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ORIGINAL RESEARCH

SURGERY

Sex Differences in DeBakey Type I/II Acute Aortic Dissection Outcomes

The Tokyo Acute Aortic Super-network

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ABSTRACT

BACKGROUND Sex differences in the clinical presentation and outcomes of DeBakey type I/II (Stanford type A) acute aortic dissection (AAD) remain unclear.

OBJECTIVES The authors aimed to determine the impact of sex on the clinical presentation and in-hospital outcomes of surgically or medically treated patients with type I/II AAD.

METHODS We studied 3,089 patients with type I/II AAD enrolled in multicenter Japanese registry between 2013 and 2018. The patients were divided into 2 treatment groups: surgical and medical. Multivariable logistic regression was used to examine the association between sex and in-hospital mortality.

RESULTS In the entire cohort, women were older and more likely to have hyperlipidemia, previous stroke, altered consciousness, and shock/hypotension at presentation than men. Women had higher proportions of intramural hematomas and type II dissections than men. In the surgical group (n = 2,543), men had higher rates of preoperative end-organ malperfusion ($P = 0.003$) and in-hospital mortality ($P = 0.002$) than women. Multivariable analysis revealed that male sex was associated with higher in-hospital mortality after surgery (OR: 1.71; 95% CI: 1.24-2.35; $P < 0.001$). In the medical group (n = 546), women were older and had higher rates of cardiac tamponade ($P = 0.004$) and in-hospital mortality ($P = 0.039$) than men; no significant association between sex and in-hospital mortality was found after multivariable adjustment (OR: 0.95; 95% CI: 0.56-1.59; $P = 0.832$).

CONCLUSIONS Male sex was associated with higher in-hospital mortality for type I/II AAD in the surgical group but not in the medical group. Further research is needed to understand the mechanisms responsible for worse surgical outcomes in men. (JACC Adv 2023;2:100661) © 2023 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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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AAD = acute aortic dissection

CCU = cardiovascular care unit

CT = computed tomography

HD = hemodialysis

IMH = intramural hematoma

IRAD = International Registry of Acute Aortic Dissection

Despite recent diagnostic and therapeutic advances, acute aortic dissection (AAD) remains a life-threatening condition associated with high morbidity and mortality rates.[1] AAD involving the ascending aorta, DeBakey type I or II (or Stanford type A), requires urgent intensive treatment, including surgical aortic repair.

Female sex is reported to be associated with poorer outcomes after surgery for DeBakey type I/II AAD according to cohort studies from the International Registry of Acute Aortic Dissection (IRAD).[2,3] However, other studies have shown conflicting results on the association between sex and type I/II AAD outcomes.[4-9] No significant association of sex with operative mortality related to type I/II AAD was documented in some studies,[4-8] whereas another study showed that men had higher rates of operative mortality associated with more extensive surgical procedures than women.[9] Furthermore, most studies on sex differences in type I/II AAD were conducted among patients who underwent surgical repair but not among patients who were medically managed.[3-9] Patients who are deemed fit for surgery but die before reaching the operating room have not been included in such studies. In real-life clinical practice, many patients with type I/II AAD are medically managed because they are considered at high operative risk owing to advanced age and comorbidities. Accordingly, treatment-specific sex differences in the clinical presentation and outcomes of type I/II AAD remain poorly understood. It is unclear whether sex is associated with in-hospital outcomes of patients with type I/II AAD according to treatment.

In this study, we assessed the sex-related differences in clinical presentation and in-hospital outcomes, particularly mortality, in surgically or medically treated patients with type I/II AAD using our multicenter AAD registry data.

METHODS

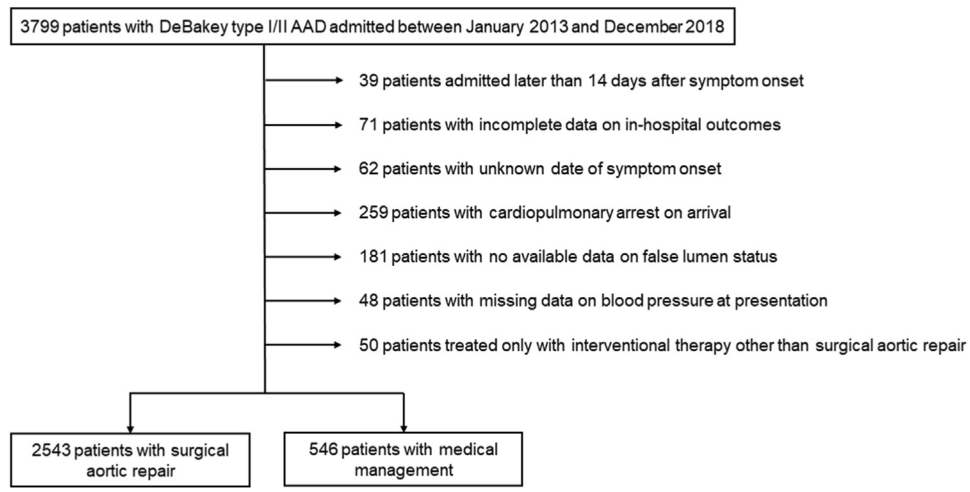
AORTIC NETWORK AND DATABASE. The Tokyo Cardiovascular Care Unit (CCU) Network is an emergent transfer system for patients with all types of cardiovascular diseases that covers the entire Tokyo metropolitan region except the island areas.[10,11] As reported previously,[12-15] we inaugurated the Tokyo Acute Aortic Super-network in November 2010, established based on the Tokyo CCU Network, to develop an effective and safe transfer system for patients with AAD and ruptured aortic aneurysm using ambulance units through the control room of the Tokyo Fire Department. Detailed data of all patients treated in their emergency departments, cardiovascular surgery departments, and CCUs are routinely recorded and submitted to the data management center on specific survey forms.

ETHICS STATEMENTS. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research of the Japanese government. The study was approved by the Institutional Review Boards of the Tokyo CCU Network Scientific Committee and the Tokyo Saiseikai Central Hospital. According to the guidelines, the study satisfied the conditions for waiving informed consent from individual participants.

STUDY POPULATION AND DESIGN. We used the data from 3,799 consecutive patients who were hospitalized for DeBakey type I/II AAD between January 2013 and December 2018 and enrolled in our multicenter AAD registry database. The exclusion criteria were as follows: patients who were admitted later than 14 days after symptom onset (n = 39); patients with no available data on mortality (n = 71); patients with unknown date of symptom onset (n = 62); patients with cardiopulmonary arrest on arrival (n = 259); patients with no available data on false lumen status (n = 181); patients with missing data on blood pressure at presentation (n = 48); and patients who were treated only with thoracic endovascular aortic repair or other interventional techniques such as branch stenting, bypass, and fenestration (n = 50). Finally, 3,089 remaining patients were divided into the following treatment groups: surgical (n = 2,543) and medical (n = 546) (**Figure 1**). The clinical characteristics and in-hospital outcomes were assessed and compared between both sexes in the entire cohort and subsequently in each treatment group.

DEFINITIONS OF AORTIC DISSECTION AND OTHER BASELINE VARIABLES. Classic aortic dissection is characterized by a separation of the aortic wall layers with an intimal tear, creating a dissection flap that divides the true from the false lumen. We classified AAD with a patent or partially thrombosed false lumen as classic aortic dissection and AAD with a completely thrombosed false lumen as an intramural hematoma (IMH) according to the computed tomography (CT) findings. Aortic dissections with ulcer-like projection in the thrombosed false lumen on CT imaging were included in the IMH group as previously reported.[14,15] AAD was categorized into type I, II, or III according to the DeBakey classification.

FIGURE 1 **Flowchart of Patient Selection**



AAD = acute aortic dissection.

Altered consciousness was defined as a Glasgow Coma Scale score of ≤14 or a Japan Coma Scale score of >1, as previously reported.[14] Hypotension was defined as systolic blood pressure <90 mm Hg at presentation. Cardiac arrest was defined as circulatory collapse associated with loss of consciousness, absence of spontaneous respiration, and loss of central pulsation that required a period of cardiopulmonary resuscitation. The cause of out-of-hospital cardiac arrest was evaluated at the time of admission.

DEFINITION OF OUTCOMES. The primary outcomes of interest were in-hospital mortality and/or 30-day mortality. To obtain the data on 30-day mortality, patients were followed after hospital discharge, although 41 patients were lost to follow-up. The secondary outcome of interest was major complications during the hospital admission including cardiac tamponade, aortic rupture, and end-organ malperfusion. Cardiac tamponade was defined as blood in the pericardium that clinically affected the heart's hemodynamic performance. Aortic rupture was detected on CT imaging or postmortem examination. End-organ malperfusion was defined as any organ ischemia associated with aortic branch vessel hypoperfusion, including cerebral, myocardial, renal, mesenteric, spinal, or limb ischemia. Malperfusion was diagnosed based on clinical symptoms and signs as previously reported.[13]

STATISTICAL ANALYSIS. Categorical variables are expressed as the number of patients (%). Continuous variables were presented as mean ± SD or as median (IQR) if the distribution was skewed. The chi-squared or Fisher's exact test was performed to compare categorical variables. The unpaired Student's *t*-test or Mann-Whitney U test was performed to compare continuous variables. Multivariable logistic regression analysis was performed to assess the association of male sex with in-hospital mortality in the entire cohort and each treatment group. Variable selection was based on the findings from previous studies,[1,13,14] clinically relevant variables, including age, sex, and other baseline characteristics. Collinearity was considered as needed. We also assessed the associations of male sex with major complications (cardiac tamponade, aortic rupture, and end-organ malperfusion) in the entire cohort and surgical treatment group by multivariable logistic regression analysis. Clinically relevant variables were selected as potential risk factors for these complications.

Additionally, we performed the analysis only in the subgroup of patients with classic aortic dissection because the clinical features and outcomes of IMH were distinct from those of aortic dissection.[16] A 2-sided *P* value of <0.05 was considered statistically significant. *P* values and 95% CIs have not been adjusted for multiple comparisons; therefore, inferences drawn from these statistics should be interpreted with caution. All statistical analyses were performed using SPSS version 29 (IBM Corp).

TABLE 1 Baseline Characteristics of the Entire Cohort

	Total (N = 3,089)	Men (n = 1,626)	Women (n = 1,463)	P Value
Age (y)	70 (58-79)	62 (52-73)	76 (67-83)	<0.001
Hypertension	2,175 (70.4)	1,139 (70.0)	1,036 (70.8)	0.642
Hyperlipidemia	767 (24.8)	360 (22.1)	407 (27.8)	<0.001
Diabetes mellitus	259 (8.4)	128 (7.9)	131 (9.0)	0.279
Previous coronary artery disease	110 (3.6)	58 (3.6)	52 (3.6)	0.985
Previous stroke	217 (7.0)	96 (5.9)	121 (8.3)	0.010
Previous peripheral artery disease	20 (0.6)	10 (0.6)	10 (0.7)	0.813
History of heart failure admission	57 (1.8)	21 (1.3)	36 (2.5)	0.016
End-stage renal disease on HD	52 (1.7)	24 (1.5)	28 (1.9)	0.345
Time from onset to admission				0.402
<24 h	2,840 (91.9)	1,501 (92.3)	1,339 (91.5)	
1-6 d	200 (6.5)	97 (6.0)	103 (7.0)	
7-14 d	49 (1.6)	28 (1.7)	21 (1.4)	
Back pain	1,062 (34.4)	597 (36.7)	465 (31.8)	0.004
Chest pain	1,716 (55.6)	960 (59.0)	756 (51.7)	<0.001
Abdominal pain	160 (5.2)	84 (5.2)	76 (5.2)	0.971
Lumbago	98 (3.2)	59 (3.6)	39 (2.7)	0.127
Dyspnea	129 (4.2)	68 (4.2)	61 (4.2)	0.986
Altered consciousness	809 (26.2)	374 (23.0)	435 (29.7)	<0.001
Shock/hypotension	688 (22.3)	336 (20.7)	352 (24.1)	0.024
Cardiac arrest at admission	94 (3.0)	53 (3.3)	41 (2.8)	0.460
Systolic blood pressure (mm Hg)	124 (102-147)	129 (106-151)	120 (100-141)	<0.001
Heart rate (beats/min)	75 (62-90)	75 (63-90)	74 (62-89)	0.142
Status of the false lumen				<0.001
Classic aortic dissection	2,122 (68.7)	1,173 (72.1)	949 (64.9)	
IMH	967 (31.3)	453 (27.9)	514 (35.1)	
DeBakey classification				<0.001
Type I	2,565 (83.0)	1,413 (86.9)	1,152 (78.7)	
Type II	524 (17.0)	213 (13.1)	311 (21.3)	

Values are median (IQR) or n (%). Chi-squared test or Fisher's exact test was performed to compare categorical variables, and the Mann-Whitney U test was performed to compare continuous variables.
HD = hemodialysis; IMH = intramural hematoma.

RESULTS

BASELINE CHARACTERISTICS. The baseline characteristics of the entire cohort are summarized in Table 1. The median age of the patients was 70 (IQR: 58-79) years, and 1,463 (47.4%) patients were women. Women were significantly older than men (76 [IQR: 67-83] years vs 62 [IQR: 52-73] years; $P < 0.001$). The proportion of men and women by decade of age is shown in Figure 2. More women from the older age groups were admitted than women from the younger age groups, with 72.8% of patients aged ≥80 years and only 12.5% of patients aged <50 years being women. Compared with men, women were more likely to have hyperlipidemia (27.8% vs 22.1%; $P = 0.001$), a history of stroke (8.3% vs 5.9%; $P = 0.010$), and heart failure admission (2.5% vs 1.3%; $P = 0.016$). Women were less likely to present with back pain (27.3% vs 36.7%; $P = 0.004$) and chest pain (51.7% vs 59.9%; $P < 0.001$) and more likely to have altered consciousness (29.7% vs 23.0%; $P < 0.001$) and shock/hypotension (24.1% vs 20.7%; $P = 0.024$) than men. The median systolic blood pressure at presentation was lower in women than in men (120 mm Hg vs 129 mm Hg; $P < 0.001$). Additionally, women had higher proportions of IMH (35.1% vs 27.9%; $P < 0.001$) and DeBakey type II dissections (21.3% vs 13.1%; $P < 0.001$) than men (Central Illustration). In the subgroup of classic aortic dissection, sex differences in baseline characteristics were similarly found (Supplemental Table 1).

The baseline characteristics of the surgical and medical groups are summarized in Supplemental Tables 2 and 3. Women were significantly older than men in both groups ($P < 0.001$). Compared with men, women in the surgical group were more likely to have hyperlipidemia and a history of stroke, but not so in the medical group. In the medical group, women were more likely to have a history of heart failure admission than men, but not so in the surgical group. Compared with women, men in the surgical group were more likely to present with chest pain, and those in the medical group with back pain. Women in the surgical group were more likely to have altered consciousness than men, but not so in the medical group. In both groups, women were more likely to have shock/hypotension with a lower median systolic blood pressure at presentation than men. As seen in the entire cohort, women in the surgical group had higher proportions of IMH and DeBakey type II dissections than men.

IN-HOSPITAL OUTCOMES. Table 2 shows the in-hospital management and outcomes of the entire cohort. Women were more likely to be medically managed than men (20.7% vs 14.9%; $P < 0.001$). There were no significant differences in in-hospital mortality (14.4% vs 14.4%; $P = 0.980$) and the 30-day mortality (13.1% [211/1,609] vs 13.2% [190/1,439]; $P = 0.942$) between men and women. During hospitalization, women had higher frequencies of cardiac tamponade (20.6% vs 16.4%; $P = 0.003$) and aortic rupture (5.5% vs 3.9%; $P = 0.036$) than men. Men had a higher frequency of end-organ malperfusion (19.2% vs 13.9%; $P < 0.001$), including renal and limb ischemia, than women. In the subgroup of classic aortic dissection, sex differences in in-hospital management and outcomes were similarly found (Supplemental Table 4).

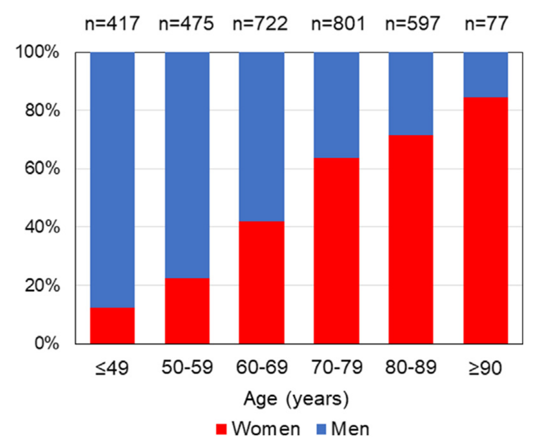
Supplemental Table 5 shows the in-hospital management and outcomes of the surgical group. In-hospital mortality was significantly higher in men than in women (11.6% vs 7.9%; $P = 0.002$) (**Central Illustration**), although women had longer lengths of hospital stay. The 30-day mortality was also higher in men than in women (10.2% [139/1,368] vs 6.7% [76/1,141]; $P = 0.002$). During hospitalization, preoperative cardiac tamponade occurred more frequently in women than in men (14.4% vs 11.6%; $P = 0.034$). Men had a higher frequency of preoperative end-organ malperfusion, including limb ischemia, than women (12.0% vs 8.4%; $P = 0.003$). Postoperative renal ischemia occurred more frequently in men than in women (1.8% vs 0.7%, $P = 0.013$).

Supplemental Table 6 shows the in-hospital management and outcomes of the medical group. Regarding the reasons for medical management, men were more likely to die before surgery and to receive an initial medical treatment strategy for IMH than women. In contrast, women tended to refuse surgery more than men. In-hospital mortality was significantly higher in women than in men (38.9% vs 30.5%; $P = 0.039$) (**Central Illustration**). The 30-day mortality was also higher in women than in men (39.6% [118/298] vs 30.3% [73/241]; $P = 0.025$). During hospitalization, women had a higher frequency of cardiac tamponade than men (23.8% vs 14.0%; $P = 0.004$), whereas men had a higher frequency of myocardial ischemia than women (5.3% vs 2.0%; $P = 0.033$). There were no differences in the rates of other in-hospital complications related to AAD between the sexes.

MULTIVARIABLE ANALYSES OF IN-HOSPITAL MORTALITY AND COMPLICATIONS. In the entire cohort, multivariable logistic regression analysis revealed that male sex was associated with a higher risk of in-hospital mortality (OR: 1.40; 95% CI: 1.08-1.82; $P = 0.011$) (**Table 3**, **Central Illustration**). A history of hypertension was associated with a lower risk of in-hospital mortality. In contrast, age, a history of heart failure admission, altered consciousness, shock/hypotension, cardiac arrest at admission, DeBakey type I, classic aortic dissection, end-organ malperfusion, and medical treatment were associated with a higher risk of in-hospital mortality (**Table 3**). The multivariable analysis performed in the subgroup of classic aortic dissection also showed that male sex was associated with a higher risk of in-hospital mortality (OR: 1.63; 95% CI: 1.12-2.08; $P = 0.006$) (Supplemental Table 7).

In the surgical group, multivariable logistic regression analysis revealed that male sex was associated with a higher risk of in-hospital mortality (OR: 1.71; 95% CI: 1.24-2.35; $P < 0.001$) (**Table 4**, **Central Illustration**). Similar to the results from the analysis of the entire cohort, a history of hypertension was associated with a lower risk of in-hospital mortality. In contrast, age, a history of heart failure admission, dyspnea, altered consciousness, shock/hypotension, cardiac arrest at admission, DeBakey type I, classic aortic dissection, and preoperative end-organ malperfusion were associated with a higher risk of in-hospital mortality (**Table 4**, **Figure 3A**). The multivariable analysis performed in the subgroup of classic aortic dissection also showed that male sex was associated with a higher risk of in-hospital mortality (OR: 1.65; 95% CI: 1.17-2.34; $P = 0.004$) (Supplemental Table 8).

FIGURE 2 Proportion of Men and Women by a Decade of Age

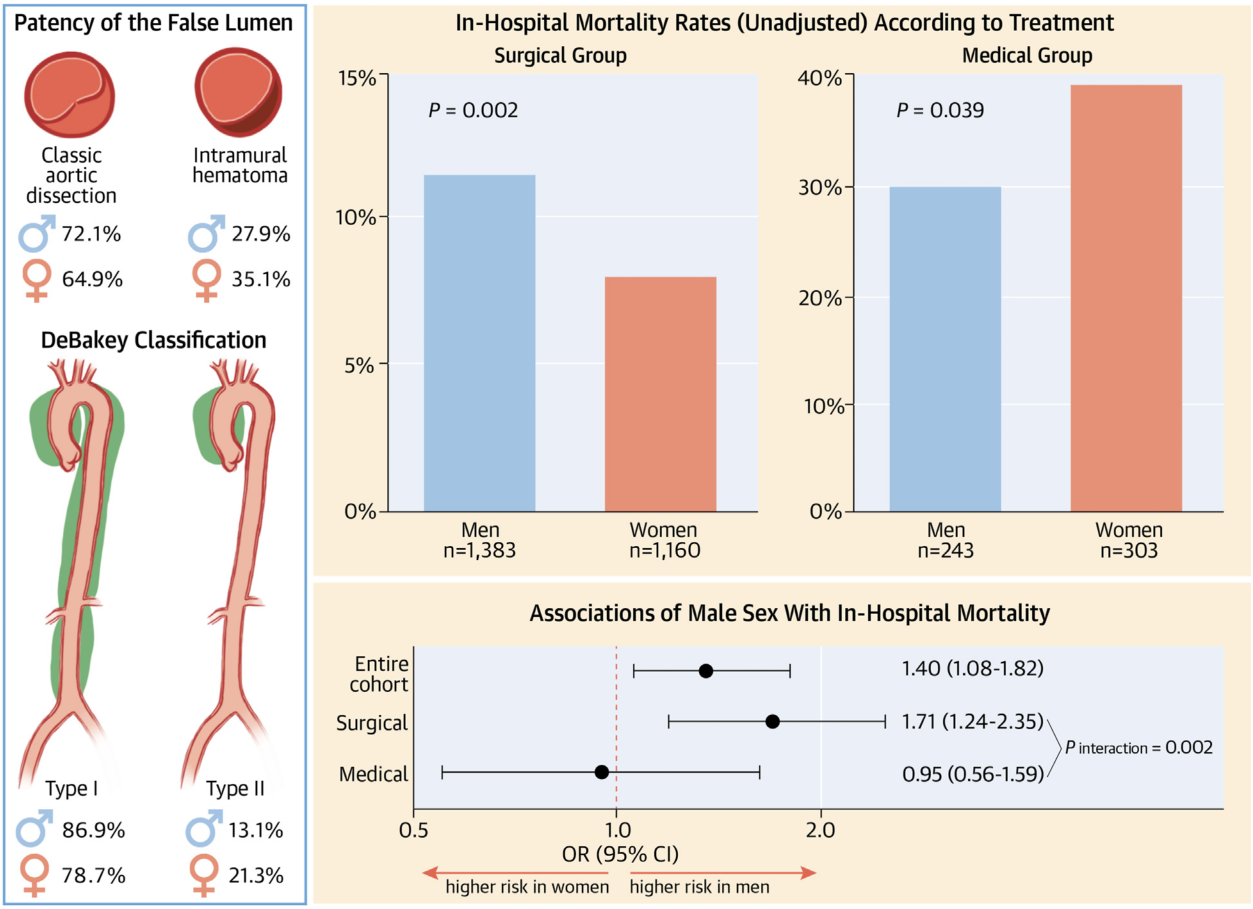


More women from the older age groups were admitted than women from the younger age groups in the entire cohort.

In the medical group, multivariable logistic regression analysis revealed that age, altered consciousness, shock/hypotension, classic aortic dissection, and end-organ malperfusion were associated with a higher risk of in-hospital mortality, whereas male sex was not significantly associated with in-hospital mortality (OR: 0.95; 95% CI: 0.56-1.59; $P = 0.832$) (**Table 5**, **Figure 3B**, **Central Illustration**).

In the entire cohort, multivariable analyses revealed that male sex was not significantly associated with cardiac tamponade and aortic rupture. However, male sex was associated with a higher risk of end-organ malperfusion (**Table 6**). There were no significant associations between sex and any major preoperative complications in the surgical group (Supplemental Table 9).

CENTRAL ILLUSTRATION Sex Differences in In-Hospital Mortality of Type I/II AAD in the Surgical and Medical Treatment Groups



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After multivariable adjustment, male sex was associated with a higher risk of in-hospital mortality for type I/II AAD in the surgical group but not in the medical group. AAD = acute aortic dissection.

DISCUSSION

In the present study, we assessed sex differences in clinical presentation and in-hospital outcomes according to treatment among patients with DeBakey type I/II AAD using our registry data. The main findings from our study were as follows: 1) women presented at an older age were more likely to have hyperlipidemia, a history of stroke and heart failure admission, altered consciousness and shock/hypotension at presentation, and had higher proportions of IMH and less extensive (type II) dissections than men; 2) men had higher rates of preoperative end-organ malperfusion and operative mortality than women; 3) women were older and had a higher frequency of cardiac tamponade than men in the medical group; and 4) male sex was associated with higher in-hospital mortality in the surgical group but not in the medical group.

Sex differences in clinical features and outcomes of AAD have been disputed even in the contemporary era. An earlier study from the IRAD demonstrated that women had poorer outcomes after surgery for type I/II AAD than men.[2] Furthermore, the IRAD study group recently reported a trend toward higher in-hospital mortality in women but not in the last decade of enrollment.[3] Other studies have reported conflicting results, showing no significant association of sex with operative mortality of type I/II AAD.[4-8] A meta-analysis study by Lawrence et al[17] showed that female sex was not associated with an increased risk of short-term mortality or with major postoperative complications among patients treated surgically for type I/II AAD and that male sex was associated with a greater risk of postoperative bleeding. A more updated meta-analysis study by Carbone et al[18] also demonstrated that in-hospital surgical mortality did not differ between sexes, whereas 5- and 10-y survival rates were higher among men.

Contrary to these findings, we found that male sex was associated with a higher in-hospital mortality rate after surgical repair for type I/II AAD in this study. This result is consistent with that of a previous report which showed that men had higher operative mortality associated with more extensive surgical procedures than women.[9] However, there were no available data on types of surgical procedures and postoperative bleeding complications in our study. Men possibly had more extensive surgical procedures than women because men had higher frequencies of classic aortic dissections, more extensive (type I) dissections, and preoperative end-organ malperfusion than women. Rylski et al[8] showed that both men and women with type I/II AAD had similar involvement of the aortic arch and arch branch vessels; however, men had a greater extent of dissection into the descending thoracic and abdominal aorta, and men had more spinal, visceral, and renal malperfusion. Although they did not show a significant difference in mortality between the sexes, men may be more susceptible than women to an extension of dissection into the descending thoracic and abdominal aorta, leading to more distal malperfusion.

The pathogenic process of aortic disease may differ between the sexes owing to hormonal, molecular, and hemodynamic differences, although the pathophysiologic mechanisms remain unknown. In this study, women presented at an older age and had higher proportions of IMH and type II dissections than men. Additionally, we previously reported that women were older and had more IMH than men among those with type III (or Stanford type B) AAD.[15] These findings indicate that a higher prevalence of IMH in women may be associated with age-related increased stiffness of the aortic wall, leading to a limited extension of the dissection. Compared with patients with classic aortic dissection, those with IMH have been reported to be older,[19-22] have a greater intima-media thickness,[23] experience dissection with limited extension to the supraceliac aorta more frequently, and exhibit lower incidences of leg ischemia and renal failure.[21,24] Patients with IMH have more favorable outcomes than those with classic aortic dissection, irrespective of DeBakey type I/II or III.[25-28] It is widely accepted, especially in Asian countries, that uncomplicated IMH without risk factors of fatal events can be medically managed with close follow-up tests during the acute phase.[16,26,29] In the present study, compared with IMH, classic aortic dissection was associated with a higher in-hospital mortality rate in surgical and medical groups.

TABLE 2 In-hospital Management and Outcomes in the Entire Cohort

	Total (N = 3,089)	Men (n = 1,626)	Women (n = 1,463)	*P* Value
Treatment				<0.001
Surgical	2,543 (82.3)	1,383 (85.1)	1,160 (79.3)	
Medical	546 (17.7)	243 (14.9)	303 (20.7)	
In-hospital mortality	445 (14.4)	234 (14.4)	211 (14.4)	0.980
Length of hospital stay (d)	20 (12-32)	20 (12-31)	21 (12-34)	0.505
In-hospital complications				
Cardiac tamponade	568 (18.4)	267 (16.4)	301 (20.6)	0.003
Aortic rupture	145 (4.7)	64 (3.9)	81 (5.5)	0.036
End-organ malperfusion	516 (16.7)	312 (19.2)	204 (13.9)	<0.001
Cerebral ischemia	216 (7.0)	115 (7.1)	101 (6.9)	0.854
Myocardial ischemia	105 (3.4)	59 (3.6)	46 (3.1)	0.458
Renal ischemia	72 (2.3)	52 (3.2)	20 (1.4)	<0.001
Mesenteric ischemia	52 (1.7)	34 (2.1)	18 (1.2)	0.063
Spinal cord ischemia	33 (1.1)	23 (1.4)	11 (0.8)	0.078
Limb ischemia	155 (5.0)	107 (6.6)	48 (3.3)	<0.001

Values are n (%) or median (IQR). Chi-squared test or Fisher's exact test was performed. Mann-Whitney U test was performed to compare continuous variables.

Similar to previous reports,[1,2,30] the in-hospital mortality of patients with type I/II AAD treated medically was higher than that of those treated surgically in this study. However, in the medical group, we found no significant association between sex and in-hospital mortality after multivariable adjustment. In this group, men were more likely to have IMH and be medically managed as an initial treatment strategy than women. In contrast, women were older and had a history of heart failure admission and shock/hypotension more frequently than men. In addition, women tended to refuse surgery more than men. Regarding in-hospital complications, women had cardiac tamponade more frequently than men, whereas men had myocardial ischemia more frequently than women. As these complications are believed to be fatal without any prompt

TABLE 3 Univariable and Multivariable Analyses for In-Hospital Mortality in the Entire Cohort

	Univariable Analysis (n = 3,089)			Multivariable Analysis (n = 3,089)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age (y)	1.03	1.02-1.04	<0.001	**1.02**	**1.01-1.03**	**0.001**
Male	1.00	0.82-1.23	0.980	**1.40**	**1.08-1.82**	**0.011**
Hypertension	0.61	0.49-0.75	<0.001	**0.61**	**0.48-0.79**	**<0.001**
Hyperlipidemia	0.76	0.60-0.97	0.029	1.04	0.78-1.39	0.808
Diabetes	1.06	0.74-1.51	0.755	1.13	0.74-1.71	0.579
Previous coronary artery disease	1.25	0.76-2.07	0.384	0.99	0.76-1.79	0.971
Previous stroke	1.24	0.86-1.80	0.251	0.91	0.59-1.40	0.655
Previous peripheral artery disease	1.05	0.31-3.59	0.940	1.00	0.23-4.29	0.999
History of heart failure admission	2.59	1.45-4.60	0.001	**2.10**	**1.05-4.35**	**0.045**
End-stage renal disease on HD	1.08	0.51-2.31	0.839	1.36	0.58-3.21	0.482
Time from onset to admission >24 h	0.58	0.38-0.91	0.017	0.89	0.55-1.46	0.645
Back pain	0.62	0.50-0.78	<0.001	0.91	0.70-1.18	0.469
Chest pain	0.70	0.57-0.85	<0.001	1.20	0.94-1.54	0.146
Abdominal pain	1.28	0.84-1.95	0.253	1.49	0.91-2.42	0.112
Lumbago	1.26	0.74-2.14	0.400	1.71	0.94-3.13	0.080
Dyspnea	1.61	1.04-2.49	0.033	1.57	0.94-2.62	0.085
Altered consciousness	4.27	3.47-5.26	<0.001	**2.45**	**1.88-3.18**	**<0.001**
Shock/hypotension	3.21	2.60-3.97	<0.001	**2.18**	**1.67-2.85**	**<0.001**
Cardiac arrest at admission	8.99	5.89-13.7	<0.001	**4.31**	**2.62-7.09**	**<0.001**
DeBakey type I[a]	1.23	0.93-1.63	0.153	**1.51**	**1.08-2.11**	**0.017**
Classic aortic dissection[b]	2.12	1.65-2.72	<0.001	**3.57**	**2.62-4.86**	**<0.001**
End-organ malperfusion	2.93	2.26-3.81	<0.001	**1.85**	**1.36-2.54**	**<0.001**
Medical treatment[c]	4.97	4.00-6.18	<0.001	**7.52**	**5.57-10.20**	**<0.001**

Number of events (in-hospital mortality) = 445. Clinically relevant variables related to baseline characteristics and conditions at admission were selected as potential risk factors for in-hospital mortality. All the variables shown in the above table were entered in the multivariable model. The **bold** values indicate statistically significant associations in the multivariable analysis. [a]DeBakey type II as a reference. [b]Intramural hematoma as a reference. [c]Surgical treatment as a reference.

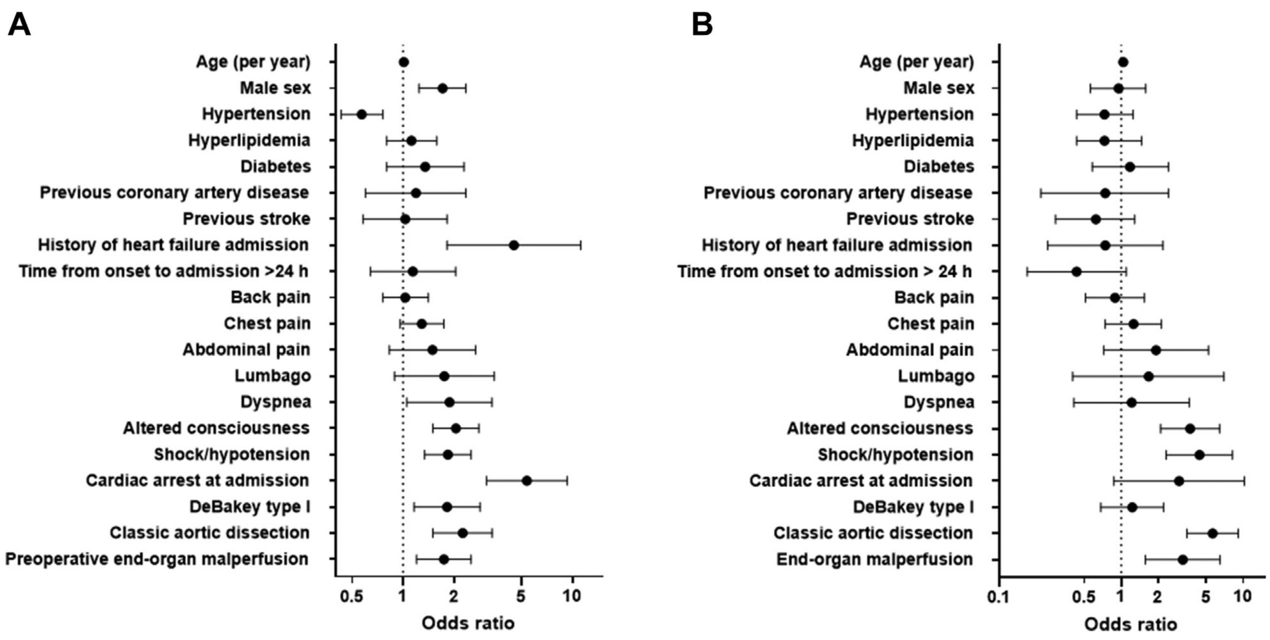
HD = hemodialysis.

TABLE 4 Univariable and Multivariable Analyses for In-Hospital Mortality in the Surgical Group

	Univariable Analysis (n = 2,543)			Multivariable Analysis (n = 2,543)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age (y)	1.00	0.99-1.01	0.872	**1.01**	**1.00-1.03**	**0.037**
Male	1.52	1.16-1.99	0.002	**1.71**	**1.24-2.35**	**<0.001**
Hypertension	0.55	0.42-0.72	<0.001	**0.57**	**0.43-0.76**	**<0.001**
Hyperlipidemia	0.87	0.64-1.18	0.368	1.12	0.80-1.58	0.507
Diabetes	1.14	0.70-1.85	0.594	1.35	0.80-2.29	0.260
Previous coronary artery disease	1.50	0.80-2.80	0.205	1.19	0.60-2.35	0.627
Previous stroke	1.00	0.58-1.70	0.988	1.03	0.58-1.82	0.920
History of heart failure admission	2.58	1.11-6.03	0.028	**4.51**	**1.82-11.2**	**0.001**
Time from onset to admission >24 h	0.72	0.42-1.25	0.245	1.14	0.64-2.04	0.654
Back pain	0.83	0.63-1.10	0.201	1.03	0.76-1.41	0.842
Chest pain	0.98	0.76-1.28	0.898	1.29	0.96-1.74	0.093
Abdominal pain	1.43	0.85-2.43	0.181	1.49	0.83-2.68	0.182
Lumbago	1.81	0.98-3.32	0.057	1.75	0.89-3.45	0.107
Dyspnea	1.83	1.07-3.14	0.027	**1.88**	**1.05-3.35**	**0.034**
Altered consciousness	2.82	2.16-3.69	<0.001	**2.05**	**1.50-2.80**	**<0.001**
Shock/hypotension	2.86	2.18-3.74	<0.001	**1.84**	**1.34-2.52**	**<0.001**
Cardiac arrest at admission	10.1	6.15-16.4	<0.001	**5.39**	**3.11-9.32**	**<0.001**
DeBakey type I[a]	1.76	1.17-2.67	0.007	**1.82**	**1.16-2.85**	**0.009**
Classic aortic dissection[b]	2.55	1.74-3.73	<0.001	**2.25**	**1.50-3.36**	**<0.001**
Preoperative end-organ malperfusion	2.63	1.88-3.67	<0.001	**1.74**	**1.20-2.52**	**0.003**

Number of events (in-hospital mortality) = 252. Clinically relevant variables related to baseline characteristics and preoperative conditions were selected as potential risk factors for in-hospital mortality. All the variables shown in the above table were entered in the multivariable model. The **bold** values indicate statistically significant associations in the multivariable analysis. [a]DeBakey type II as a reference. [b]Intramural hematoma as a reference.

FIGURE 3 Variables Associated With In-Hospital Mortality of DeBakey Type I/II Acute Aortic Dissection



Forest plots depict the adjusted odds ratios for in-hospital mortality. (A) In the surgical group, a history of hypertension was associated with a lower risk of in-hospital mortality. In contrast, age, male, a history of heart failure admission, dyspnea, altered consciousness, shock/hypotension, cardiac arrest at admission, DeBakey type I, classic aortic dissection, and preoperative end-organ malperfusion were associated with a higher risk of in-hospital mortality. (B) In the medical group, age, altered consciousness, shock/hypotension, classic aortic dissection, and end-organ malperfusion were associated with a higher risk of in-hospital mortality. In contrast, male sex was not significantly associated with in-hospital mortality. Odds ratios and 95% confidence intervals are plotted in log-scale.

interventions, sex-specific risk assessment and management for type I/II AAD is essential.

STUDY LIMITATIONS. First, this study was observational; therefore, unmeasured confounders that affect mortality might be present. Second, our AAD registry includes data from all-comers with type I/II AAD in the urban Tokyo metropolitan area, where the aging of the population is more advanced than in other countries. Because geographic differences in management and outcomes for AAD exist,[31] our results may not be extrapolated to other regions. Third, it is important to note that the analysis in the present study did not incorporate adjustments for the study site to account for potential differences in care standards and practices across the participating sites. Although surgical treatment at high-volume centers was reported to be associated with reduced mortality in patients with AAD,[32] our previous study showed no significant difference in in-hospital mortality between the high- and low-volume centers in our aortic network.[14] Further investigation is warranted to elucidate any potential sex-related differences in the outcomes of AAD across the various participating center. Fourth, it is important to note that a portion of the outcome data, such as those presented in Table 2, comprises results from crude analyses that have not been adjusted for the baseline differences between sexes. Therefore, it is imperative to interpret these findings with caution. Fifth, in some patients transferred from another hospital, no detailed data were obtained at the initial hospital. In such cases, we used only clinical data obtained at the hospital where patients were treated finally. Sixth, long-term outcomes were not assessed in this study. Further investigation is warranted to confirm sex differences in long-term outcomes. Lastly, no specific data on the different surgical techniques were available, which could affect outcomes in surgically treated patients. Further studies are needed to clarify sex differences in the surgical type and complications associated with postoperative outcomes in patients with type I/II AAD.

Despite these limitations, we believe that our data from the large Japanese AAD registry will provide useful information on the management of patients with type I/II AAD and insightful perspectives on sex differences in AAD.

TABLE 5 Univariable and Multivariable Analyses for In-Hospital Mortality in the Medical Group

	Univariable Analysis (n = 546)			Multivariable Analysis (n = 546)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age (y)	1.04	1.02-1.05	<0.001	**1.04**	**1.01-1.06**	**0.003**
Male	0.69	0.48-0.98	0.039	0.95	0.56-1.59	0.832
Hypertension	0.64	0.43-0.93	0.020	0.73	0.43-1.25	0.255
Hyperlipidemia	0.53	0.35-0.82	0.004	0.82	0.45-1.47	0.490
Diabetes	0.55	0.32-0.95	0.033	1.18	0.58-2.44	0.645
Previous coronary artery disease	0.75	0.31-1.84	0.530	0.74	0.22-2.44	0.616
Previous stroke	1.16	0.65-2.05	0.621	0.62	0.29-1.29	0.199
History of heart failure admission	1.24	0.55-2.82	0.605	0.74	0.25-2.20	0.591
Time from onset to admission >24 h	0.32	0.15-0.70	0.004	0.43	0.17-1.10	0.079
Back pain	0.30	0.20-0.45	<0.001	0.89	0.51-1.55	0.675
Chest pain	0.66	0.46-0.95	0.024	1.26	0.74-2.14	0.389
Abdominal pain	0.92	0.44-1.93	0.820	1.93	0.72-5.19	0.193
Lumbago	0.52	0.17-1.59	0.250	1.68	0.40-6.95	0.477
Dyspnea	1.24	0.55-2.81	0.610	1.22	0.41-3.61	0.726
Altered consciousness	8.11	5.45-12.1	<0.001	**3.68**	**2.11-6.40**	**<0.001**
Shock/hypotension	8.87	5.49-14.3	<0.001	**4.38**	**2.34-8.19**	**<0.001**
Cardiac arrest at admission	8.09	2.99-21.9	<0.001	2.98	0.87-10.2	0.082
DeBakey type I[a]	0.81	0.52-1.27	0.362	1.23	0.68-2.22	0.497
Classic aortic dissection[b]	7.58	5.10-11.3	<0.001	**5.62**	**3.46-9.11**	**<0.001**
End-organ malperfusion	4.32	2.54-7.34	<0.001	**3.20**	**1.58-6.48**	**0.001**

Number of events (in-hospital mortality) = 192. Clinically relevant variables related to baseline characteristics and conditions at admission were selected as potential risk factors for in-hospital mortality. All the variables shown in the above table were entered in the multivariable model. The **bold** values indicate statistically significant associations in the multivariable analysis. [a]DeBakey type II as a reference. [b]Intramural hematoma as a reference.

CI = confidence interval; OR = odds ratio.

CONCLUSIONS

Our registry data indicated that male sex was associated with higher in-hospital mortality after surgical repair for type I/II AAD but not after medical treatment. Despite presenting at an older age, women had more favorable postoperative outcomes than men. Further research is needed to clarify the underlying mechanisms for worse postoperative outcomes in men than in women.

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TABLE 6 Multivariable Logistic Regression Analyses for Major Complications in the Entire Cohort

	Cardiac Tamponade (n = 568)			Aortic Rupture (n = 145)			End-Organ Malperfusion (n = 516)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age (y)	1.02	1.01-1.03	<0.001	1.05	1.03-1.06	<0.001	0.99	0.98-1.00	0.018
Male	0.92	0.75-1.12	0.398	1.14	0.79-1.65	0.494	1.26	1.02-1.57	0.034
Hypertension	0.82	0.67-1.00	0.055	0.77	0.53-1.11	0.156	0.74	0.60-0.91	0.005
Hyperlipidemia	0.76	0.61-0.96	0.023	1.30	0.88-1.94	0.193	0.81	0.64-1.03	0.090
Diabetes	0.81	0.56-1.16	0.253	0.39	0.17-0.91	0.030	1.10	0.78-1.59	0.561
Previous coronary artery disease	1.46	0.92-2.31	0.108	0.70	0.27-1.79	0.451	1.77	1.11-2.82	0.016
Previous stroke	1.47	1.06-2.04	0.022	1.41	0.80-2.48	0.232	1.19	0.82-1.72	0.368
Previous peripheral artery disease	0.74	0.21-2.59	0.642	3.68	1.02-13.3	0.046	4.11	1.63-10.3	0.003
History of heart failure admission	0.65	0.31-1.36	0.255	1.56	0.60-4.08	0.361	1.05	0.50-2.19	0.903
End-stage renal disease on HD	1.20	0.62-2.34	0.584	1.54	0.54-4.44	0.423	1.45	0.74-2.82	0.277
Time from onset to admission >24 h	0.52	0.35-0.79	0.002	0.48	0.21-1.11	0.088	0.74	0.50-1.10	0.136
Classic aortic dissection[a]	1.34	1.09-1.66	0.006	1.90	1.27-2.84	0.002	1.69	1.34-2.14	<0.001
DeBakey type I[b]	0.80	0.63-1.02	0.069	1.06	0.68-1.65	0.807	1.02	0.78-1.34	0.881

Sample size = 3,089 in each analysis. Clinically relevant variables were selected as potential risk factors for the complications (cardiac tamponade, aortic rupture, and end-organ malperfusion). All the variables shown in the above table were entered in the multivariable models. [a]Intramural hematoma as a reference. [b]DeBakey type II as a reference.

HD = hemodialysis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Real-world data of DeBakey type I/II AAD from a large Japanese registry showed that women tended to be older, had higher proportions of IMHs and type II dissections, and were less likely to experience end-organ malperfusion than men. Male sex was associated with a higher in-hospital mortality rate after surgical repair for type I/II AAD but not after medical treatment.

TRANSLATIONAL OUTLOOK: Further research is warranted to determine sex-specific risk assessment and therapeutic strategies for patients with DeBakey type I/II AAD.

REFERENCES

1. Evangelista A, Isselbacher EM, Bossone E, et al. Insights from the international registry of acute aortic dissection: a 20-year experience of collaborative clinical research. *Circulation*. 2018;137:1846–1860.

2. Nienaber CA, Fattori R, Mehta RH, et al. Gender-related differences in acute aortic dissection. *Circulation*. 2004;109:3014–3021.

3. Huckaby LV, Sultan I, Trimarchi S, et al. Sex-based aortic dissection outcomes from the International Registry of Acute Aortic Dissection. *Ann Thorac Surg*. 2022;113:498–505.

4. Conzelmann LO, Weigang E, Mehlhorn U, et al. Mortality in patients with acute aortic dissection type A: analysis of pre- and intraoperative risk factors from the German Registry for Acute Aortic Dissection Type A (GERAADA). *Eur J Cardiothorac Surg*. 2016;49:e44–e52.

5. Smedberg C, Steuer J, Leander K, Hultgren R. Sex differences and temporal trends in aortic dissection: a population-based study of incidence, treatment strategies, and outcome in Swedish patients during 15 years. *Eur Heart J*. 2020;41:2430–2438.

6. Fukui T, Tabata M, Morita S, Takanashi S. Gender differences in patients undergoing surgery for acute type A aortic dissection. *J Thorac Cardiovasc Surg*. 2015;150:581–587.

7. Suzuki T, Asai T, Kinoshita T. Clinical differences between men and women undergoing surgery for acute Type A aortic dissection. *Interact Cardiovasc Thorac Surg*. 2018;26:944–950.

8. Rylski B, Georgieva N, Beyersdorf F, et al. Gender-related differences in patients with acute aortic dissection type A. *J Thorac Cardiovasc Surg*. 2021;162:528–535.

9. Norton EL, Kim KM, Fukuhara S, et al. Differences among sexes in presentation and outcomes in acute type A aortic dissection repair. *J Thorac Cardiovasc Surg*. 2023;165:972–981.

10. Miyachi H, Yamamoto T, Takayama M, et al. 10-Year temporal trends of in-hospital mortality and emergency percutaneous coronary intervention for acute myocardial infarction. *JACC Asia*. 2022;2:677–688.

11. Yamamoto T, Yoshida N, Takayama M, Tokyo CCU Network. Temporal trends in acute myocardial infarction incidence and mortality between 2006 and 2016 in Tokyo — report from the Tokyo CCU Network. *Circ J*. 2019;83:1405–1409.

12. Akutsu K, Yoshino H, Shimokawa T, et al. Is systolic blood pressure high in patients with acute aortic dissection on first medical contact before hospital transfer? *Heart Vessels*. 2019;34:1748–1757.

13. Yamasaki M, Yoshino H, Kunihara T, et al. Risk analysis for early mortality in emergency acute type A aortic dissection surgery: experience of Tokyo Acute Aortic Super-Network. *Eur J Cardiothorac Surg*. 2021;60:957–964.

14. Takahashi T, Yoshino H, Akutsu K, et al. In-hospital mortality of patients with acute type A aortic dissection hospitalized on weekends versus weekdays. *JACC Asia*. 2022;2:369–381.

15. Takahashi T, Yoshino H, Akutsu K, et al. Sex-related differences in clinical features and in-hospital outcomes of type B acute aortic dissection: a registry study. *J Am Heart Assoc*. 2022;11:e024149.

16. Ahn JM, Kim H, Kwon O, et al. Differential clinical features and long-term prognosis of acute aortic syndrome according to disease entity. *Eur Heart J*. 2019;40:2727–2736.

17. Lawrence KW, Yin K, Connelly HL, et al. Sex-based outcomes in surgical repair of acute type A aortic dissection: a meta-analysis and meta-regression. *J Thorac Cardiovasc Surg*. Published online February 10, 2022. https://doi.org/10.1016/j.jtcvs.2022.02.005

18. Carbone A, Ranieri B, Castaldo R, et al. Sex differences in type A acute aortic dissection: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2023;30(11):1074–1089.

19. Akutsu K, Yoshino H, Tobaru T, et al. Acute type B aortic dissection with communicating vs. non-communicating false lumen: analysis of 502 patients from the Tokyo CCU-Network Database. *Circ J*. 2015;79:567–573.

20. Sandhu HK, Tanaka A, Charlton-Ouw KM, et al. Outcomes and management of type A intramural hematoma. *Ann Cardiothorac Surg*. 2016;5:317–327.

21. Tolenaar JL, Harris KM, Upchurch GR Jr, et al. The differences and similarities between intramural hematoma of the descending aorta and acute type B dissection. *J Vasc Surg*. 2013;58:1498–1504.

22. Sueyoshi E, Sakamoto I, Fukuda M, Hayashi K, Imada T. Long-term outcome of type B aortic intramural hematoma: comparison with classic aortic dissection treated by the same therapeutic strategy. *Ann Thorac Surg*. 2004;78:2112–2117.

23. Makita S, Ohira A, Naganuma Y, et al. Increased carotid artery stiffness without atherosclerotic change in patients with aortic dissection. *Angiology*. 2006;57:478–486.

24. Harris KM, Braverman AC, Eagle KA, et al. Acute aortic intramural hematoma: an analysis from the International Registry of Acute Aortic Dissection. *Circulation*. 2012;126:S91–S96.

25. Kaji S, Akasaka T, Katayama M, et al. Long-term prognosis of patients with type B aortic intramural hematoma. *Circulation*. 2003;108:II307–II311.

26. Kitai T, Kaji S, Yamamuro A, et al. Clinical outcomes of medical therapy and timely operation in initially diagnosed type A aortic intramural hematoma: a 20-year experience. *Circulation*. 2009;120(11 Suppl):S292–S298.

27. Tanaka A, Sakakibara M, Ishii H, et al. Influence of the false lumen status on clinical outcomes in patients with acute type B aortic dissection. *J Vasc Surg*. 2014;59:321–326.

28. Mehta RH, Suzuki T, Hagan PG, et al. Predicting death in patients with acute type A aortic dissection. *Circulation*. 2002;105:200–206.

29. Vilacosta I, San Román JA, di Bartolomeo R, et al. Acute aortic syndrome revisited: JACC state-of-the-art review. *J Am Coll Cardiol*. 2021;78:2106–2125.

30. Harris KM, Nienaber CA, Peterson MD, et al. Early mortality in type A acute aortic dissection: insights from the International Registry of Acute Aortic Dissection. *JAMA Cardiol*. 2022;7:1009–1015.

31. Raghupathy A, Nienaber CA, Harris KM. Geographic differences in clinical presentation, treatment, and outcomes in type A acute aortic dissection (from the International Registry of Acute Aortic Dissection). *Am J Cardiol*. 2008;102:1562–1566.

32. Reutersberg B, Salvermoser M, Trenner M, et al. Hospital incidence and in-hospital mortality of surgically and interventionally treated aortic dissections: secondary data analysis of the nationwide German diagnosis-related group statistics from 2006 to 2014. *J Am Heart Assoc*. 2019;8:e011402.

KEY WORDS aortic dissection, mortality, sex difference, stanford type A, surgical repair

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