Featured Article

Male-female differences in contemporary elective ascending aortic surgery: insights from the Netherlands Heart Registration

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Background: Scientific research regarding male-female differences in ascending aortic surgery is scarce. The objective of this study was to identify male-female differences in presentation, treatment and peri-operative outcome in elective ascending aortic surgery.

Methods: Elective ascending aortic surgery procedures that took place in the Netherlands between 01/01/2013–31/12/2017 were identified from the Netherlands Heart Registration. Male-female differences in presentation, treatment characteristics, and in-hospital mortality and morbidity were explored.

Results: The study population consisted of 887 females (31%) and 1,972 males (69%). Females were older (median age 67 versus 62 years, P<0.001), more often had chronic lung disease (12.3% versus 9.1%, P=0.011), New York Heart Association (NYHA) class III–IV (21.5% versus 15.5%, P=0.003), and less often a history of percutaneous coronary intervention (PCI) (3.2% versus 5.0%, P=0.033). Isolated supracoronary aortic replacement was performed in 47.7% of females versus 30.6% of males (P<0.001), and ascending aorta with root replacement in 40.6% of females versus 56.7% of males (P<0.001). Females more often underwent concomitant interventions of the aortic arch (33.1% versus 20.2%, P<0.001) and the mitral valve (8.2% versus 5.2%, P=0.002), and less often concomitant coronary artery bypass grafting (CABG) (14.4% versus 19.1%, P=0.002). Overall, in-hospital mortality was significantly higher in females (5.1% versus 2.7%, P=0.003). In multivariable regression analysis, being female was an independent risk factor for in-hospital mortality [odds ratio (OR) 1.55, 95% confidence interval (CI): 1.02–2.37].

Conclusions: This nation-wide cohort shows clear differences between females and males in patient presentation, procedural characteristics, in-hospital outcomes, and risk factors for in-hospital mortality in elective ascending aortic surgery. Further exploration of these differences, and of modifiable within-male and within-female risk factors, may offer great opportunities in improving treatment and thereby outcomes for both males and females.

Keywords: Sex; gender; aortic surgery; aortic aneurysm

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Introduction

The exact incidence of thoracic aortic aneurysm (TAA) remains uncertain because of its asymptomatic character but is estimated to be 6–10 per 100,000 person years (1,2). The death rate due to aortic aneurysm in Western Europe in 2010 was estimated to be 7.68 per 100,000 (3). As a result of improved diagnosis, monitoring and treatment options, morbidity and mortality have improved in recent years (4). While there has been a lot of attention to male-female differences in diagnosis and surgical treatment of coronary artery disease, little is known about potential male-female differences in presentation, treatment and outcomes in TAA and current guidelines acknowledge the lack of male-female specific literature regarding aortic disease (5). The scarcely available published evidence, often single center with a limited sample size, provides contradicting insights (6-8).

Knowledge of the differences between men and women in determinants of outcome is important to provide patient-tailored treatment decision-making. With this knowledge, hopefully, outcomes in both men and women can be improved. Therefore, the aim of this study was to identify male-female differences in diagnosis, treatment and in-hospital mortality and morbidity in contemporary [2013–2017] elective ascending aortic aneurysm surgery, using data from the Netherlands Heart Registration.

Methods

Study design and patient selection

A retrospective analysis of data from the Netherlands Heart Registration (NHR) was performed. The NHR is a Dutch nationwide prospective registry that contains anonymized peri-operative patient data of all cardiothoracic surgical procedures and percutaneous cardiac interventions performed in the Netherlands. Approval from the board of the NHR was obtained on 18-01-2019 to analyze the requested dataset. The study was reported following the STROBE statement (9).

The NHR database was queried for all adult patients (≥18 years) undergoing thoracic aortic surgery between 01-01-2013 and 31-12-2017, totaling 6,114 procedures. Exclusion criteria were isolated descending aortic surgery or isolated thoracic endovascular aortic repair (N=536 and N=14 respectively), isolated aortic arch surgery (N=85), no aortic surgery performed or type of surgery could not be determined (N=15 and N=14 respectively), cardiac transplant (N=1), duplicate patient (N=2), and non-elective surgery (urgent N=685, emergency/salvage N=1,133, missing N=770). A total of 2,859 patients undergoing elective ascending aortic surgery, with or without concomitant cardiac or aortic surgery, were included.

Endpoints and definitions

The primary endpoint of this study was in hospital mortality stratified by sex. Secondary endpoints were patient characteristics, procedural characteristics, in-hospital morbidity, and risk factors for in-hospital mortality stratified by sex.

Statistical analysis

Descriptive statistical analyses

Normally distributed continuous variables were presented as mean ± standard deviation and compared using the Student's *t*-test. Skewed continuous variables were presented as median and interquartile range and compared using the Mann-Whitney *U* test. Normality of the distributions was tested using the Kolmogorov-Smirnov test. Categorical variables were presented as counts and percentages and compared using the χ^2-test or the Fisher's exact test, as appropriate. The descriptive statistical analyses were performed on the original dataset.

Imputation of missing values

An imputed dataset was used for the exploration of risk factors for in-hospital mortality, using multivariable logistic regression modelling. The missing values were presented in Table S1. Missing values were assumed to be missing at random: inspection of missing data pattern plots was performed, and for variables with >5% missing associations between the missing values and the other variables eligible for the logistic regression analyses were investigated by student's *t*-tests and cross tabulation inspection. Assuming missing at random, multiple imputation was performed to impute missing covariate values for the logistic regression analyses (10). Covariates exceeding 15% missing values were omitted from imputation and the logistic regression analysis. To prevent the induction of bias, we excluded for imputation those variables that are present after a treatment decision is made (e.g., procedural characteristics). The imputed variables were: age, sex, body mass index (BMI), creatinine level, left ventricular ejection fraction (LVEF) (categorized), chronic pulmonary disease, arterial pathology, prior cardiac or aortic surgery, neurological dysfunction, active endocarditis, recent myocardial infarction, prior percutaneous coronary intervention (PCI), pulmonary artery pressure and diabetes. Five imputed datasets were generated using 5 iterations each. The imputations were visually checked by strip plots and density plots.

Logistic regression analyses

The imputed datasets were used to develop the multivariable logistic regression models. Preoperative and procedural variables were eligible as covariates if they did not exceed 15% missing values, and if there were at least 10 events due to in-hospital mortality (for categorical variables: at least 10 events per category). Correlations between covariates were checked using Pearson and Spearman correlation coefficients, as appropriate. In the case of high correlation (between ±0.50 and ±1.0) the clinically most relevant variable was chosen. Variables with a P value <0.1 in univariate modelling were selected for inclusion in the multivariable model. A full multivariable model was chosen to be presented. The analyses were performed on all five imputed datasets and the results were aggregated using Rubin's rules for multiple imputation (11). Odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) were reported.

To further explore male-female differences in risk factors for in-hospital mortality, multivariable logistic regression models for the male and female subpopulation were developed. These models were developed to explore male-female differences in both the independent risk factors, as well as in the weight of these risk factors for in-hospital mortality. For these models subsets of the imputed datasets were used: one subset was created of the female population and one subset of the male population. These subsets of the imputed datasets were then used to develop multivariable logistic regression models, as described above for the complete study population: preoperative and procedural variables were eligible as covariates if they did not exceed 15% missing values, if there were at least 10 events due to in-hospital mortality, and in the case of highly correlated covariates the clinically most relevant variable was chosen. Variables with a P value <0.1 in univariate modelling were selected for inclusion in the multivariable model, and a full multivariable model was presented. The analyses were performed on all five imputed datasets and the results were aggregated. ORs with corresponding 95% CIs were reported. Figures S1-S5 show missing data pattern plots and imputed data plots for the variables that were used in the multivariable logistic regression model.

All statistical analyses were performed in computing and statistical program *R* (The R foundation for Statistical Computing, Vienna, Austria. Version 3.6.1.) using packages "*glm*" and "*MICE*". A P value <0.05 was considered significant for all statistical tests.

Results

Patient characteristics

Table 1 displays preoperative patient characteristics for the entire cohort, and the female and male subcohorts. Females presented at an older age [median 67 (IQR, 59–73) versus median 62 (IQR, 53–70) years old, P<0.001], with a higher EuroSCORE [median 14.7 (IQR, 9.4–21.7) versus median 8.8 (IQR, 4.8–14.5), P<0.001], with more often chronic pulmonary disease (12.3% versus 9.1%, P=0.011), and a higher New York Heart Association (NYHA) class (class III–IV 21.5% versus 15.5%, P=0.003) compared to males. Males presented with a higher BMI [median 26.3 (IQR, 24.3–29.0) versus median 25.7 (IQR, 22.8–29.0), P<0.001] and creatinine level [median 88 (IQR, 79–100) versus median 72 (IQR, 63–83), P<0.001].

Procedural characteristics

Table 2 displays procedural characteristics for the entire cohort, and the female and male subcohorts. Female patients underwent supracoronary ascendens replacement significantly more often (47.7% versus 30.6%, P<0.001), whereas male patients underwent aortic root and aorta ascendens replacement significantly more often (56.7% versus 40.6%, P<0.001). Female patients received concomitant aortic arch surgery (33.1% versus 20.2%, P<0.001) and mitral valve surgery (8.2% versus 5.2%, P=0.002) significantly more often, whereas male patients received concomitant coronary artery bypass grafting (CABG) significantly more often (19.1% versus 14.4%, P=0.002).

In-hospital mortality and morbidity

Table 3 displays postoperative in-hospital mortality and morbidity. In-hospital mortality was significantly higher in female patients (5.1% versus 2.7%, P=0.003). Furthermore, female patients had a longer admission duration [median days 8 (IQR, 6–12) versus median days 7 (IQR, 5–10), P<0.001], more often had extended intubation (>24 hours,

Table 1 Patient characteristics of patients undergoing elective ascending aortic surgery

Patient characteristic	Overall (N=2,859)	Female (N=887, 31%)	Male (N=1,972, 69%)	P value
Age	64 [54–71]	67 [59–73]	62 [53–70]	<0.001
Body mass index (kg/m^2)	26.1 [23.9–29.0]	25.7 [22.8–29.0]	26.3 [24.3–29.0]	<0.001
Creatinine level (μmol/L)	84 [73–97]	72 [63–83]	88 [79–100]	<0.001
Creatinine (>200 μmol/L)	25 (0.9)	4 (0.5)	21 (1.1)	0.129
Logistic EuroSCORE	10.6 [6.4–17.2]	14.7 [9.4–21.7]	8.8 [4.8–14.5]	<0.001
Diabetes mellitus	189 (6.8)	60 (7.0)	129 (6.7)	0.807
LVEF				0.205
LVEF <30%	62 (2.2)	13 (1.5)	49 (2.5)	
LVEF 30–55%	2,052 (72.3)	638 (72.3)	1,414 (72.3)	
LVEF >55%	725 (25.5)	231 (26.2)	494 (25.2)	
Chronic pulmonary disease	289 (10.1)	109 (12.3)	180 (9.1)	0.011
Chronic arterial pathology	274 (9.6)	94 (10.6)	180 (9.1)	0.216
Neurological dysfunction	63 (2.2)	17 (1.9)	46 (2.3)	0.582
Active endocarditis	41 (1.4)	7 (0.8)	34 (1.7)	0.082
Recent myocardial infarction	34 (1.2)	7 (0.8)	27 (1.4)	0.061
PA pressure (mmHg)	25 [25–25]	25 [25–25]	25 [25–25]	0.812
Prior CVA	89 (4.6)	20 (3.3)	69 (5.1)	0.099
Dialysis	6 (0.3)	2 (0.3)	4 (0.3)	>0.99
NYHA class				0.003
I–II	1,471 (82.7)	421 (78.5)	1,050 (84.5)	
III–IV	307 (17.3)	115 (21.5)	192 (15.5)	
CCS class IV	18 (0.9)	3 (0.5)	15 (1.0)	0.303
Prior PCI	118 (4.4)	26 (3.2)	92 (5.0)	0.033
Prior aortic surgery	246 (10.0)	80 (10.4)	166 (9.8)	0.663
Prior cardiac surgery	502 (17.6)	153 (17.3)	349 (17.7)	0.832

Continuous variables presented as median with interquartile range, and categorical variables presented as counts with percentages. LVEF, left ventricular ejection fraction; PA, pulmonary artery; CVA, cerebrovascular accident; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

7.7% versus 4.9%, P=0.004), and more often had urinary tract infections (3.2% versus 1.2%, P<0.001).

Risk factors in-hospital mortality

Table 4 shows the uni- and multi-variable risk factor analysis for in-hospital mortality for the entire study population. Independent risk factors for in-hospital mortality were: older age (OR 1.04, 95% CI: 1.02–1.06), being female (OR 1.55, 95% CI: 1.02–2.37), chronic lung disease (OR 2.65, 95% CI: 1.64–4.30), previous cardiac or aortic surgery (OR 2.05, 95% CI: 1.25–3.35), and concomitant CABG and/or valve surgery (other than the aortic valve) (OR 2.82, 95% CI: 1.85–4.31).

Table 2 Procedural characteristics of patients undergoing elective ascending aortic surgery

Patient characteristic	Overall (N=2,859)	Female (N=887, 31%)	Male (N=1,972, 69%)	P value
Surgery type				<0.001
Aortic root and ascendens replacement	1,479 (51.7)	360 (40.6)	1,119 (56.7)	
Supracoronary ascendens replacement	1,027 (35.9)	423 (47.7)	604 (30.6)	
Ascendens replacement (location unknown)	353 (12.3)	104 (11.7)	249 (12.6)	
Aortic root and ascendens replacement	1,479 (51.7)	360 (40.6)	1,119 (56.7)	<0.001
Without valve intervention	146 (5.1)	34 (3.8)	112 (5.7)	
With biological prosthesis	650 (22.7)	190 (21.4)	460 (23.3)	
With mechanical prosthesis	488 (17.1)	94 (10.6)	394 (20.0)	
With homograft	10 (0.3)	4 (0.5)	6 (0.3)	
With autograft	7 (0.2)	4 (0.5)	3 (0.2)	
Valve-sparing root replacement	178 (6.2)	34 (3.8)	144 (7.3)	
Supracoronary ascendens replacement	1,027 (35.9)	423 (47.7)	604 (30.6)	<0.001
Without valve intervention	481 (16.8)	236 (26.6)	245 (12.4)	
With aortic valve plasty	56 (2.0)	26 (2.9)	30 (1.5)	
With biological prosthesis	344 (12.0)	122 (13.8)	222 (11.3)	
With mechanical prosthesis	145 (5.1)	38 (4.3)	107 (5.4)	
With homograft	1 (0.0)	1 (0.1)	0 (0.0)	
Ascendens replacement (location unknown)*	353 (12.3)	104 (11.7)	249 (12.6)	0.001
Without valve intervention	37 (1.3)	12 (1.4)	25 (1.3)	
With aortic valve plasty	35 (1.2)	19 (2.1)	16 (0.8)	
With biological prosthesis	183 (6.4)	56 (6.3)	127 (6.4)	
With mechanical prosthesis	80 (2.8)	12 (1.4)	68 (3.4)	
With homograft	1 (0.0)	0 (0.0)	1 (0.1)	
With valve replacement, type unknown	17 (0.6)	5 (0.6)	12 (0.6)	
Concomitant arch surgery	692 (24.2)	293 (33.1)	399 (20.2)	<0.001
Concomitant descending aortic surgery	77 (2.7)	31 (3.5)	46 (2.3)	0.081
Concomitant CABG	505 (17.7)	128 (14.4)	377 (19.1)	0.002
Concomitant mitral valve surgery	176 (6.2)	73 (8.2)	103 (5.2)	0.002
Concomitant pulmonary valve surgery	13 (0.5)	4 (0.5)	9 (0.5)	1.000
Concomitant tricuspid valve surgery	59 (2.1)	25 (2.8)	34 (1.7)	0.064
Other concomitant surgery	209 (7.3)	87 (9.8)	122 (6.2)	0.001
Circulatory arrest performed	766 (26.8)	320 (36.2)	446 (22.6)	<0.001

Continuous variables presented as median with interquartile range, and categorical variables presented as counts with percentages. *, in the database it was unknown which parts of the ascending aorta were replaced exactly. CABG, coronary artery bypass grafting. CPB, cardiopulmonary bypass.

Table 3 Mortality and morbidity outcome of patients undergoing elective ascending aortic surgery

Outcome variable	Overall (N=2,859)	Female (N=887, 31%)	Male (N=1,972, 69%)	P value
In-hospital mortality	99 (3.5)	45 (5.1)	54 (2.7)	0.003
Admission in days	7 [5–11]	8 [6–12]	7 [5–10]	<0.001
Perioperative myocardial infarction				0.475
One criterion	86 (4.6)	21 (3.7)	65 (5.0)	
Two or more criteria	34 (1.8)	11 (1.9)	23 (1.8)	
Pneumonia	131 (5.2)	31 (4.0)	100 (5.8)	0.065
Urinary tract infection	46 (1.8)	25 (3.2)	21 (1.2)	<0.001
Reintubation during admission	83 (3.3)	34 (4.3)	49 (2.8)	0.070
Extended intubation (exceeding 24 hours)	165 (5.8)	68 (7.7)	97 (4.9)	0.004
Readmission to ICU	135 (4.8)	49 (5.6)	86 (4.4)	0.183
CVA with permanent damage	68 (2.4)	27 (3.1)	41 (2.1)	0.143
CVA without permanent damage	20 (0.8)	9 (1.2)	11 (0.6)	0.225
Renal failure	79 (2.8)	26 (3.0)	53 (2.7)	0.712
Gastrointestinal complications				0.832
Unknown	2 (0.1)	0 (0.0)	2 (0.1)	
Yes, type unknown	4 (0.1)	1 (0.1)	3 (0.2)	
Bleeding	11 (0.4)	4 (0.5)	7 (0.4)	
Yes, other	23 (0.8)	9 (1.0)	14 (0.7)	
Vascular complications	18 (0.6)	6 (0.7)	12 (0.6)	0.802
Heart rhythm complications	964 (34.8)	313 (36.3)	651 (34.1)	0.282
Rethoracotomy				0.805
Bleeding/tamponade	203 (10.7)	57 (9.7)	146 (11.2)	
Cardiac	37 (2.0)	12 (2.0)	25 (1.9)	
Other	8 (0.4)	2 (0.3)	6 (0.5)	
Deep sternal wound infection	7 (0.4)	1 (0.2)	6 (0.5)	0.445

Continuous variables presented as median with interquartile range, and categorical variables presented as counts with percentages. ICU, intensive care unit; CVA, cerebrovascular accident.

Table 5 shows the uni- and multi-variable risk factor analysis for in-hospital mortality for the female and male subpopulations. For the female subpopulation, chronic lung disease (OR 3.00, 95% CI: 1.51–5.99) and concomitant CABG and/or valve surgery (other than the aortic valve) (OR 3.74, 95% CI: 1.97–7.10) were independent risk factors. For the male subpopulation, older age (OR 1.04, 95% CI: 1.01–1.07), chronic lung disease (OR 2.10, 95% CI: 1.05–4.18), arterial pathology (OR 2.34, 95% CI: 1.20–4.57), concomitant aortic arch surgery (OR 2.01, 95% CI: 1.08–3.71) and concomitant CABG and/or valve surgery (other than the aortic valve) (OR 2.08, 95% CI: 1.17–3.67) were independent risk factors.

Discussion

This nation-wide cohort shows clear male-female differences in patient presentation, procedural characteristics, in-

Table 4 Uni- and multi-variable logistic regression results of in-hospital mortality in the entire study population

Risk factors	Entire study population			
	Univariate		Multivariable	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age (years)	1.05 (1.03–1.07)	<0.001	1.04 (1.02–1.06)	0.001
Female	1.90 (1.27–2.83)	0.002	1.55 (1.02–2.37)	0.041
Body mass index (kg/m^2)	0.99 (0.94–1.04)	0.656		
Creatinine (μmol/L)	1.00 (1.00–1.01)	0.263		
Left ventricular ejection fraction 30–55%*	1.22 (0.75–1.99)	0.427	1.18 (0.71–1.97)	0.530
Left ventricular ejection fraction <30%*	2.92 (1.06–8.00)	0.039	2.51 (0.87–7.21)	0.089
Chronic lung disease	3.56 (2.25–5.64)	<0.001	2.65 (1.64–4.30)	<0.001
Arterial pathology	2.48 (1.51–4.14)	<0.001	1.51 (0.88–2.59)	0.135
Previous cardiac or aortic surgery	1.73 (1.12–2.72)	0.021	2.05 (1.25–3.35)	0.005
Aortic root replacement**	0.79 (0.51–1.25)	0.317		
Aortic ascendens replacement, location unspecified**	1.32 (0.73–2.36)	0.357		
Concomitant aortic arch surgery	1.84 (1.21–2.77)	0.005	1.53 (0.98–2.40)	0.061
Concomitant CABG and/or valve surgery (other than aortic valve)	3.35 (2.23–5.00)	<0.001	2.82 (1.85–4.31)	<0.001

*, reference category is left ventricular ejection fraction >55%; **, reference category is supracoronary replacement. CABG, coronary artery bypass surgery.

hospital mortality and morbidity, and risk factors for in-hospital mortality in contemporary elective ascending aortic surgery in The Netherlands.

Patient and procedural characteristics

Patient characteristics were significantly different between male and female patients, including known risk factors for cardiovascular surgery. It is obvious from the observed differences in patient characteristics that female patients are older, tend to present in a worse clinical condition with a higher NYHA class and more often chronic pulmonary disease, while male patients more often had a previous percutaneous coronary intervention (PCI). These differences are also reflected in the higher logistic EuroSCORE found in female patients.

The older age at the time of surgery has been found in previous studies (6,7,12) and can be attributed to biological factors, such as the protective effect of estrogen on cardiovascular diseases, causing a delayed aortic aneurysm incidence in female patients (13). However, socio-cultural factors related to gender such as a delayed presentation due to patient and/or physician delay may also be a contributing factor, and remains to be explored as no evidence in the context of TAA surgery is available in this regard. However, a delayed recognition by physicians in female patients has been observed in aortic dissection (14).

In the current study, aortic diameter at surgery was not available. However, as the study comprised elective surgical patients, we can assume the 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases were followed regarding timing of surgery (5). However, in published literature, it has been shown that female patients undergo surgery at a larger body size indexed aortic diameter than male patients (7), and aortic dilatation rates in female patients are higher (15), both of which are risk factors for aortic dissection. Furthermore, population-based studies show that female patients have higher out of hospital deaths caused by acute aortic dissection than male patients (16,17). Considering the above, it is possible worse outcomes due to aortic disease in female patients unfortunately remain undocumented. In the light of elective surgery, it

Table 5 Uni- and multi-variable logistic regression results of in-hospital mortality in the female and male subcohorts

Risk factors	Female population				Male population			
	Univariate		Multivariable		Univariate		Multivariable	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age (years)	1.04 (1.00–1.07)	0.023	1.03 (1.00–1.06)	0.096	1.06 (1.03–1.09)	<0.001	1.04 (1.01–1.07)	0.005
Body mass index (kg/m^2)	1.01 (0.96–1.07)	0.619			0.96 (0.90–1.03)	0.328		
Creatinine (μmol/L)	1.01 (1.00–1.01)	0.094	1.01 (1.00–1.01)	0.103	1.00 (1.00–1.01)	0.347		
Left ventricular ejection fraction 30–55%*	1.39 (0.66–2.94)	0.389	1.38 (0.64–2.97)	0.418	1.12 (0.58–2.14)	0.748		
Left ventricular ejection fraction <30%*	4.53 (0.87–23.57)	0.073	2.72 (0.46–16.12)	0.272	2.59 (0.70–9.39)	0.154		
Chronic lung disease	3.97 (2.05–7.61)	<0.001	3.00 (1.51–5.99)	0.002	2.97 (1.54–5.75)	0.001	2.10 (1.05–4.18)	0.035
Arterial pathology	1.31 (0.54–3.19)	0.553			3.71 (1.97–6.96)	<0.001	2.34 (1.20–4.57)	0.013
Previous cardiac or aortic surgery	1.80 (0.92–3.53)	0.104			1.68 (0.91–3.10)	0.101		
Aortic root replacement**	1.46 (0.77–2.77)	0.242			0.58 (0.32–1.08)	0.088	0.93 (0.49–1.79)	0.840
Ascending aorta replacement, location unspecified**	1.14 (0.41–3.13)	0.805			1.48 (0.71–3.06)	0.295	1.99 (0.90–4.35)	0.086
Concomitant aortic arch surgery	1.25 (0.67–2.32)	0.492			2.20 (1.25–3.90)	0.007	2.01 (1.08–3.71)	0.027
Concomitant CABG and/or valve surgery (other than aortic valve)	4.76 (2.59–8.76)	<0.001	3.74 (1.97–7.10)	<0.001	2.61 (1.51–4.48)	<0.001	2.08 (1.17–3.67)	0.012

*, reference category is left ventricular ejection fraction >55%; **, reference category is supracoronary replacement. CABG, coronary artery bypass surgery.

is important to be aware of these differences, to prevent dissections through timely interventions.

The differences observed in the procedural characteristics might indicate different underlying pathophysiology of aneurysm development, as male patients more often underwent a procedure including the root, whereas female patients more often underwent a procedure without root replacement and with arch replacement. Sokolis *et al.* found differences between male and female patients in ascending TAAs in mechanics and matrix, which supports the possibility of different underlying pathophysiology (18). Furthermore, male patients more often underwent concomitant CABG surgery which indicates more atherosclerotic disease in male patients, as observed by previous studies (6,12).

Mortality and morbidity

We observed a higher unadjusted in-hospital mortality in female patients. Published literature on ascending aortic surgery shows contradicting estimates of male-female post-operative mortality differences (6-8,12,19). However, these studies are usually single center with a limited sample size and concern diverging patient populations, for example including emergency surgery (7,8,19), or focusing on a specific surgical technique (12). Beller *et al.* found a comparable short-term mortality between male and female patients undergoing elective ascending aortic aneurysm surgery, whereas Chung *et al.* found a higher mortality in female patients undergoing thoracic aortic surgery with deep hypothermic circulatory arrest (6,19). Beller and colleagues had a comparable population to ours, and although they did not find a significant difference in 30-day mortality, they had a smaller population, a smaller number of events, and there was a trend towards a significant difference (30-day mortality rate in males of 3.5%, in females 7.9%, P value of 0.058) (6).

Female patients experienced more morbidity postsurgery: a longer admission time, more often extended intubation, and more urinary tract infections. Other adverse in-hospital outcomes were comparable. Awareness of the differences is important, in order to take preventative measures wherever possible (e.g., removing bladder catheters as soon as possible).

Risk factor differences between male and female patients for in-hospital mortality

Previous studies utilizing the NHR data in isolated mitral valve surgery, tricuspid valve surgery and combined aortic valve and CABG surgery have shown differences between male and female patients in risk factors and the weights of risk factors for in-hospital mortality (20-22). This demonstrates the presence of differences and the importance to investigate these differences in an aortic surgery population.

The added value of our study is that it allows, due to its national multicenter character with a large sample size and enough events to provide adequate power for a meaningful in-hospital mortality risk factor analysis. In multivariable testing, being female was an independent risk factor for in-hospital mortality. Older age, chronic pulmonary disease, previous cardiac or aortic surgery, and concomitant CAGB and/or valve surgery proved to be independent risk factors. Older age, chronic pulmonary disease, and concomitant mitral valve surgery were also more prevalent in female patients. Regardless of the causative factors underlying the higher observed mortality, we urge clinicians to be aware of these associations.

In this study, we indeed found that the risk factors and weights of the risk factors for in-hospital mortality differ between male and female patients. Beller *et al.* also found that the relevant risk factors for short-term mortality in ascending aortic aneurysm surgery differed between males and females (e.g., age and myocardial infarction in males, arch involvement and renal insufficiency in females) (6). As the data used in our study was registered patient data, not all possible modifiable risk factors could be included in these analyses, especially aortic diameter at surgery and cardiovascular risk factors such as hypertension and hypercholesterolemia would be valuable to include in the analyses. However, it underlines the importance of further investigating modifiable risk factors to improve personalized clinical care for both male and female patients.

Relevance to patient centered clinical decision making and recommendations

It is likely that there are underlying pathophysiological differences in male and female patients, because comorbidities differ, location of aneurysms differ, and risk factors differ. We recommend more fundamental and translational science to investigate these underlying pathophysiological differences, to aid in (preventive) clinical interventions and decision-making.

Furthermore, investigating the different clinical risk factors for male and female patients is equally important to aid in (preventive) clinical interventions and shared decision-making. Knowledge of specific risk factors can help clinicians to better inform patients of their risks and help patients make an informed decision fitting to their personal values. In this light, we recommend large dedicated multicenter prospective databases specifically set up for patients with thoracic aortic disease, regardless of their treatment trajectory, in order to follow patients over time. Such databases could aid in the further investigation of male-female differences in this specific patient group, including diagnoses, treatment, prognosis, time-to-event data, and include both clinical and non-clinical risk factors (such as aortic diameters before surgery, socio-cultural and economic factors).

Aside from important adverse clinical outcomes, health related quality of life (HRQOL) is an outcome important to the patient undergoing surgery. Prior to surgery, patients with thoracic aortic disease experience a lower health related quality of life, especially the female patients (23). Furthermore, in-depth interviews showed that determinants of HRQOL included physical symptoms, coping strategies, impact on social and professional life, and disease-related knowledge. We recommend clinicians to be aware of these factors influencing HRQOL, to aid in shared decision-making for the individual patient.

Finally, good scientific practice includes the use of standardized terms and definitions. The terms sex and gender are often used interchangeably or incorrectly. We recommend the proper use of these terms (24).

Limitations

This study was a retrospective analysis of registered data. Missing values and mistakes could not be corrected for.

Some variables had many missing values, and this should be taken into account when interpreting data, e.g., 12.3% of the study population for whom it was not registered whether they received a supracoronary ascending aorta replacement or an ascending aorta replacement including the aortic root. Valuable information regarding aortic diameter and detailed disease etiology was not present in the registered data.

Conclusions

This nation-wide cohort shows clear male-female differences in patient presentation, procedural characteristics, in-hospital outcomes, and risk factors for mortality in contemporary elective ascending aortic surgery. Further exploration of these male-female differences and of modifiable within-male and within-female risk factors, offers great opportunities in improving treatment and thereby outcomes for both men and women.

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Footnote

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

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Supplementary

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Table S1 Missing data specification

Variable	Missing percentage female population (N=887)	Missing percentage male population (N=1,972)
Age	0	0
Body mass index (kg/m^2)	5.3	4.2
Creatinine level (μmol/L)	1.1	0.8
Creatinine (>200 μmol/L)	0	0
Logistic EuroSCORE	0.3	0.3
Diabetes mellitus	3.4	2.7
LVEF	0.6	0.8
Chronic pulmonary disease	0.5	0.2
Chronic arterial pathology	0.3	0.1
Neurological dysfunction	0.3	0.1
Active endocarditis	0.5	0.2
Recent myocardial infarction	0.3	0.2
PA pressure (mmHg)	1.2	1.5
Prior CVA	32.2	31.7
Dialysis	31.6	27.7
NYHA class	39.6	37.0
CCS class IV	30.4	26.2
Prior PCI	7.6	6.9
Prior aortic surgery	13.5	14.1
Prior cardiac surgery	0.2	0.1
Surgery type	0	0
Concomitant arch surgery	0.1	0
Concomitant descending aortic surgery	0	0
Concomitant CABG	0	0
Concomitant mitral valve surgery	0	0
Concomitant pulmonary valve surgery	0	0
Concomitant tricuspid valve surgery	0	0
Other concomitant surgery	0	0
Circulatory arrest performed	0.3	0.1
In-hospital mortality	0	0
Admission in days	0.2	0.4
Perioperative myocardial infarction	36	33.6
Pneumonia	11.7	12.7
Urinary tract infection	11.7	12.7

Table S1 (*continued*)

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Table S1 (*continued*)		
Variable	Missing percentage female population (N=887)	Missing percentage male population (N=1,972)
Reintubation during admission	11.6	12.8
Extended intubation (exceeding 24 hours)	0.6	0.4
Readmission to ICU	0.9	1.1
CVA with permanent damage	0.6	0.5
CVA without permanent damage	12.4	13.6
Renal failure	0.7	0.5
Gastrointestinal complications	0.6	0.4
Vascular complications	0.9	0.5
Heart rhythm complications	2.7	3.3
Rethoracotomy	33.8	33.8
Deep sternal wound infection	37.8	38.4

CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PA, pulmonary artery; PCI, percutaneous coronary intervention.

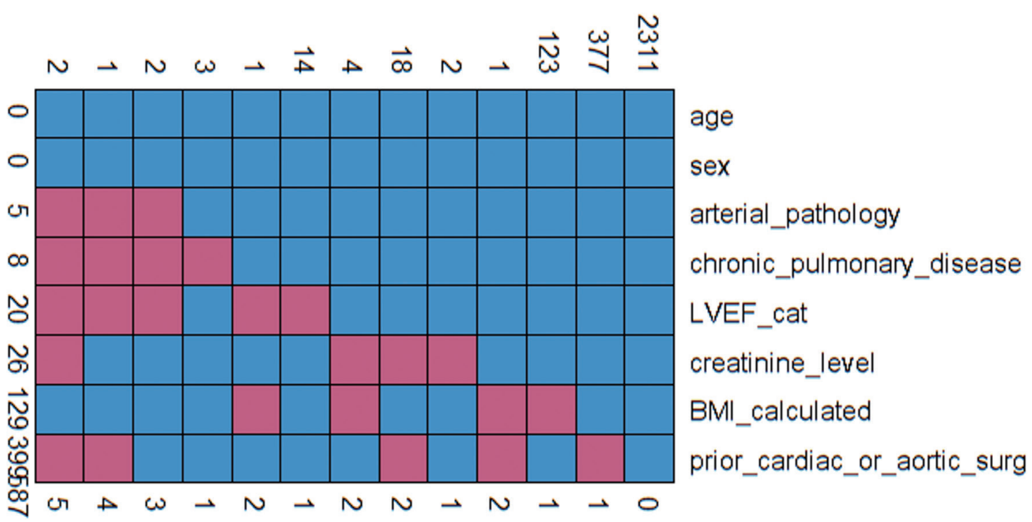

Figure S1 Missing data pattern plot.

 https://dx.doi.org/10.21037/acs-2022-adw-fs-0139

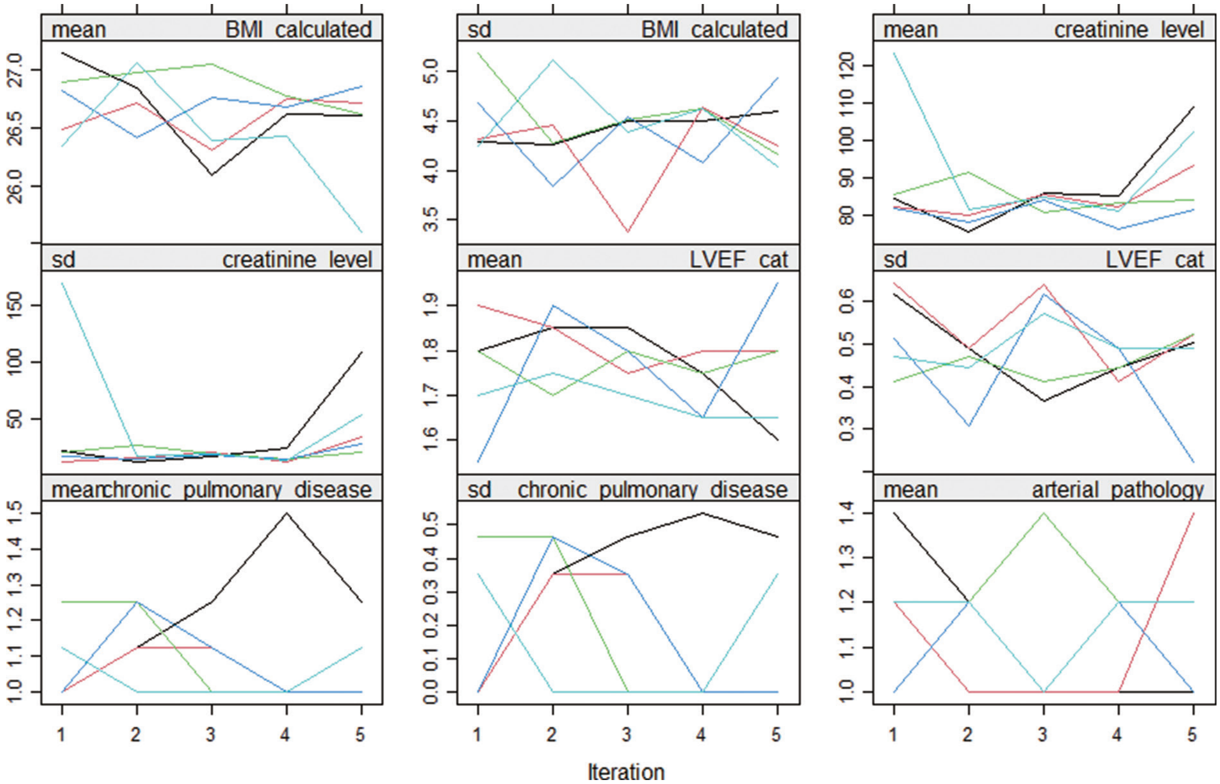

Figure S2 Imputation plots 1/2.

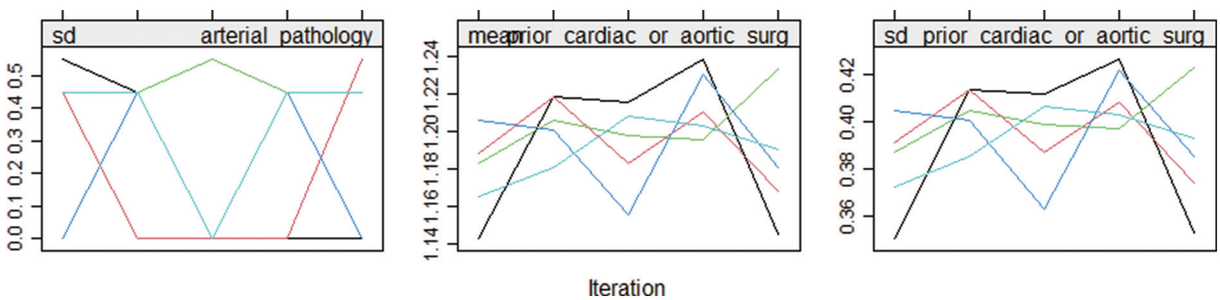

Figure S3 Imputation plots 2/2.

https://dx.doi.org/10.21037/acs-2022-adw-fs-0139

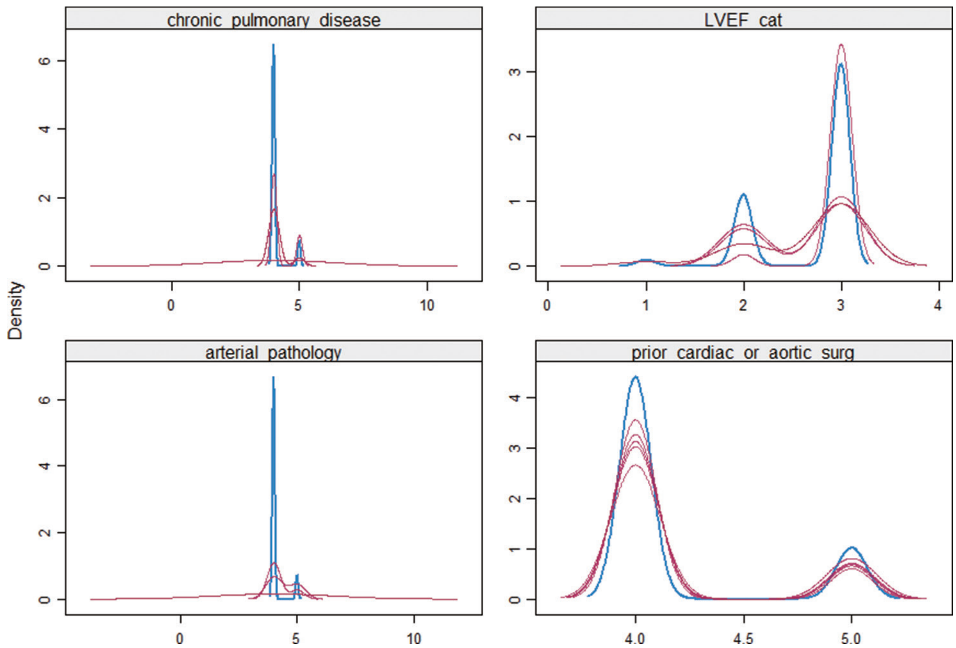

Figure S4 Density plot of imputed data.

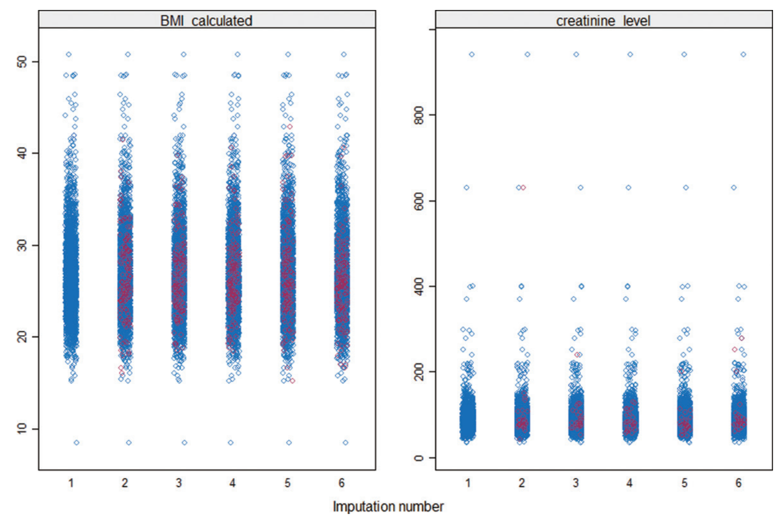

Figure S5 Stripplot of imputed data.

https://dx.doi.org/10.21037/acs-2022-adw-fs-0139