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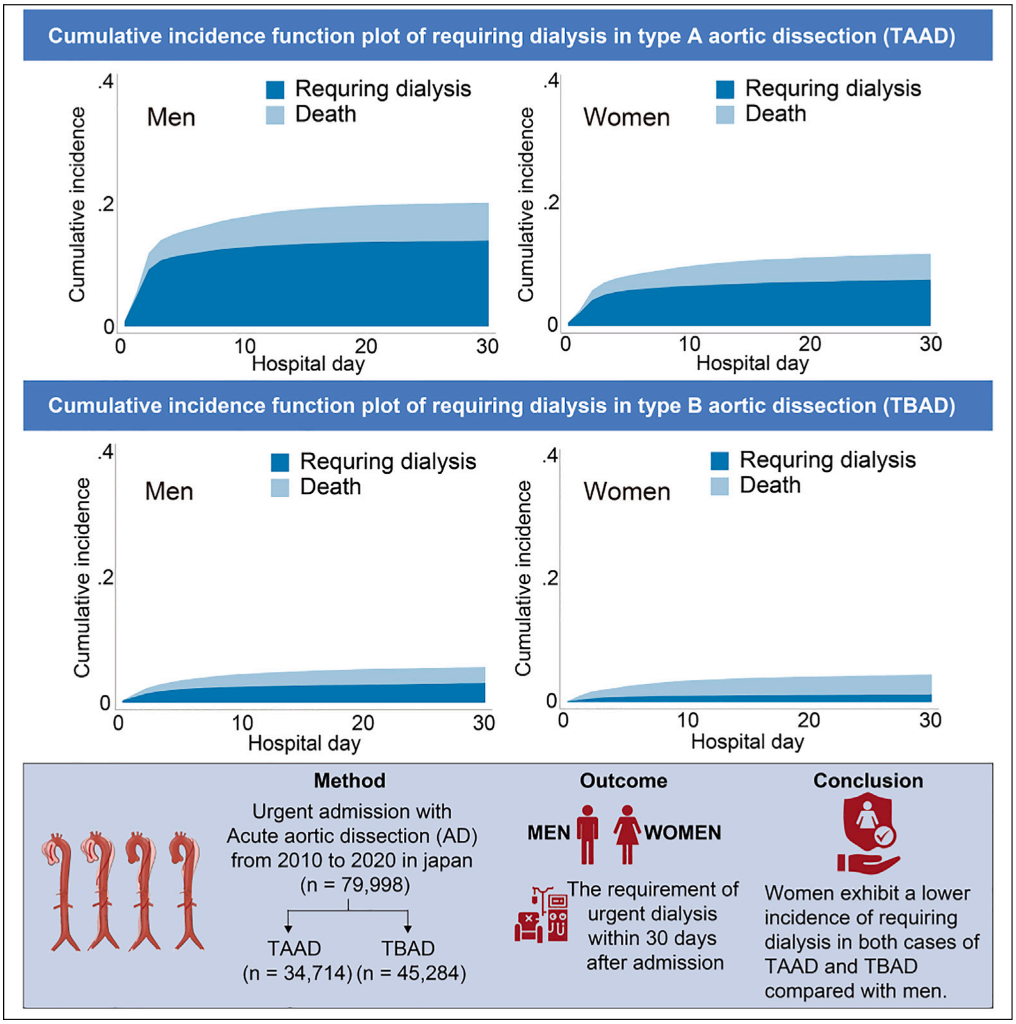

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Highlights

We found a link between sex and the risk of urgent dialysis in aortic dissections

The Fine and Gray model showed a lower risk of requiring urgent dialysis in women

Further research is needed to unveil the mechanism of the sex-vascular-kidney axis

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Sex disparities in the risk of urgent dialysis following acute aortic dissections in Japan

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SUMMARY

The global outcome of acute aortic dissection (AD) remains poor, with a high risk of the need for urgent dialysis. This study aimed to clarify the association between sex and the requirement for urgent dialysis within 30 days after admission among patients with AD. This study included 79,998 cases who were hospitalized due to AD in Japan from 2010 to 2020 using an administrative claims database. The association between the risk of urgent dialysis and sex was investigated using the Fine and Gray model. Patients were classified into two groups based on the Stanford classification: type A AD (TAAD) and type B AD (TBAD). The lower subdistribution hazard ratio (SHR) in women was observed in both groups: TAAD (SHR: 0.58, 95% confidence interval [CI]: 0.54–0.62); TBAD (SHR: 0.49, 95% CI: 0.41–0.58). Our study revealed that women had a lower risk of requiring urgent dialysis than men in TAAD and TBAD.

INTRODUCTION

Acute aortic dissection (AD) is a life-threatening disease that occurs suddenly and leads to high mortality and morbidity.[1] According to the Stanford classification, AD is classified into type A AD (TAAD, involving the ascending aorta) and type B AD (TBAD, not involving the ascending aorta).[1] Sex differences in AD have been identified and considered crucial in many previous studies as they affect prognosis and clinical decision-making in patients with AD.[2,3] The incidence of TAAD is known to be higher in men than in women, and this could be explained by the protective effects of female sex hormones.[2] Clinical presentation also differs between men and women. Women typically present with TAAD and TBAD at an older age and with more severe symptoms.[2,4] They are also more likely to arrive at the hospital later from the onset of symptoms[5] and experience delays in diagnosis.[6] These factors seem to contribute to higher mortality in women with AD.[2] However, recent studies have shown that this discrepancy in mortality has been reduced.[3,7,8]

Acute kidney injury (AKI) is a common complication in AD and is associated with higher mortality in patients with AD.[9,10] A recent nationwide registry study from Germany showed that 24.6% of patients with TAAD and 8.2% of patients with TBAD required postoperative dialysis.[11] Mild AKI is not associated with higher mortality, but severe AKI is strongly associated with short- and long-term mortality in patients with TAAD.[12] Therefore, it is important to focus on the risk of urgent dialysis, which represents the most severe form of AKI. However, there are only a few studies focusing on the sex differences in the risk of requiring urgent dialysis among patients with AD. A recent meta-analysis and international registry study suggest that women may be associated with a lower risk of requiring postoperative dialysis in TAAD, although the difference compared to men is not statistically significant.[3,7] Among patients with TBAD, previous studies have shown a lower incidence of ischemic renal complications and AKI in women,[4,13] but the risk of requiring urgent dialysis remains unexplored. Although it is anticipated that women may be associated with a lower risk of requiring dialysis in patients with AD, the sex differences in the risk of requiring urgent dialysis in AD are yet to be determined.

Therefore, this study aimed to clarify the association between sex and the requirement for urgent dialysis within 30 days after admission among patients with AD using a nationwide administrative database in Japan. To the best of our knowledge, this is the first study to focus on sex differences in the requirement for urgent dialysis, encompassing both Stanford classifications and various treatment modalities, including medical and surgical management. Our study could provide significant insights suggesting underlying associations among sex, vascular disease, and kidney involvements.

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Table 1. Characteristics of patients

	TAAD			TBAD		
	Men	Women	*p* value	Men	Women	*p*-value
	n = 17,054	*n* = 17,660		*n* = 30,685	*n* = 14,599	
Age	62 (52–72)	74 (67–81)	<0.001	70 (60–79)	76 (66–83)	<0.001
Body mass index (kg/m^2)	24 (22–27)	22 (20–25)	<0.001	24 (21–26)	22 (20–25)	<0.001
Cardiovascular diseases	6,804 (39.9%)	6,985 (39.6%)	0.51	10,865 (35.4%)	4,963 (34.0%)	0.003
Diabetes mellitus	1,807 (10.6%)	1,945 (11.0%)	0.21	3,333 (10.9%)	1,422 (9.7%)	<0.001
Chronic pulmonary disease	667 (3.9%)	584 (3.3%)	0.003	1,574 (5.1%)	560 (3.8%)	<0.001
Consciousness						
Alert	13,450 (78.9%)	13,157 (74.5%)	<0.001	27,780 (90.5%)	12,686 (86.9%)	<0.001
1-digit	1,908 (11.2%)	2,450 (13.9%)		2,435 (7.9%)	1,608 (11.0%)	
2-digit	618 (3.6%)	928 (5.3%)		240 (0.8%)	167 (1.1%)	
3-digit	1,078 (6.3%)	1,125 (6.4%)		230 (0.7%)	138 (0.9%)	
Hospital volume						
Very low (<16)	1,855 (10.9%)	2,111 (12.0%)	0.017	8,720 (28.4%)	4,436 (30.4%)	<0.001
Low (16–30)	4,207 (24.7%)	4,340 (24.6%)		7,748 (25.3%)	3,709 (25.4%)	
High (31–49)	4,945 (29.0%)	5,017 (28.4%)		7,787 (25.4%)	3,573 (24.5%)	
Very high (>49)	6,047 (35.5%)	6,192 (35.1%)		6,430 (21.0%)	2,881 (19.7%)	
Admission year						
2010/2011	1,603 (9.4%)	1,641 (9.3%)	0.21	3,207 (10.5%)	1,550 (10.6%)	<0.001
2012/2013	2,637 (15.5%)	2,749 (15.6%)		5,055 (16.5%)	2,210 (15.1%)	
2014/2015	3,261 (19.1%)	3,518 (19.9%)		6,180 (20.1%)	2,837 (19.4%)	
2016/2017	3,854 (22.6%)	4,031 (22.8%)		6,868 (22.4%)	3,317 (22.7%)	
2018/2019	3,844 (22.5%)	3,913 (22.2%)		6,377 (20.8%)	3,168 (21.7%)	
2020	1,855 (10.9%)	1,808 (10.2%)		2,998 (9.8%)	1,517 (10.4%)	
Ambulance transfer	14,395 (84.4%)	14,634 (82.9%)	<0.001	22,019 (71.5%)	10,204 (69.9%)	<0.001
ICU admission	13,949 (81.8%)	14,409 (81.6%)	0.63	14,103 (46.0%)	6,186 (42.4%)	<0.001
HLM use	16,668 (97.7%)	17,335 (98.2%)	0.005	791 (2.6%)	262 (1.8%)	<0.001

Data are presented as numbers (percentages) or medians (IQR). *p* values were calculated using the Wilcoxon rank-sum test for continuous variables or the chi-squared test for categorical variables. ICU, intensive care unit; IQR, interquartile range; HLM, heart-lung machine.

RESULTS

Patient characteristics

The patient characteristics of the present study are presented in Table 1. A total of 79,998 patients were included and divided into two groups based on the Stanford classification: 34,714 patients with TAAD and 45,284 patients with TBAD (Figure S1). The overall median age at admission for AD was 70 years (interquartile range [IQR], 61–79 years). In all groups, women were older than men with a statistically significant difference (TAAD: median age for women 74 years and for men 62 years; TBAD: median age for women 76 years and for men 70 years; $p < 0.001$). Compared to men, women showed a lower proportion of a history of chronic pulmonary disease in all groups. The proportion of patients with a history of cardiovascular diseases and diabetes mellitus was not significantly different between women and men in the TAAD group ($p = 0.51$ and $p = 0.21$, respectively). Still, it was significantly lower in the TBAD group ($p = 0.003$ and $p < 0.001$, respectively). Women exhibited higher proportions of abnormal consciousness, as indicated by JCS 1-, 2-, and 3-digit scores, than men, particularly in the TAAD group (women: 13.9%, 5.3%, 6.4%; men: 11.2%, 3.6%, 6.3%, respectively). The proportion of high or very high hospital volume was higher in the TAAD group (very high: 35.5% in men and 35.1% in women; high: 29.0% in men and 28.4% in women) than in the TBAD group (very high: 21.0% in men and 19.7% in women; high: 25.4% in men and 24.5% in women).

Treatment frequency in TAAD and TBAD

The frequency of treatments was compared between sexes and Stanford classifications in patients identified with TAAD and TBAD during the follow-up period (Figure 1; Table S1). In cases of TAAD, 1.0% of men and 1.2% of women did not receive surgical treatments within

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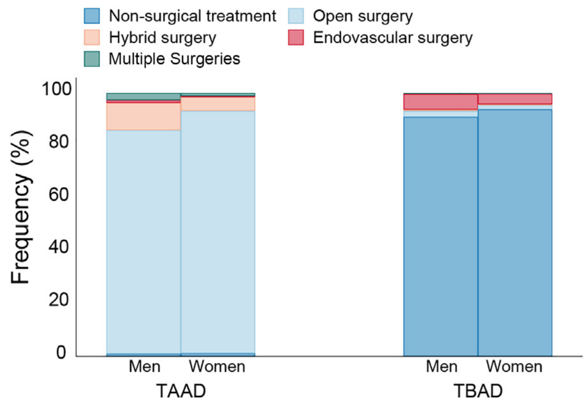

Figure 1. Treatment frequency in type A and type B aortic dissection

The treatments received were categorized into medical management, open surgery, hybrid surgery, endovascular surgery, and multiple surgeries. TAAD, type A aortic dissection; TBAD, type B aortic dissection.

the follow-up period. In the TAAD group, a higher proportion of women (92.0%) underwent open surgery compared to men (84.9%), while a smaller proportion of women (5.2%) received hybrid surgery, in contrast to men (10.3%). A high frequency of non-surgical treatment was observed in the TBAD group, with non-surgical treatment being applied to 93.9% of women and 91.0% of men.

Sex differences in the cumulative incidence of requiring dialysis within 30 days after admission

During a median follow-up period of 22 days (IQR, 16–30 days), a total of 4,691 cases required urgent dialysis (Figure 2). Within the follow-up period, 3,203 deaths were observed. Figure 1 shows the cumulative incidence of requiring dialysis for the TAAD and TBAD groups using cumulative incidence function. In the TAAD group, the cumulative incidence of requiring dialysis within 30 days after admission was 7.4% (95% CI: 7.0–7.8) in women and 13.8% (95% CI: 13.3–14.3) in men (Figure 2). In the TBAD group, the cumulative incidence of requiring dialysis within 30 days after admission was 1.1% (95% CI: 1.0–1.3) in women and 2.8% (95% CI: 2.7–3.0) in men (Figure 2). The difference in cumulative incidence of requiring dialysis between women and men was statistically significant using Gray's test in the TAAD ($p < 0.001$) and TBAD ($p < 0.001$) groups.

Comparison of sex in the rate of requiring urgent dialysis stratified by age

The rate of requiring urgent dialysis within 30 days during admission was examined, stratified by age (Figure 3). The results revealed higher rates of requiring urgent dialysis in the TAAD group in all age categories than in the TBAD group. Furthermore, lower rates of requiring urgent dialysis were observed in women compared to men in the TAAD and TBAD groups, across all age categories.

Adjusted models for sex differences in requiring dialysis among Stanford classifications

The Fine and Gray model was used to estimate the subdistribution hazard ratio (SHR) for requiring dialysis between women and men. Women showed lower SHR in all models compared to men in the TAAD group [model 1, SHR: 0.52 (95% CI: 0.48–0.55); model 2, SHR: 0.58 (95% CI: 0.54–0.63); model 3, SHR: 0.58 (95% CI: 0.54–0.62); model 4, SHR: 0.58 (95% CI: 0.54–0.62); and model 5, SHR: 0.58 (95% CI: 0.54–0.62)] and the TBAD group [model 1, SHR: 0.40 (95% CI: 0.34–0.47); model 2, SHR: 0.47 (95% CI: 0.40–0.56); model 3, SHR: 0.47 (95% CI: 0.40–0.56); model 4, SHR: 0.48 (95% CI: 0.40–0.57); and model 5, SHR: 0.49 (95% CI: 0.41–0.58)] (Figure 4). To validate the multiple imputation models, a complete case analysis was performed with all models (Table S2). These results showed similar estimations to the multiple imputation analysis.

To further examine if surgical treatment modulates the association between the risk of urgent dialysis and sex, we also evaluated the risk of urgent dialysis within 30 days after admission among treatment subgroups including TAAD or TBAD patients who received medical management or surgeries. The Fine and Gray model showed a lower risk of requiring urgent dialysis in women who received surgeries after TAAD (SHR: 0.57, 95% CI: 0.53–0.62) (Table S3). A marked decrease in SHR was seen in women who received medical management after TBAD (SHR: 0.42, 95% CI: 0.34–0.52), while the association between women and lower risk of urgent dialysis did not remain statistically significant after adjusting covariates in TBAD patients who received surgeries (SHR: 0.77, 95% CI: 0.57–1.03).

DISCUSSION

In this community-based study, we aimed to investigate the sex disparities in the risk of requiring urgent dialysis in patients with AD. Consistent with previous studies, our findings revealed that women were older at the time of AD admission.[2,4,8,14] Notably, we observed a significantly reduced risk of requiring urgent dialysis in women with TAAD or TBAD. To the best of our knowledge, this is the first comprehensive

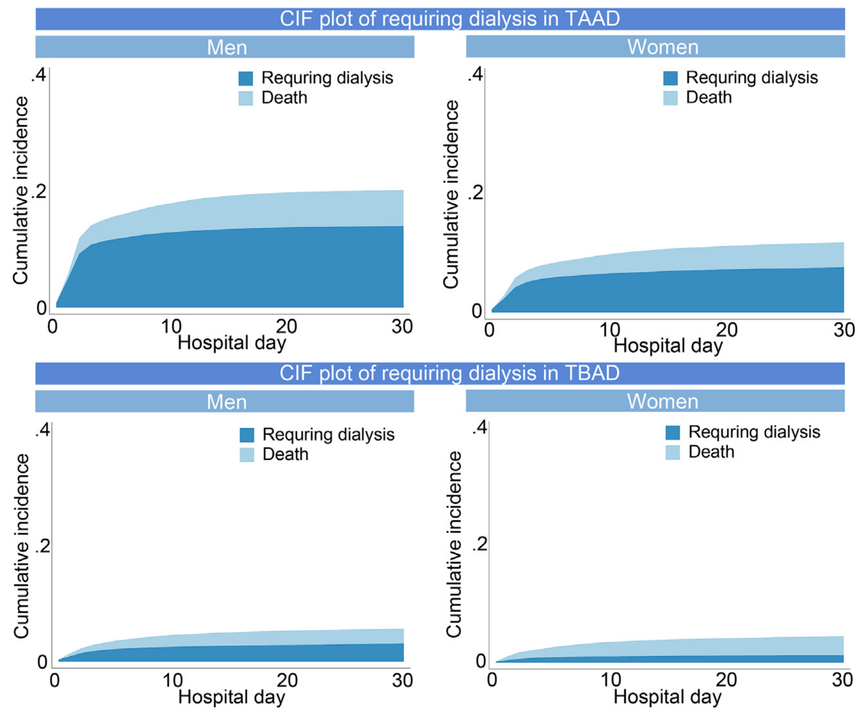

Figure 2. Cumulative incidence function plot of requiring urgent dialysis

This plot displays the cumulative incidence of requiring dialysis within 30 days after admission. CIF, cumulative incidence function; TAAD, type A aortic dissection; TBAD, type B aortic dissection.

evaluation of sex disparities in the requirement of urgent dialysis, which represents the most severe kidney involvement event, in patients with AD. In a complete case analysis, we found a robust association between sex and the requirement for urgent dialysis.

Sex differences in AKI

Sex differences in the epidemiology of kidney disease play a crucial role in the prevention and treatment of AKI. Previous studies have shown that women are at an independent risk for AKI following cardiac surgery.[15–17] However, a recent meta-analysis has suggested that sex may not be associated with AKI in cardiac surgery,[18] and in general surgery, women may even have a reduced risk of AKI.[19,20] Population-based studies have also demonstrated that the risk of developing AKI, including the requirement for dialysis, is lower in women.[21–23] These findings align with our findings, which demonstrated that women with AD are less likely to require urgent dialysis. Our study provides strong evidence for a protective factor against kidney involvement in AD among women. These findings are consistent with previous research indicating that female sex has a protective effect against renal ischemia-reperfusion injury in animal models, possibly due to the association of this protective role with female sex hormones or the negative effect of male hormones.[24–27] Given that renal malperfusion and ischemia are significant risk factors for AKI in AD,[10,28] the protective roles of female sex hormones against renal ischemia-reperfusion injury could potentially reduce the risk of requiring dialysis in women with AD. Previous reports from Japan have also suggested the possibility of a reduced risk of end-organ malperfusion in women with TAAD and TBAD.[4,8] Therefore, further studies are needed to investigate the protective effect of female sex on malperfusion in AD.

Clinical perspectives in the sex-vascular-kidney axis

Our study has revealed a significant association between sex, AD, and kidney involvement, with women having significantly lower SHRs for requiring dialysis in TAAD and TBAD. These findings provide valuable insights that can inform clinical decision-making in the management of AD. Our findings suggest that considering the patient's sex is crucial for predicting the risk of requiring dialysis in patients with AD. Furthermore, our findings highlight the importance of investigating the interactions between sex and kidney involvement in AD as a potential target for improving patient outcomes. In the context of AKI, our study contributes to the growing clinical evidence supporting the protective role of women in mitigating malperfusion and ischemic kidney injury.

In this study, we found that men had a higher risk of requiring urgent dialysis after AD compared to women. Given that the incidence rate of AD is higher in men than women,[2] it is crucial to focus on reducing the risk of urgent dialysis in men with AD. Although renal malperfusion is recognized as an independent risk factor for AKI, Helgason et al. reported that renal malperfusion was observed in only 9% of AKI cases in their cohort of TAAD.[29] This suggests that there may be multiple factors contributing to the development of AKI, and a multidisciplinary approach

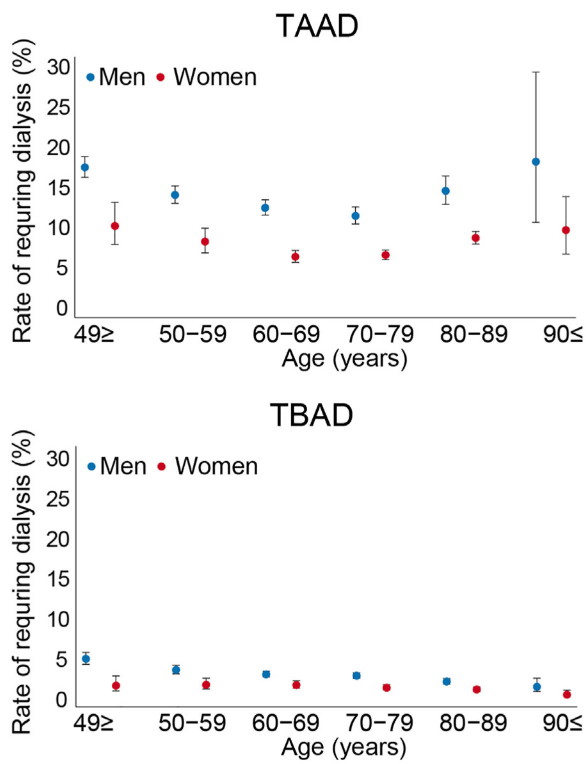

Figure 3. Rate of requiring urgent dialysis stratified by sex and age

This figure shows the rate of requiring dialysis within 30 days after admission, stratified by sex and age, with a 95% confidence interval. TAAD, type A aortic dissection; TBAD, type B aortic dissection.

should be considered to prevent AKI in patients with AD. Careful control of blood pressure and fluid volume management can help reduce the risk of kidney hypoperfusion. Additionally, it is important to avoid nephrotoxic medications and minimize the use of contrast agents, using ultrasound as an alternative when possible.[9,30]

Conclusions

Our study found that women consistently had a lower risk of requiring urgent dialysis than men in TAAD and TBAD cases. These findings provide significant evidence of the complex interaction between AD, kidney involvement, and sex differences. To improve patient care in AD and AKI, further research is needed to clarify the underlying mechanisms involved in the sex-vascular-kidney axis.

Limitations of the study

This study has several strengths, including its large-scale nature, national representation of the Japanese population, and rigorous validation.[31] However, it is important to acknowledge several limitations. First, the study population consisted of a single race and ethnicity in Japan. Second, as an observational study based on a claim database, there may be residual confounders that were not accounted for, such as the laboratory data. Third, the database used in this study did not provide information on long-term prognoses after discharge. Therefore, it is difficult to assess the long-term risks and outcomes associated with sex differences in AD. Finally, the study lacked preadmission data on the time from symptom onset to hospital arrival, which could have influenced the prognosis of patients with AD.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

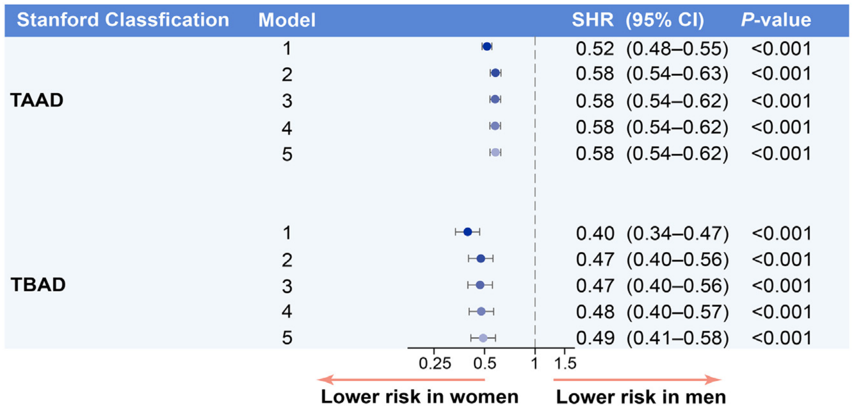

Figure 4. Sex differences in the subdistribution hazard ratio for requiring urgent dialysis

These forest plots illustrate the SHRs for requiring dialysis within 30 days after admission in women compared to men. The SHRs were estimated using the Fine and Gray model, employing sequential models from 1 to 5. SHR, subdistribution hazard ratio; TAAD, type A aortic dissection; TBAD, type B aortic dissection.

- METHOD DETAILS
  - Dataset
  - Covariate and outcome definitions
- QUANTIFICATION AND STATISTICAL ANALYSIS

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.110577.

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AUTHOR CONTRIBUTIONS

Conceptualization, Y.N. and S.M.; study design, Y.N., and S.M, ; formal analysis, Y.N. and S.M. ; data acquisition, Y.N., S.M., and K.F.; data curation, Y.N., S.M., D.T., K.I., Y.M., F.A., K.S., T.M., S.I., S.N., E.S., K.F., and S.U.; software, Y.N. ; visualization, Y.N.; writing–original draft, Y.N.; writing–review and editing, S.M., D.T., K.I., Y.M., F.A., K.S., T.M., S.I., S.N., E.S., K.F., and S.U.; supervision, S.M. and S.U.; funding acquisition: K.F.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Diagnosis procedure combination database	Ministry of Health, Labor and Welfare	https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/dpc/index.html
Software and algorithms		
Stata 17 SE	StataCorp LLC	https://www.stata.com/ (RRID: SCR_012763)
R version 4.3.2	R Foundation	https://www.r-project.org/ (RRID: SCR_001905)

RESOURCE AVAILABILITY

Lead contact

Request for further information should be directed to and will be fulfilled by the lead contact, Shintaro Mandai (smandai.kid@tmd.ac.jp).

Materials availability

This study did not create new unique reagents.

Data and code availability

- The data reported in this study were provided by a third party and cannot be deposited in a public repository as the data custodians have not granted permission.
- This paper does not report the original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

In this study, 150,687 admissions from the years 2010 to 2020 in the Diagnosis Procedure Combination database were included. The inclusion criteria for this study were a diagnosis of AD at admission, identified by the International Classification of Disease and Related Health Problems, 10th Revision (ICD-10) codes along with the Japanese classification information of AD. Specifically, TAAD was identified by ICD-10 code I710 with Stanford A or DeBakey I, DeBakey II, TBAD was identified by ICD-10 code I710 with Stanford B or DeBakey IIIa/IIIb, and AD with an unspecified Stanford classification was identified by ICD-10 code I710 with an undetermined Stanford classification.[32] Based on the claim codes for treatment, the types of surgeries were classified as open surgery, hybrid surgery, or endovascular surgery.[11] The TAAD, TABD, or unspecified AD group were defined mainly based on the diagnosis code at admission. If the diagnosis code implied unspecified AD at admission but the patient had treatment codes specific for TAAD or TBAD, they were classified accordingly.[11,32,14] As high mortality in medical management for TAAD, surgical treatment is recommended for TAAD except for patients who have a prohibitively high risk for surgery.[33] Therefore, in this study, we have excluded from the TAAD group those patients who did not receive surgical treatment during their entire admission stay. After excluding admissions with unspecified AD, patients under 18 years old, planned admissions, missing information on admission status, second or later admissions, patients with a history of chronic kidney disease (CKD) dependent or independent of chronic dialysis, and patients who did not undergo surgery during admission for TAAD (Figure S1), 79,998 eligible cases were included in the analysis. The study was conducted following the ethical principles of the Declaration of Helsinki and was approved by the institutional review board of Tokyo Medical and Dental University (approval number: M2000-788). Informed consent was not required due to the anonymity of the data.

METHOD DETAILS

Dataset

This observational population-based cohort study was conducted using the Diagnosis Procedure Combination database. This is an administrative claims database that includes over half of all admission cases in Japan from more than 1,000 hospitals, including all 82 university hospitals.[34] The database provides information on diagnosis at admission, comorbidities, complications during admission, and causes of death coded according to ICD-10.[35] Patient information such as age, sex, body mass index, procedure types, comorbidity score (the Charlson comorbidity index)[36] updated for risk adjustment,[37,38] and admission and discharge status are also included in the database.

Covariate and outcome definitions

Clinical data were collected upon hospital arrival, including age, sex, body mass index, history of cardiovascular diseases, diabetes mellitus, chronic pulmonary disease, and CKD, including kidney replacement therapy (KRT), consciousness status, ambulance transfer, hospital volume, and admission year. After admission, the intensive care unit (ICU) admission, use of the heart-lung machine (HLM), initiation of dialysis, and receiving medical or surgical management were documented. Consciousness status was assessed using the Japan Coma Scale (JCS), which classifies patients as alert (JCS 0), awake without any stimulation but with disorientation (JCS 1-digit, 1 to 3), awake with stimulation (JCS 2-digit, 10 to 30), or in a coma (JCS 3-digit, 100 to 300).[39] As the annual admission volume of AD is known to impact clinical outcomes, hospitals were categorized into four categories based on quantile annual admission volume: very high volume (>49 cases per year), high volume (31–49 cases per year), low volume (16–30 cases per year), and very low volume (<16 cases per year).[11] Patients were classified according to their treatments, including only medical management, only open surgery, only hybrid surgery, only endovascular surgery, or a combination of multiple surgeries.[11,32]

We defined urgent dialysis as the initiation of dialysis for patients who were not dependent on KRT before admission. Chronic or urgent dialysis during hospitalization was identified based on information regarding comorbidity at admission of end-stage kidney disease, diagnosis of AKI or new-onset end-stage kidney disease during hospitalization, and the coding of patient care procedures such as chronic maintenance hemodialysis with <4 h per session, ≥4 h and <5 h per session, or ≥5 h per session, chronic maintenance hemodiafiltration or continuous peritoneal dialysis, continuous renal replacement therapy, dialysis for AKI, or initiation of dialysis.[40] All patients were followed up until 30 days after arrival or until requiring dialysis, death, or censorship due to discharge or transfer within 30 days. Covariates were included if they were observed within the follow-up period. The outcome was defined as the requirement for urgent dialysis within 30 days after admission, with in-hospital death considered a competing risk event.

QUANTIFICATION AND STATISTICAL ANALYSIS

Baseline characteristics were presented as numbers (percentages) or medians with an interquartile range (IQR). Age was classified according to a previous study, with the following categories: 49≥, 50–59, 60–69, 70–79, 80–89, and 90≤ years (Figure 3).[8] The Wilcoxon rank-sum test was used to compare nonnormally distributed continuous variables between two groups, while the chi-squared test was used to compare categorical variables (Tables 1 and S1). The cause-specific cumulative incidence function (CIF) was estimated to investigate the absolute risk of requiring dialysis while accounting for the competing risk of death (Figure 2).[41–43] The Fine and Gray model was used to adjust for covariates in the CIF analysis (Figure 4; Tables S2 and S3).[41,44] Sequential adjustments were performed to track the association between sex and the outcome for different variables. Model 1 included only sex. Model 2 included the variable from Model 1, along with age, body mass index, history of cardiovascular diseases, diabetes mellitus, chronic pulmonary disease, hospital volume, and admission year. Model 3 included the variables from Model 2, along with consciousness status and ambulance transfer. Model 4 included the variables from Model 3, along with ICU admission and the use of the HLM. Model 5 included the variables from Model 4, along with information on treatment received. To compare the crude CIF between the two groups, Gray's test was used (Figure 2).[45] As 6,740 cases lacked body mass index data, multiple imputations were performed using the predictive mean matching imputation method. A total of 20 filled-in complete data sets were created with imputed values for the following covariates: age, sex, cardiovascular diseases, diabetes mellitus, chronic pulmonary disease, consciousness status, ambulance transfer, hospital volume, admission year, ICU admission, HLM use, outcomes, treatments, and Stanford classification.[46] Rubin's rule was applied to calculate the final estimate for each model.[47] In addition, a complete case analysis was performed to validate the results. Statistical analyses were performed using Stata software version 17.0 SE (Stata Corp., College Station, TX, USA) in imputation of missing values, Fine and Gray modeling, and visualization. Additionally, R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for Gray's test. *P*-values less than 0.05 were considered statistically significant.