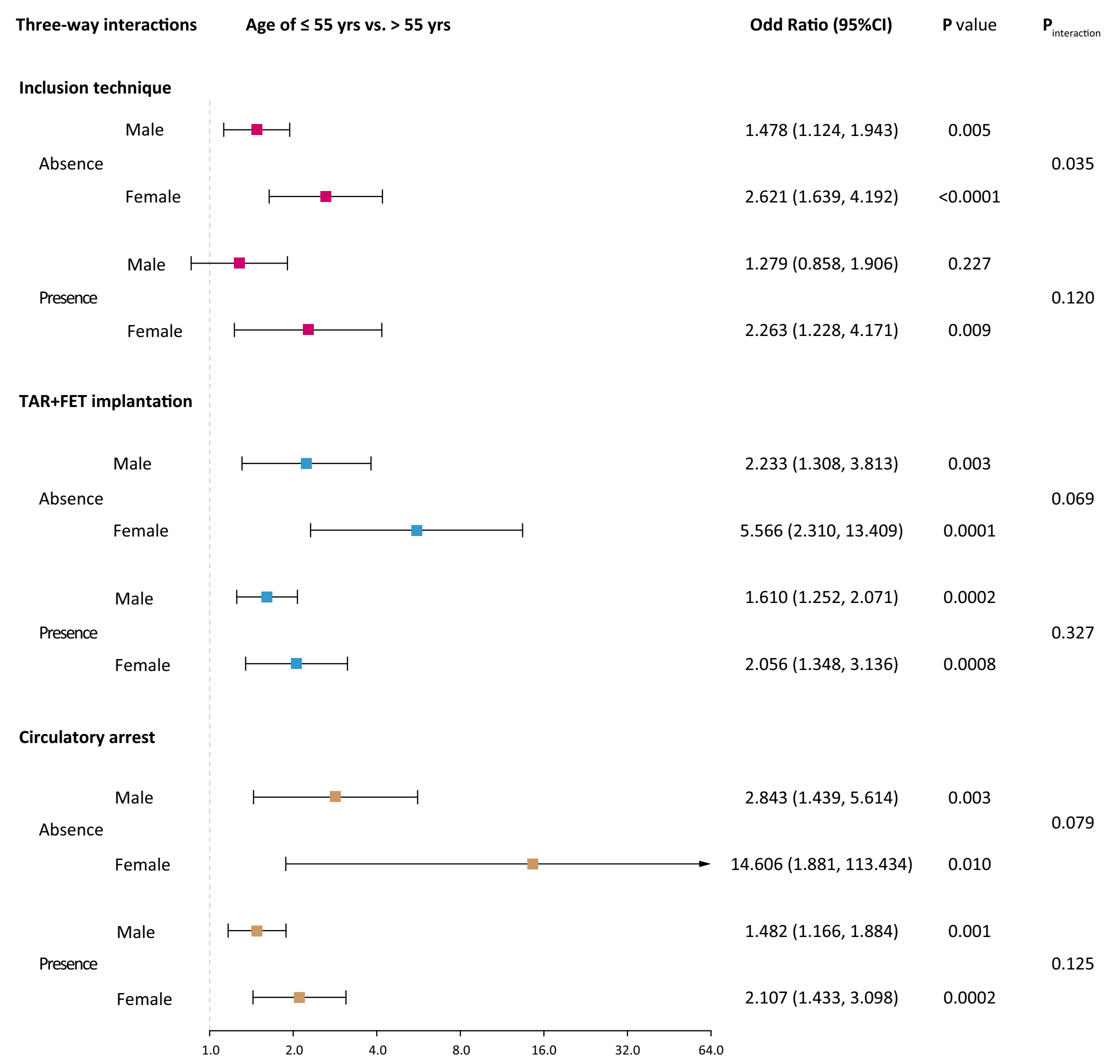


FIGURE 4 3-Way Interaction Analysis of Sex, Age, and Operative Mortality by Procedural Factors

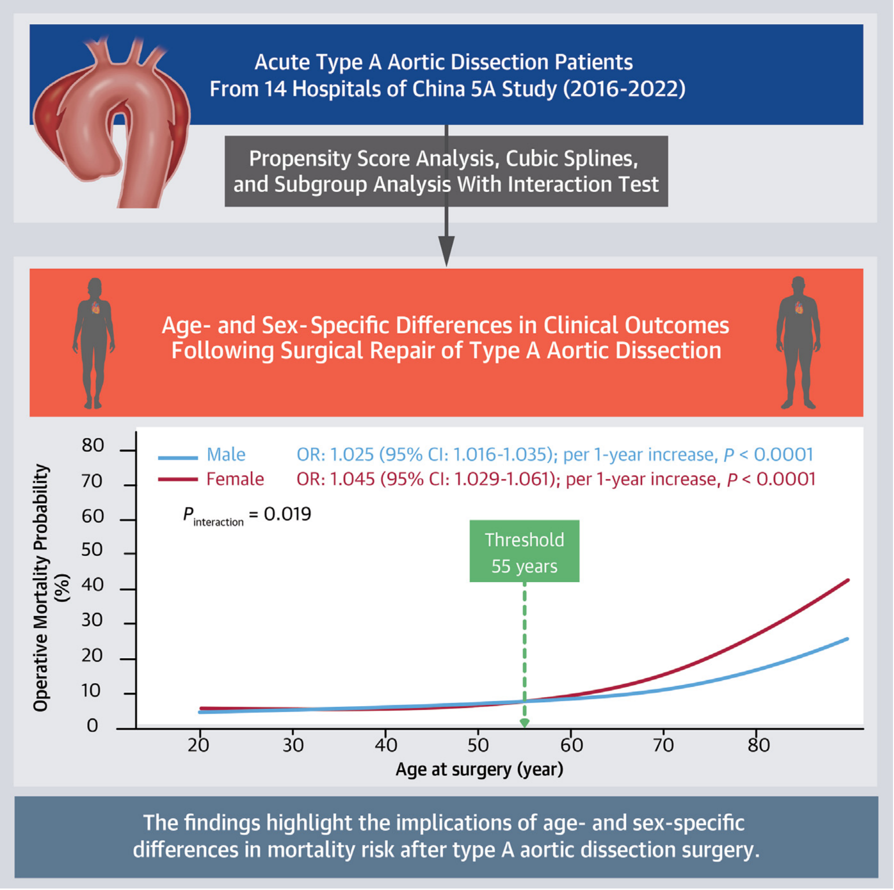


The figure represents the OR with 95% confidence interval for each subgroup. FET = frozen elephant trunk; TAR = total arch replacement.

>80 years had a 6.8-fold increased risk of in-hospital mortality ($P < 0.001$). Wang et al[36] showed the tendency of mortality was increased with age. As expected, our finding showed operative mortality significantly increased with increased age (OR: 1.032 [95% CI: 1.024-1.040] per 1-year increase; $P < 0.00001$). In our recent work,[34] we constructed and validated a risk model (named alphabet risk model) for predicting operative mortality after ATAAD surgery including age and other variables, in which older age significantly contributed to an increased risk of mortality, and found extensive aortic repair is associated with significantly higher risk of operative mortality than proximal repair when the predicted probability exceeded a certain threshold. These findings suggested that some high-risk patients, such as the aged individuals, are more likely to benefit from proximal repair rather than extensive repair.

However, little was known regarding the impact of sex on the association between age and early mortality. Morjan et al[37] reported females had higher in-hospital mortality than male counterparts among patients under 75 years old, however, this difference disappeared among patients over 75 years old. Unlike Morjan's findings, we observed that age of

CENTRAL ILLUSTRATION Age and Sex Differences in Operative Mortality After Type A Aortic Dissection Surgery



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Under the age of 55 years, females have similar risk of operative mortality compared with males, however, over the age of 55 years females have higher risk than males. Understanding differences in risk allows for individualized treatment strategies.

55 years is an important inflection point for operative mortality between males and females. Under the age of 55 years, females had similar odds of operative mortality compared with males, however, over the age of 55 years females had higher odds than males. These findings suggested that older women, especially those over the age of 55 years, were likely to lead to higher odds of operative mortality, which highlighted the individualized treatment for this special population. Until now, there is still no a unified definition of "older age" and a standardized design of sex- and gender-oriented research and registries for ATAAD. An international, multicenter study is wanted, which will allow a sufficient number of patients to compare different geographic and cultural aspects that may explain the disparities or inconsistency in reporting.[38] ATAAD is a highly heterogeneous syndrome, individual differences in age and sex likely have important effects on treatment effect, which highlights the need for individualizing the selection of optimal therapeutic strategies for these ATAAD patients.[39]

STRENGTHS AND LIMITATIONS

The main limitation of the study relates to the retrospective nature of our investigation. Despite similar risk profiles between female and male patients mostly achieved using propensity score analysis, the complexity and variability of the pathophysiology and morphology of ATAAD do not allow for perfect matching. Another limitation is that the study did not include those patients who did not reach the hospital and those to whom surgery was denied because it would be futile, but only patients who had surgical repair of ATAAD, which might result in selection bias to a great extent. Besides, the results should be interpreted with caution as we had limited statistical power to assess the sex-specific relationships of age with operative mortality between subgroups due to relatively low patient numbers in those groups, although we test for 3-way interactions among sex, age, and procedural factors.

CONCLUSIONS

In this large multicenter study, we found that while females had higher operative mortality than males, this difference was no longer observed after adjustment for confounders. There was an important interaction between sex and age: females and males under 55 years had similar operative mortality, but females over 55 years had higher odds compared to males. These patterns of differences in operative mortality based on sex and age will aid clinicians to formulate individualized treatment strategies for ATAAD patients. Further studies are needed to understand the reasons for sex and age differences in outcomes and how individualized risks can be incorporated into clinical decision-making.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this Chinese cohort study of ATAAD, females under the age of 55 years had similar risk of operative mortality compared with males, however, over the age of 55 years females had higher risk than males. Our findings highlight the important interplay between sex with age in the perioperative mortality in patients type A aortic dissection.

TRANSLATIONAL OUTLOOK: Future research is warranted to investigate whether individualized therapeutic strategies may target the sex- and age-specific patients with ATAAD. Furthermore, the pathophysiological mechanisms behind age- and sex-specific differences in type A aortic dissection should be examined.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.