Research Square

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Intraoperative Hemodynamics and Associated Sex Based Outcomes Following Ascending Aortic Aneurysm Repair

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Abstract

Background

Sex-based differences in thoracic ascending aortic aneurysm outcomes persist despite adjustment for preoperative factors, suggesting intraoperative variables may contribute to this disparity. While prior studies have examined surgical variables like bypass time and transfusions, modifiable intraoperative hemodynamic factors such as hypotension, hypoxia, and vasopressor requirements remain understudied. The objective of this study was to determine whether sex-based differences in intraoperative hemodynamics are associated with mortality differences following thoracic aortic aneurysm repair.

Methods

This was a retrospective study of 749 patients over 18 years of age who underwent non-emergent ascending aortic aneurysm repair from 2013–2020 at a single university hospital. Intraoperative variables assessed for both females and males included presence and duration of intraoperative hypotension and hypoxemia, surgical duration, Vasoactive-Inotrope Score (VIS), blood product transfusions, crystalloid and colloid infusion volumes, and hemoglobin levels. The primary outcome was 1-year mortality and secondary outcomes included 30-day mortality and days to death after surgery.

Results

Comparison of sex-based perioperative variables demonstrated that females, as compared to males, preoperatively were significantly older and had lower starting hemoglobin values. Intraoperatively, females had less hypotension, shorter operative duration, and less blood loss. Postoperatively, females experienced greater 1-year mortality, and less days to death than males. Multivariable regression analysis controlling for significant covariates found no significant association between hemodynamic variables or female sex and postoperative 1-year mortality. Instead, lower intraoperative hemoglobin levels and increased surgical duration were found to be independent predictors of increased 1-year mortality in both males and females undergoing ascending aortic surgical repair.

Conclusions

The results of this study suggest that differences in intraoperative modifiable hemodynamic variables are likely not associated with the sex-based differences seen in mortality after ascending aortic aneurysm repair. Further studies are needed to determine the underlying cause of sex-based differences in mortality and improve outcomes in this patient population.

Introduction

There is a growing body of research demonstrating important differences in cardiovascular disease development, epidemiology, and outcomes related to biological sex [1–11]. While males account for 70% of the patients with thoracic ascending aortic aneurysms, females who develop thoracic aneurysms have three-times faster aneurysmal growth rate and greater risk of aneurysm dissection [12,13]. Additionally, following surgical aneurysm repair, females have worse outcomes including longer intensive care unit (ICU) length of stay, higher rates of postoperative stroke, and increased 30-day postoperative mortality, as compared to males[14–17]. These sex-based differences in the pathophysiology, treatment, and importantly worsening outcomes for females with aortic aneurysms have prompted “a call to action” for a sex-specific approach to clinical research designed to better understand the clinical drivers of postoperative mortality in this patient population[18].

As differences in preoperative factors between males and females have been proposed to explain this disparity in postoperative outcomes, studies investigating sex-based differences have focused primarily on the preoperative phase of care. Females, as compared to males, have been found to be older at the time of surgery, with a greater incidence of relevant comorbidities (hypertension, renal insufficiency, anemia)[14,15], and a larger average indexed aortic diameter at diagnosis[15,17,19]. However, despite these preoperative differences, female sex remains an independent predictor of adverse outcomes, even after adjusting for the aforementioned factors [14,15]. Thus, these findings suggest there may be other variables outside of the preoperative phase of care, such as intraoperative factors, driving the sex-based differences in outcomes seen following thoracic ascending aortic aneurysm repair.

Studies investigating the association between intraoperative variables and differential sex-based outcomes have been limited in scope. Previous publications have focused primarily on the relationship between outcomes and surgical variables such as bypass time, operative duration[21,22], and recently blood product transfusions[19]. The effects of intraoperative hemodynamic factors such as hypotension, hypoxia, and vasopressor requirements have not been extensively studied. These intraoperative variables are of important clinical interest because they are modifiable risk factors. If hemodynamic variables are found to be predictive of adverse postoperative outcomes, intraoperative anesthetic and pharmacologic therapies could be adjusted to mitigate this risk.

The aim of this study was to determine if differences in intraoperative hemodynamic variables between females versus males are associated with sex-based mortality differences following thoracic ascending aortic aneurysm repair. We hypothesized that females will have greater hypotension and vasopressor requirements and that these intraoperative factors may be associated with increased mortality for females following aortic aneurysm repair.

Methods

Study Context and Patient Population

We conducted a single-center, retrospective analysis of patients aged > 18 years who underwent ascending aortic aneurysm repair from 2013–2020 at the University of Pittsburgh Medical Center. Patients undergoing a Bentall procedure, valve sparing aortic repair, transverse arch repair, or homograft root replacement for a primary diagnosis of ascending aortic aneurysm were eligible for inclusion. Emergency procedures were excluded from analysis. The study was approved by the hospital's institutional review board (Study #20050148 approved 6/1/2020). This cohort study follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines, and the checklist is provided in Supplemental Table 1[20]. Due to the observational and retrospective nature of the data obtained, the requirement for written consent was waived.

Variables of Interest

We collected preoperative, intraoperative, and postoperative variables up to 1 year after surgery from our institutional electronic medical record database and the Society for Thoracic Surgery (STS) outcomes database (https://www.sts.org/sts-national-database). Preoperative factors included the surgical procedure to be performed, surgical indication, age, sex, insurance status, and area deprivation index (ADI) which is a measure of socioeconomic disadvantage based on place of residence[23], as well as comorbidities including hypertension, coronary artery disease, valvular heart disease, COPD, and renal failure. ASA physical status and preoperative hemoglobin concentration were also included. Relevant intraoperative variables included blood product transfusion volumes, crystalloid and colloid volumes, lowest intraoperative hemoglobin level, urine output, temperature, presence of hypotension or hypoxemia, surgical duration, and average Vasoactive-Inotrope Score (VIS) as defined below[24]:

VIS = *dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 100 × norepinephrine dose(μg/kg/min) + 10,000 × vasopressin dose (U/kg/min) + 10 × milrinone dose (μg/kg/min).*

Vitals signs were recorded at 1-minute intervals. Blood pressure measurements were obtained via arterial line and oxygen saturation measurements were obtained via pulse oximeter. Intraoperative hemoglobin measurements were obtained via arterial blood gas samples. Data were organized to determine the presence or absence as well as total duration (in minutes) of hypotension defined as mean arterial pressure (MAP) of < 65 mmHg and peripheral hypoxemia defined as peripheral oxygen saturation of < 96%. A cutoff of MAP < 65 mmHg for defining hypotension was chosen as this threshold has previously been shown to be associated with worse postoperative outcomes following cardiac surgery[25], however we also evaluated time spent in a moderate (MAP < 60 mmHg) or severe (MAP < 55 mmHg) hypotensive range. Although there is no formal definition of hypoxemia based on pulse oximetry, it is commonly defined as spO2 of < 96%[26] and we categorized hypoxemia as mild (90%-95%) or severe (< 90%).

Outcomes

The outcomes for this study were defined by the STS standard definitions. The primary outcome was 1-year all-cause mortality. Secondary outcomes included days to death after surgery and length of stay.

Statistical Analysis

No a-priori power calculation was performed as data were gathered from a sample of all available patients during this time frame (2013–2020). All data were examined for normality. Data with normal distribution is presented as mean ± standard deviation (SD) and data with non-normal distribution is presented as median and interquartile range. Baseline and clinical (preoperative and intraoperative) characteristics were summarized overall and by group (sex or 1-year mortality) and compared with two-sample t test or Chi square test (or Fisher's exact test).

Any characteristics with a $p < 0.05$ comparing groups by 1-year mortality were selected for model fitting in a subsequent multiple logistic regression analysis using a stepwise approach. The level of significance to enter or remain in the model was set to 0.05, and the variable sex was forced to be included in all steps. Model selection was based on the model that minimized the Bayesian Information Criterion. For the multivariable model, the magnitude of associations between each characteristic and outcome was quantified using the odds ratio (OR) and the corresponding 95% confidence interval (CI). Performance of the logistic regression model was tested by means of Hosmer-and-Lemeshow goodness-of-fit test.

Causal mediation analysis (main effects and interaction between main effects were included in the model) was performed to evaluate if intraoperative hemoglobin mediates the relationship between sex and 1-year mortality. Mediation analysis was additionally adjusted for covariates including age, total surgery time, and preoperative hemoglobin. Main causal mediation effects (total effect, controlled direct effect, natural direct effect, and natural indirect effect) and percent of mediated effect are presented with 95% confidence intervals. All analyses were two-sided and the alpha level was set to 0.05. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Data was pulled for 766 patients, of which 5 were removed due to exclusion criteria and 12 removed due to incomplete data sets. We analyzed complete data for 749 patients, and differences in pre- and intraoperative characteristics between males and females undergoing ascending aortic root repair are summarized in Table 1. Preoperatively, females were significantly older (63 vs 58 years, $p < 0.001$), had higher BMI (32 vs 29 Kg/m^2, $p = 0.006$), and had lower preoperative hemoglobin values (12.1 vs 13.0 g/dL, $p < 0.001$) when compared to males.

Intraoperatively, females had less estimated blood loss (873 vs 1095 ml, $p = 0.001$), but lower minimum intraoperative hemoglobin values (7.3 vs 8.8 g/dL, $p < 0.001$) and lower immediate postoperative

hemoglobin values (8.7 vs 9.4 g/dl, $p < 0.001$), as compared to males. In addition, females, as compared to males, had shorter average periods of hypotension defined as MAP < 65 mmHg (140 vs 161 minutes, $p = 0.049$), shorter length of surgery (311 vs 335 minutes, $p = 0.008$), and shorter cross clamp time (134 vs 156 minutes, $p = 0.002$). No significant difference was seen between females and males with regard to total blood product transfusions, vasopressor use, or time spent in the hypoxemic range.

Table 1
Demographic, preoperative, and intraoperative characteristics by sex

Characteristic	**Mean ± SD or Frequency (%)**		
	Males (N = 506)	**Females (N = 243)**	**p-value**
Preoperative			
Age (years)	58.1 ± 14.4	62.6 ± 14.7	**< 0.001**
Race	American Indian: 1 (0.2%) Black: 22 (4.4%) Chinese: 2 (0.4%) Declined: 7 (1.4%) Not specified: 17 (3.4%) Other Pacific Islander: 1 (0.2%) White: 456 (90.1%)	American Indian: 0 (0%) Black: 6 (2.5%) Chinese: 0 (0%) Declined: 0 (0%) Not specified: 13 (5.4%) Other Pacific Islander: 0 (0%) White: 224 (92.2%)	0.18
BMI (Kg/m^2)	29.2 ± 9.8	31.6 ± 14.1	**0.006**
Insurance	Commercial: 221 (43.6%) Medicaid: 58 (11.5%) Medicare: 217 (43.0%) Self-pay/ Other 10 (2.0%)	Commercial: 72 (29.6%) Medicaid: 22 (9.1%) Medicare: 148 (60.9%) Self-pay/ Other 1 (0.4%)	**< 0.001**
Area Deprivation Index (ADI)	State: 5.8 ± 2.7 National: 57.2 ± 22.6	State: 5.9 ± 2.5 National: 58.4 ± 21.0	State: 0.67 National: 0.51
Comorbidities			
Arrhythmias	61/433 (14.1%)	24/216 (11.1%)	0.32
Diabetes	40/433 (9.2%)	20/216 (9.3%)	1.00
Hypertension	193/433 (44.6%)	97/216 (44.9%)	1.00
Hyperlipidemia	135/433 (31.2%)	86/216 (39.8%)	**0.03**
Coronary Artery Disease	71/433 (16.4%)	30/216 (13.9%)	0.42

SD, standard deviation

Characteristic	Mean ± SD or Frequency (%)		
	Males (N = 506)	Females (N = 243)	p-value
Atrial Fibrillation	44/433 (10.2%)	17/216 (7.9%)	0.39
Valvular Heart Disease	265/433 (61.2%)	134/216 (62.0%)	0.86
COPD	27/433 (6.2%)	15/216 (6.9%)	0.74
Renal Failure	27/433 (6.2%)	8/216 (3.7%)	0.20
ASA Class	1: 0 (0%) 2: 4 (0.8%) 3: 90 (17.8%) 4: 404 (79.8%) 5: 8 (1.6%)	1: 0 (0%) 2: 0 (0%) 3: 42 (17.3%) 4: 197 (81.1%) 5: 4 (1.7%)	0.70
Preoperative Hemoglobin (g/dL)	13.0 ± 2.3	12.1 ± 2.0	**< 0.001**
Use of Beta Blocker	252/433 (58.2%)	130/216 (60.2%)	0.67
Intraoperative			
Transfusions			
Blood Transfusion	140/506 (28%)	76/243 (31%)	0.35
PRBC volume (ml)	142.8 ± 387.8	180.0 ± 380.0	0.034
Platelet volume (ml)	97.5 ± 230.1	111.8 ± 256.0	0.67
Plasma volume (ml)	55.3 ± 258.4	28.7 ± 145.3	0.54
Cryoprecipitate volume (ml)	31.2 ± 93.5	32.7 ± 91.5	0.63
Blood salvage product volume (ml)	1543.9 ± 993.5	1531.5 ± 2821.0	**< 0.001**
Estimated Blood Loss (ml)	1094.7 ± 1190.4	872.5 ± 839.2	**0.001**
Estimated Blood loss per kg (ml/kg)	12.6 ± 15.5	11.6 ± 11.1	0.33
Urine Output (ml)	928.0 ± 552.0	962.9 ± 607.3	0.61
Crystalloid Volume (ml)	2678.9 ± 1295.4	2460.3 ± 1124.2	0.05
Albumin Volume (ml)	220.9 ± 455.7	146.8 ± 268.9	0.08
SD, standard deviation			

Characteristic	Mean ± SD or Frequency (%)		
	Males (N = 506)	Females (N = 243)	p-value
Hemodynamics			
# Minutes MAP < 65	160.7 ± 135.8	139.9 ± 114.9	**0.049**
# Minutes MAP < 60	98.1 ± 100.9	87.3 ± 88.7	0.18
# Minutes MAP < 55	59.4 ± 73.7	54.2 ± 67.6	0.55
# Minutes SpO2 < 90%	5.6 ± 16.4	5.1 ± 13.2	0.37
# Minutes SpO2 90–95%	10.9 ± 22.9	10.1 ± 21.6	0.40
Vasoactive-Inotrope Score	18.1 ± 60.4	11.2 ± 28.9	0.41
Lowest Intraoperative Hemoglobin (g/dL)	8.8 ± 2.0	7.3 ± 1.3	**< 0.001**
Postoperative hemoglobin (g/dL)	9.4 ± 1.7	8.7 ± 1.3	**< 0.001**
Operative			
Surgical Procedure			
Procedure coded	Value Sparing: 239 (47.2%) Bentall: 234 (46.3%) Transverse Arch: 22 (4.4%) Homograph: 11 (2.2%)	Value Sparing: 108 (44.4%) Bentall: 121 (49.8%) Transverse Arch: 10 (4.1%) Homograph: 4 (1.7%)	0.83
Length of Surgery (min)	334.5 ± 125.5	310.7 ± 116.8	**0.008**
Cardiopulmonary Bypass Time (min)	197 ± 72	179 ± 117	0.06
Cross-clamp time (min)	156 ± 59	134 ± 58	**0.002**
SD, standard deviation			

Differences in postoperative outcomes between male and female patients can be seen in Table 2. Notably, females had a greater 1-year mortality (15.2% vs 9.1%, p = 0.02) and shorter days to death (387.3 vs 666.1 days, p = 0.02) than males. No significant differences were seen between males and females with regard to length of hospital stay.

Table 2
Descriptive statistics for postoperative outcomes by sex

Outcome	Mean ± SD or Frequency (%)		
	Males (n = 506)	**Females (n = 243)**	**p-value**
1-year mortality	47 (9%)	37 (15%)	**0.02**
Days to death	666.1 ± 781.1	387.3 ± 646.6	**0.02**
Length of stay (days)	11.7 ± 13.0	12.2 ± 19.6	0.66
SD, standard deviation			

Table 3 summarizes results from the stepwise multivariable logistic regression analysis for 1-year mortality. Independent predictors of 1-year mortality across the cohort of both males and females included intraoperative hemoglobin (odds ratio (OR) = 0.66, $p < 0.0001$) and surgical duration (OR = 1.01, $p < 0.0001$).

Table 3
Multivariable logistic regression model predicting 1-year mortality

Explanatory variable	Odds Ratio	95% Confidence Interval	p-value
Female Sex	1.48	(0.87, 2.50)	0.148
Lowest intraoperative hemoglobin (g/dL)	0.66	(0.56, 0.79)	**< 0.0001**
Surgical duration (mins)	1.01	(1.00, 1.01)	**< 0.0001**

As intraoperative hemoglobin was lower in females as compared to males and was an independent predictor of 1-year mortality, a post-hoc causal mediation analysis was then performed to determine whether intraoperative hemoglobin mediates the relationship between female sex and 1-year mortality. As seen in Table 4, based on the unadjusted data, the odds ratio natural indirect effect is 2.17 ($p = 0.02$). That is, the effect of females compared to males on 1-year mortality that was due to sex induced changes in intraoperative hemoglobin corresponded to 2.17 times (95% CI 1.18, 3.17) greater odds of 1-year mortality. The proportion of mediated effect is 97%. Therefore, 97% of the sex-related effect on 1-year mortality is mediated through intraoperative hemoglobin. However, when adjusting for preoperative hemoglobin, age, and surgical duration, this result was no longer significant.

Table 4
Mediation analysis to examine whether intraoperative hemoglobin mediates the relationship between sex and 1-year mortality

Exposure: Sex **Outcome: 1-year mortality** **Mediator: Lowest intraoperative hemoglobin**	**Unadjusted Analysis**		**Adjusted Analysis***	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Total Effect	2.25 (0.88, 3.62)	0.073	1.81 (0.72, 2.89)	0.144
Controlled Direct Effect (CDE)	1.10 (0.32, 1.88)	0.796	1.44 (0.34, 2.54)	0.434
Natural Direct Effect (NDE)	1.04 (0.53, 1.55)	0.889	1.44 (0.34, 2.53)	0.434
Natural Indirect Effect (NIE)	2.17 (1.18, 3.17)	0.021	1.26 (0.81, 1.71)	0.260

*Adjusted for age, preoperative hemoglobin, and surgical duration; OR, odds ratio; CI, confidence intervals

Discussion

In this retrospective study of patients undergoing thoracic aortic aneurysm repair, we found that females as compared to males: 1) preoperatively - were older and had lower starting hemoglobin values, 2) intraoperatively - had less hypotension, shorter operative duration, and less blood loss, and 3) postoperatively - experienced greater 1-year mortality. No association was found between hemodynamic variables and postoperative 1-year mortality. Instead, lower intraoperative hemoglobin levels and increased surgical duration were found to be independent predictors of increased 1-year mortality in both males and females undergoing ascending aortic surgical repair. These results were in contradiction to our hypothesis that females would experience greater intraoperative hemodynamic derangements and that these intraoperative factors would be associated with increased postoperative mortality.

Sex-based differences in thoracic aortic disease presentation and progression have been previously defined and are now further supported by these current findings [14,15,17,19]. Our data from the preoperative phase of care demonstrate that females presenting for thoracic aortic surgical repair, as compared to males, have advanced age, lower starting hemoglobin values, and lower socioeconomic status (as demonstrated by greater distribution of Medicare vs. commercial insurance and lower area deprivation index in females). These findings in our comprehensive surgical patient population, including both thoracic aortic repair and replacement, are consistent with previous findings in other more narrow patient populations. Previous studies have been focused solely on isolated aortic root replacements, thoracic aortic surgery with hypothermic circulatory arrest only, or patients undergoing abdominal aortic aneurysm repair[14,17, 27–29]. While none of the preoperative factors remained independent predictors of

mortality in our adjusted multivariable analyses, they do highlight important sex-based differences in thoracic aortic disease presentation and progression.

Intraoperative hemodynamic instability can adversely impact postoperative outcomes, and hypotension specifically has been shown repeatedly to be associated with worse postoperative outcomes including a higher prevalence of acute kidney injury, stroke, and myocardial infarction, as well as greater mortality in both cardiac and non-cardiac surgery[25, 30, 31]. This study focused on sex-based differences in intraoperative hemodynamic variables primarily, as these variables have not been thoroughly investigated in this patient population, and the potential differences are highly clinically relevant as they are modifiable risk factors – which have the potential to be managed and optimized. Contrary to our initial hypothesis, the results from this study showed that females actually experienced less intraoperative hypotension, with no difference in hypoxemia or vasopressor scores, despite having greater 1-year morality.

The longer periods of mild intraoperative hypotension (with MAP < 65 mmHg) we observed in males is likely accounted for, in part, by the fact that males experienced longer surgical duration than females. When evaluating specifically for time spent with moderate or severe hypotension (MAP < 60 mmHg or < 55 mmHg), no difference was seen between the groups. Additionally, no significant association was found between intraoperative hypotension or vasopressor use and postoperative mortality. These findings may imply that time spent intraoperatively in the mildly hypotensive range of 60–65 mmHg is not remarkably detrimental to surgical outcomes for either males or females. This theory aligns well with other studies which have only shown more significantly detrimental outcomes with greater time spent in a more severely hypotensive range such as MAP < 55 mmHg[30,31]. Still, the results of this study indicate that intraoperative hypotension was not an independent contributor to 1-year mortality following ascending aortic aneurysm repair.

Our intraoperative findings also demonstrate that females, as compared to males, had shorter operative duration and less blood loss. Previous studies evaluating operative duration in females versus males have shown conflicting results. Chung et al., in a patient population of over 1600 thoracic aneurysm repairs, also found that females had shorter operative times as compared to males, whereas McMullen and Beller et al. both found no difference in operative duration between males and females[14, 15, 17]. Differences in these findings may be due to differences in sample size and selected surgical patient population, as Beller et al included less than 400 patients, and McMullen et al studied only patients with aortic root replacement procedures. None of the previous studies investigated sex-based differences in surgical blood loss. Importantly, while the previous studies included assessment of differences in surgical duration and intraoperative techniques between females and males, differences in intraoperative hemodynamic stability were not investigated.

The findings from this study also support previous research in demonstrating that hemoglobin levels have a significant effect on long-term cardiac surgical outcomes. Perioperative anemia is known to lead to inadequate oxygen delivery to tissues and as such, associated cell death and increased acidosis[32].

Previous studies have shown an increased incidence of pre-, intra-, and postoperative anemia in females as compared to males, and have discussed the importance of optimizing hemoglobin before undergoing cardiac surgery[27, 33], particularly in females where there is a greater expected dilutional effect of the cardiopulmonary bypass circuit[34, 35]. A large Dutch national prospective multi-center registry analysis demonstrated that preoperative anemia was linked to an increased risk of mortality as well as other morbidities such as renal failure, pneumonia and myocardial infarction[36]. Furthermore, in a retrospective analysis of the Society of Thoracic Surgeons Database, including 258,398 coronary artery bypass grafting (CABG) patients, perioperative anemia was associated with lower long-term survival. Other studies have shown that anemia is a significant risk factor for unplanned readmission after surgery[36, 38] and is also associated with reduced postoperative health-related quality of life and disability-free survival[39, 40].

In this study, a lower intraoperative hemoglobin nadir during cardiopulmonary bypass was found to be independently associated with 1-year mortality in both females and males post thoracic aortic aneurysm repair. Additionally, we found that females, as compared to males, had lower average intraoperative nadir hemoglobin values than males. Based on these results, we further investigated if differences in intraoperative hemoglobin values mediated the sex-based difference in mortality following thoracic aortic surgery through a causal mediation analysis. Based on the unadjusted data, 97% of the sex-related effect on 1-year mortality was mediated through intraoperative hemoglobin. However, when adjusting for preoperative hemoglobin, age, and surgical duration, this result was no longer significant.

The association between intraoperative anemia and increased mortality is in congruence with a recent retrospective cohort study in over 1 million isolated CABG patients which found an association between female sex and increased operative mortality[41]. However, in this previous study of CABG patients, intraoperative anemia was found to mediate female specific mortality[41]. The difference in causal mediation analysis results between our study and that of Harik et al, is likely due to differences in the surgical patient population (CABG versus ascending aortic repair), sample size, and the way in which anemia was classified. Our study used hemoglobin as a continuous variable whereas the previous study classified anemia into categories of anemia severity.

Despite the aforementioned importance of anemia both pre- and intraoperatively, no difference was seen in blood product transfusion rates between sexes. Perioperative transfusion has been well documented to be associated with worse long-term outcomes in cardiac surgery[37], however this does not appear to be a driving factor for the sex-based differences in outcomes observed in our study. Blood loss was significantly higher in males which may be associated with males having higher preoperative blood volume on average and was not associated with increased mortality.

Despite the sex-based differences in mortality that we observed, female sex was not found to be an independent predictor of 1-year mortality in this study. This finding is in congruence with a previous study in isolated aortic root replacement in which female sex was found to not be an independent

predictor of mortality[17]. However, this is in contrast to previous research which has found female sex to be independently predictive of worse outcomes after ascending aortic aneurysm repair[14–16, 42], and coronary artery bypass grafting[41, 43]. These opposing results are likely due to the differences in surgical patient populations and primary outcomes. It remains unclear as to why females undergoing cardiac surgery suffer increased mortality, but it is possible it could be related to differences in the pathophysiology of aneurysm formation between males and females, especially with regard to the protective role of estrogen in preventing aortic disease in premenopausal females and the abrupt loss of this protective effect after menopause. Estrogen has been shown to serve a crucial role in mediation of aortic smooth muscle cell turnover, suppression of matrix metalloproteinases, and limitation of oxidative stress and fibrosis of aortic tissue[1–4]. Further research is necessary to assess the underlying mechanism for these worse outcomes as this study does not support the concept of intraoperative hemodynamic instability being a major contributor, and because the differential outcomes in this study could not be explained entirely by differences in hemoglobin levels alone.

There were several notable limitations present in this study. First, all data were obtained retrospectively from a single medical center which both limits the sample size available as well as the generalizability of the results. Further studies with a broader patient population and greater number of facilities would be helpful in overcoming this limitation. Second, as this was an observational study, it cannot establish causation, but only association and could be subject to biases and hidden confounders. Finally, this study was done with a fixed sample size and therefore may not be powered for all comparisons.

In conclusion, despite females having objectively better intraoperative hemodynamic factors than males, their mortality remained increased following ascending aortic aneurysm repair and the underlying mechanism remains unclear. Further studies will be needed to evaluate possible underlying causes of differential outcomes between males and females as well as optimal management of both pre- and intraoperative anemia in both males and females undergoing ascending aortic aneurysm repair.

Declarations

Consent for Publication:

Not applicable

Acquisition, analysis, or interpretation of data

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The authors declare that they have no competing interests.

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request and execution of a data access agreement.

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Author Contribution

Concept and design: A.M., K.H., I.S. Acquisition, analysis, or interpretation of data: A.T., A.M., K.H., I.S., J.D. Drafting of the manuscript: J.D., A.T., K.H. Critical revision of the manuscript for important intellectual content: J.D., A.T., T.K., K.H., I.S. Statistical Analysis: B.R.Obtained Funding: K.H., I.S.

Data Availability

We collected preoperative, intraoperative, and postoperative variables up to 1 year after surgery from our institutional electronic medical record database and the Society for Thoracic Surgery (STS) outcomes database (https://www.sts.org/sts-national-database).

Ethics Approval:

Due to the observational and retrospective nature of the data obtained, the requirement for written consent was waived.

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