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Sex Differences in Cardiovascular Disease-Related Hospitalization and Mortality in Japan

— Analysis of Health Records From a Nationwide Claim-Based Database, the Japanese Registry of All Cardiac and Vascular Disease (JROAD) —

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Background: The prevalence of cardiovascular disease (CVD) is rising in Japan with its aging population, but there is a lack of epidemiological data on sex differences in CVD, including acute coronary syndrome (ACS), acute heart failure (AHF), and acute aortic disease.

Methods and Results: This retrospective study analyzed data from 1,349,017 patients (January 2012–December 2020) using the Japanese Registry Of All Cardiac and Vascular Diseases database. ACS patients were youngest on average (70.5±12.9 years) and had the lowest female proportion (28.9%). AHF patients had the oldest mean age (79.7±12.0 years) and the highest proportion of females (48.0%). Acute aortic disease had the highest in-hospital mortality (26.1%), followed by AHF (11.5%) and ACS (8.9%). Sex-based mortality differences were notable in acute aortic disease, with higher male mortality in Stanford Type A acute aortic dissection (AAD) with surgery (males: 14.2% vs. females: 10.4%, P<0.001) and similar rates in Type B AAD (males: 6.2% vs. females: 7.9%, P=0.52). Aging was a universal risk factor for in-hospital mortality. Female sex was a risk factor for ACS and acute aortic disease but not for AHF or Types A and B AAD.

Conclusions: Sex-based disparities in the CVD-related hospitalization and mortality within the Japanese national population have been highlighted for the first time, indicating the importance of sex-specific strategies in the management and understanding of these conditions.

Key Words: Age-specific risk factors; Cardiovascular disease; In-hospital mortality; Sex differences

The incidence of cardiovascular disease (CVD) is on the rise in Japan, primarily due to its aging population.[1] Recent statistics indicate that heart disease is the second leading cause of death, contributing to 14.8% of deaths and accounting for >330,000 deaths annually.[2] This issue is especially pronounced among older adults, reflecting Japan's demographic trends of a declining birth rate and an aging population.[1] National epidemiological data on CVD are necessary, both for healthcare policy and decision making in medical practice, but the reality is that current data are inadequate.

As medicine evolves, personalized treatment of CVD is becoming more important, a paradigm shift that recognizes the diversity of patient profiles and adjusts treatment strategies accordingly. For this reason, there is a growing focus internationally on sex disparities in CVD. For instance, in 2023 the American Heart Association reported that 32% of acute myocardial infarction (AMI) patients in

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the USA were female, and that they also faced a 3% higher mortality risk than males.[3] Heart failure incidents in Americans aged ≥55 years reached approximately 1,000,000 in 2014, with a marginally higher incidence rate in females. A Swedish study of thoracic aortic disease in 14,229 individuals in 2002 found an incidence rate of 16.3 per 100,000 per year in males and 9.1 in females.[4]

In Japan, regional studies have shed some light on CVD, but national data, particularly regarding sex differences, are limited. Several regional studies in Japan reported that the proportion of females with AMI, AHF, Type A acute aortic dissection (AAD), and Type B AAD was 20–30%,[5–7] 41–48%,[8–12] 49%,[13,14] and 29%, respectively.[15] The present study aimed to explore the hospitalization and mortality of CVD between the sexes in Japan, utilizing the comprehensive data from the Japanese Registry of All Cardiac and Vascular Disease-Diagnosis Procedure Combination (JROAD-DPC) database.

Methods

Study Setting and Patient Selection

In this retrospective observational study, the DPC database of the participating facilities in the JROAD study between January 2012 and December 2020 was analyzed. The JROAD-DPC database was established by the Japanese Society of Cardiology and has been previously described in detail.[16,17] It is a growing national claims-based registry from about 60% of Japanese teaching hospitals with beds for patients with CVD.[18] The database contains patient demographic and disease-specific data. The validity of the diagnoses included in this database has been reported.[19] Data for acute coronary syndrome (ACS), acute heart failure (AHF), and acute aortic disease among emergency admissions of patients aged ≥19 years were analyzed in this study. We investigated sex differences in annual trends in the hospitalization and mortality of ACS, AHF, acute aortic disease, Stanford Type A AAD, and Type B AAD. The annual trends in sex differences in the number of diseases were examined for all diseases. As mentioned, the number of institutions registered with JROAD increases yearly. Therefore, we focused our survey only on those facilities that had participated throughout 2012–2020. In addition, multivariable analyses of how sex differences affect in-hospital mortality, adjusted for age, were conducted for risk factors and comorbidities.

The definitions of diseases were based on the International Classification of Diseases (ICD)-10 diagnosis codes related to ACS (I20.0, I21.0, I21.1, I21.2, I21.3, I21.4, and I21.9), HF (I50.0, I50.1, and I50.9), and aortic disease (I71.0, I71.1, I71.2, I71.3, I71.4, I71.5, I71.6, I71.8, and I71.9).[16,20] Additional diagnosis codes (100 and 101) were used to exclude scheduled admissions and select only those of emergency admissions. ACS was defined using codes for AMI and unstable angina pectoris. In this study, acute aortic disease was a combination of several conditions, including ruptured aortic aneurysm, impending aortic rupture, aortitis, and AAD, because detailed information on aortic disease was unavailable in the DPC database. Only Type A and Type B AAD had been extracted from the definition tags from 2016. In this study, mortality in the DPC database was only in-hospital deaths. "Renal disease" was defined when the attending physician entered an ICD-10 code at the time of admission, DPC registration or when dialysis was performed. Surgery in the acute aortic disease study included open chest and abdominal surgery and all endovascular procedures.

Ethics Statement

The study followed the Declaration of Helsinki, was approved by the Central Ethics Committee of Nippon Medical School (approval number: 686-4-61) and authorized for implementation by the heads of the respective research institutions. The requirement for written informed consent was waived because the data were anonymized.

Statistical Analysis

Continuous variables are presented as mean±standard deviation if normally distributed or median and interquartile range (IQR) if not normally distributed. Comparisons of differences between groups were made using an unpaired t-test for continuous variables and a Chi-squared test for dichotomous variables. The predictors of in-hospital mortality were assessed using a multivariable logistic regression model. Odds ratios (ORs) and 95% confidence intervals (CIs) for in-hospital mortality were estimated. The missing values were removed and only the complete values were analyzed. Variables used in the multivariable analyses were age, year, sex (female), body mass index (BMI), hypertension (HT), dyslipidemia (DL), diabetes mellitus (DM), smoking, renal disease, Killip classification, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) in ACS; age, year, sex (female), BMI, HT, DL, DM, smoking, renal disease, and

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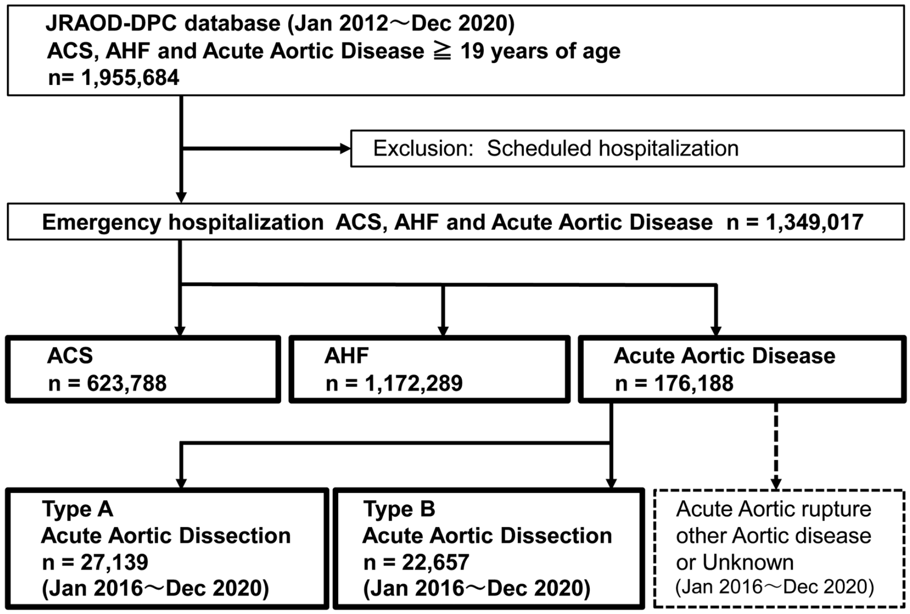

Figure 1. Study flow chart. ACS, acute coronary syndrome; AHF, acute heart failure; DPC, diagnosis procedure combination; JROAD, Japanese Registry Of All cardiac and vascular Disease.

Table 1. Baseline Characteristics of Study Subjects

	ACS (n=623,788)	AHF (n=1,172,829)	Acute aortic disease (n=176,188)
Female (%)	28.7	48.0	40.1
Age, years, mean±SD	70.5±12.9	79.7±12.0	73.7±13.0
BMI, mean±SD	23.8±3.9	22.5±4.6	22.9±4.1
HT (%)	59.7	53.1	55.7
DL (%)	56.7	20.9	17.0
DM (%)	29.6	27.6	9.8
Dementia (%)	2.5	7.5	3.9
Renal disease* (%)	7.9	18.5	7.6
Dialysis (%)	4.3	5.0	3.7
Cancer (%)	3.3	6.3	4.1
Smoker (current or ex-smoker) (%)	56.9	40.1	57.2
Killip classification	n=397,098**		
I (%)	46.6	–	–
II (%)	24.3	–	–
III (%)	7.9	–	–
IV (%)	14.0	–	–
Unknown classification (%)	7.2		
NYHA classification		n=574,031**	
III–IV (%)	–	65.5	–
Acute aortic dissection (n=49,796)			
Type A (%)	–	–	54.5
Type B (%)	–	–	45.5
In-hospital mortality (%)	8.9	11.5	26.1
Hospitalization days, median (IQR)	10 (5–16)	17 (11–28)	17 (4–28)

*Renal disease was defined by the attending physician entering International Classification of Diseases-10 (ICD-10) diagnosis codes for renal disease in the diagnosis procedure combination (DPC) disease title or dialysis. **In Killip and NYHA classification, only complete values were analyzed. ACS, acute coronary syndrome; AHF, acute heart failure; BMI, body mass index; DL, dyslipidemia; DM, diabetes mellitus; HT, hypertension; IQR, interquartile range; NYHA, New York Heart Association; SD, standard deviation.

the New York Heart Association classification in AHF; and age, year, sex (female), BMI, HT, DL, DM, smoking, renal disease, and surgery in acute aortic disease (Type A and Type B AAD). All data were analyzed using the Stata software/MP, version 18 (Stata Corp, College Station, TX, USA). Two-tailed P-values of <0.05 were considered statistically significant.

Results

A total of 1,349,017 patients were assigned to the ACS (n=623,788), AHF (n=1,172,829), acute aortic disease (n=176,188), and Type A (n=27,139) and Type B (n=22,657) AAD groups (**Figure 1**). **Table 1** shows the baseline characteristics of the patients. Of the 3 disease groups, patients with ACS had the youngest mean age (70.5±12.9 years) and the lowest female proportion (28.9%), whereas patients with AHF had the oldest mean age (79.7±12.0 years) and the highest female proportion (48.0%). The highest in-hospital mortality rate occurred in patients with acute aortic disease (26.1%), followed by those with AHF (11.5%). ACS patients had the lowest in-hospital mortality (8.9%). **Table 2** shows the characteristics of each disease categorized by sex.

Sex Differences in Hospitalization

Figure 2 shows the number of patients with each disease per decade categorized by sex. The ACS-related hospitalization peaked for males in their 70s and for females in their 80s (**Figure 2A**). This distribution was similar to that of Type B AAD (**Figure 2E**). Regarding the number of male and female patients per decade, AHF had a higher age at hospitalization than ACS, with the majority of patients in their 80s. Similarly, the disease had a higher

Table 2. Sex Differences in ACS, AHF, Acute Aortic Disease, and Type A and B AAD

(A) ACS	Male (n=444,580)	Female (n=179,208)
Age, years, mean±SD	68.1±12.6	76.4±11.6
BMI, mean±SD	24.1±3.7	22.8±4.1
HT (%)	60.7	57.2
DL (%)	59.1	50.8
DM (%)	30.8	26.6
Dementia (%)	1.5	4.9
Renal disease (%)	8.0	7.5
Dialysis (%)	4.4	4.2
Cancer (%)	3.5	2.7
Smoker (current or ex-smoker) (%)	69.8	25.0
Killip classification	n=289,003*	n=108,095*
I (%)	48.5	41.4
II (%)	24.2	24.8
III (%)	7.4	9.3
IV (%)	13.4	15.8
Unknown classification (%)	6.5	8.7
PCI (%)	74.5	60.3
CABG (%)	3.7	2.9
In-hospital mortality (%)	7.6	12.1
Hospitalization days, median (IQR)	10 (5–16)	10 (4–17)
(B) AHF	**Male (n=609,455)**	**Female (n=563,374)**
Age, years, mean±SD	76.6±12.3	83.1±10.6
BMI, mean±SD	23.0±4.4	21.9±4.7
HT (%)	52.8	54.3
DL (%)	21.7	19.9
DM (%)	31.5	23.4
Dementia (%)	4.9	10.3
Renal disease (%)	21.2	15.6
Dialysis (%)	6.5	3.4
Cancer (%)	7.7	4.9
Smoker (current or ex-smoker) (%)	61.1	17.4
NYHA classification	n=296,821*	n=277,210*
III–IV (%)	65.7	65.5
In-hospital mortality (%)	10.8	12.3
Hospitalization days, median (IQR)	17 (11–26)	18 (11–29)

(**Table 2** continued the next page.)

(C) Acute aortic disease	Male (n=105,484)	Female (n=70,704)
Age, years, mean ± SD	71.1±13.2	77.8±11.6
BMI, mean ± SD	23.3±4.0	22.1±4.1
HT (%)	57.5	52.9
DL (%)	17.5	16.3
DM (%)	11.0	8.2
Dementia (%)	2.7	5.6
Renal disease (%)	9.1	5.2
Dialysis (%)	4.5	2.5
Cancer (%)	4.9	2.8
Smoker (current or ex-smoker) (%)	71.9	35.1
Surgical procedure (%)	33.5	31.6
In-hospital mortality (%)*	22.8	30.9
Hospitalization days, median (IQR)	18 (6–28)	17 (2–28)
(D) Type A AAD	**Male (n=12,626)**	**Female (n=14,513)**
Age, years, mean ± SD	65.3±13.8	76.6±11.1
BMI, mean ± SD	24.4±4.2	22.4±4.0
HT (%)	55.2	54.0
DL (%)	14.1	16.4
DM (%)	9.4	8.6
Dementia (%)	1.7	5.1
Renal disease (%)	8.3	4.9
Dialysis (%)	5.3	2.9
Cancer (%)	3.1	2.5
Smoker (current or ex-smoker) (%)	70.7	31.6
Surgical procedure (%)	66.0	56.5
In-hospital mortality (%)*	25.0	29.5
Hospitalization days, median (IQR)	22 (10–33)	21 (5–32)
(E) Type B AAD	**Male (n=15,100)**	**Female (n=7,557)**
Age, years, mean ± SD	69.0±13.3	74.6±12.6
BMI, mean ± SD	23.9±4.1	22.5±4.3
HT (%)	81.3	79.8
DL (%)	26.4	28.5
DM (%)	11.4	9.6
Dementia (%)	3.2	7.0
Renal disease (%)	8.3	5.1
Dialysis (%)	3.1	2.0
Cancer (%)	5.4	3.3
Smoker (current or ex-smoker) (%)	73.9	31.9
Surgical procedure (%)	11.2	7.4
In-hospital mortality (%)**	4.3	4.3
Hospitalization days, median (IQR)	20 (15–27)	20 (15–27)

*In the Killip and NYHA classifications, only complete values were analyzed. **In-hospital mortality includes patients with and without surgery. AAD, acute aortic dissection; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. Other abbreviations as in Table 1.

proportion of hospitalization for people aged ≥90 years (**Figure 2B**). Type A AAD was characterized by a significant increase in the number of females, particularly those aged ≥70 years. With respect to those aged ≥80 years, the proportion of females was 2.5-fold higher than that of males (**Figure 2D**).

Sex Differences in In-Hospital Mortality

Figure 3 shows the in-hospital mortality for each disease per decade categorized by sex. Among patients with ACS, females had lower in-hospital mortality rates than males aged <80 and higher ones in those aged ≥80 (**Figure 3A**). The opposite trend was noted for patients with AHF. Females had higher in-hospital mortality rates than males aged <70, and lower ones in those aged ≥70 (**Figure 3B**). In patients with acute aortic disease, as in those with ACS, females had lower in-hospital mortality rates than males aged <60, but higher ones in those aged ≥60 (**Figure 3C**).

The mean in-hospital mortality rates for patients with Type A AAD and who underwent surgery were 14.2% for

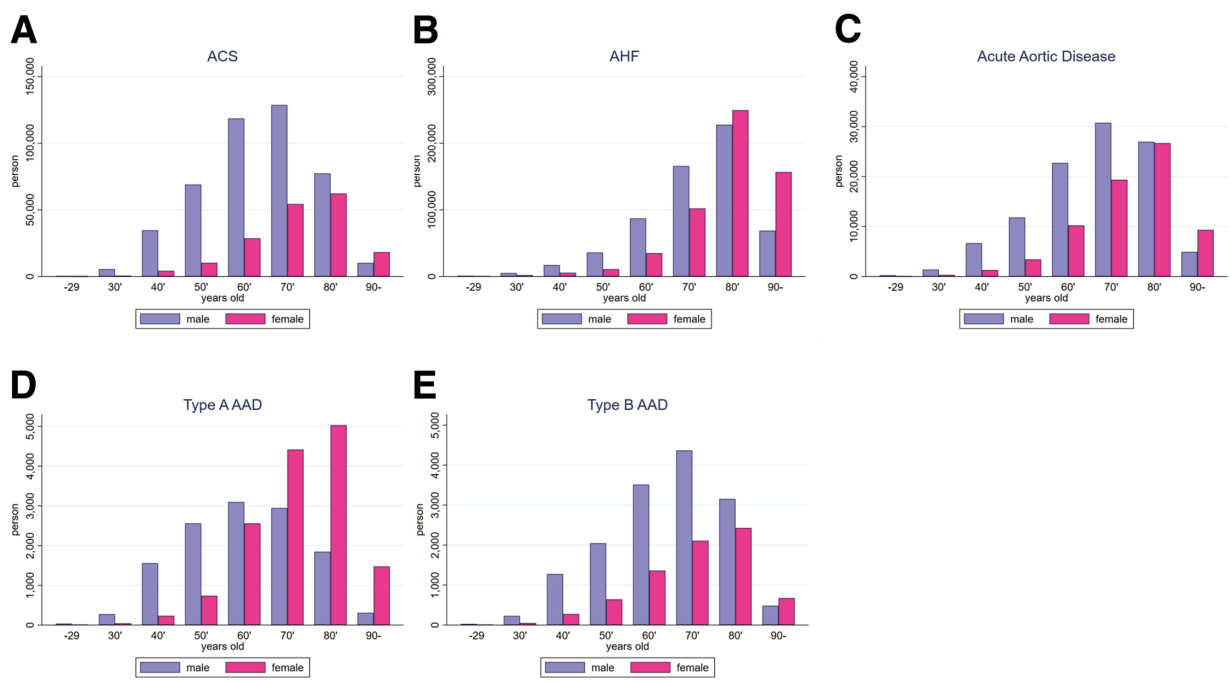

Figure 2. Sex differences in hospitalization for ACS, AHF, acute aortic disease, and Type A and Type B AAD. ACS, AHF, and acute aortic disease were surveyed between 2012 and 2020. Type A and Type B AAD were surveyed between 2016 and 2020. AAD, acute aortic dissection; ACS, acute coronary syndrome; AHF, acute heart failure.

males and 10.4% for females (P<0.001). For patients without surgery, the rates were 51.1% for males and 56.4% for females (P<0.001) (**Figure 3D-1**,**3D-2**). For patients with Type B AAD who underwent surgery, the rates were 6.2% for males and 7.9% for females (P=0.52), and for patients without surgery, 4.9% for males and 6.1% for females (P<0.001) (**Figure 3E-1**,**3E-2**).

Sex Differences in Annual Trends

Figure 4 shows that all diseases exhibited an increasing trend in the number of hospitalizations extracted only from 252 participating JROAD-registered facilities throughout the observation period. However, in 2020, the number of hospitalizations of all diseases decreased. The sex ratio remained almost unchanged throughout the year for all diseases.

Sex Differences in the Prevalence of Comorbidities

In age-specific comparisons of risk factors, HT was most common in Type B AAD and had a maximum prevalence of 86.4% in males in their 30–40s and 85.8% in females in their 50s. DL was most common in ACS and had a maximum prevalence of 70.3% in males in their 40s and 61.6% in females in their 60s. DM was most common in AHF and had a maximum prevalence of 41.1% in males in their 50s and 37.4% in females in their 60s. In contrast, DM was less common in acute aortic disease, with a prevalence of 10.3% in males in their 70s and 10.4% in females in their 50s in Type A AAD (**Supplementary Table**, **Supplementary Figure**). Smoking rates in this study were high for all patients with ACS, AHF, acute aortic disease, and Type A and Type B AAD, but were highest especially for Type B AAD (males: 73.9% vs. females: 31.9%) (**Table 2A–E**).

Multivariable Analyses of Comorbidities Related to In-Hospital Mortality

Multivariable logistic regression of in-hospital mortality was performed in ACS, AHF, acute aortic disease, and Type A and Type B AAD (**Table 3**). No collinearity was identified for any of the variables in the multivariable analyses. Older age was independently associated with an increased risk of in-hospital mortality for all of the diseases (P<0.001), and females were at risk of increased in-hospital mortality in ACS (OR: 1.04 [1.00–1.07], P=0.028) and acute aortic disease (OR: 1.16 [1.11–1.20], P<0.001). Conversely, females were at reduced risk in AHF (OR: 0.90 [0.88–0.92], P<0.001) and Type B AAD (OR: 0.80 [0.62–0.95], P=0.012). Female sex was not associated with in-hospital mortality in Type A AAD (OR: 0.93 [0.86–1.03], P=0.164). No clinically significant differences in association with in-hospital mortality were found for other factors.

Discussion

This comprehensive Japanese study revealed age-specific sex differences in the hospitalization and in-hospital mortality of ACS, AHF, acute aortic disease, and Type A and B AAD. The study noted a modest rising trend in the hospitalization of each disease, with the sex ratio remaining relatively constant. Multivariable analyses identified age as a universal risk factor for in-hospital mortality across all diseases. Interestingly, the impact of sex varied by disease: female sex was a significant risk factor for ACS and acute aortic disease, but not for AHF

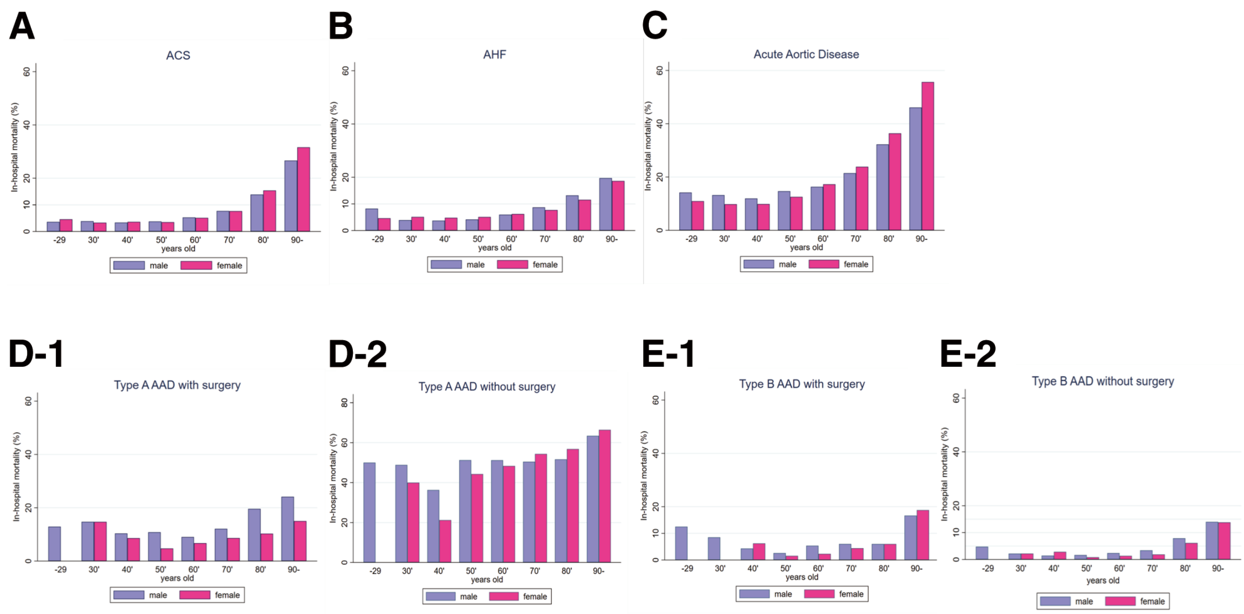

Figure 3. (**A**–**C**) Sex differences in the in-hospital mortality (%) of ACS, AHF, and acute aortic disease. (**D-1**,**D-2**,**E-1**,**E-2**) Sex differences in the in-hospital mortality (%) of Type A AAD and Type B AAD with or without surgery. AAD, acute aortic dissection; ACS, acute coronary syndrome; AHF, acute heart failure.

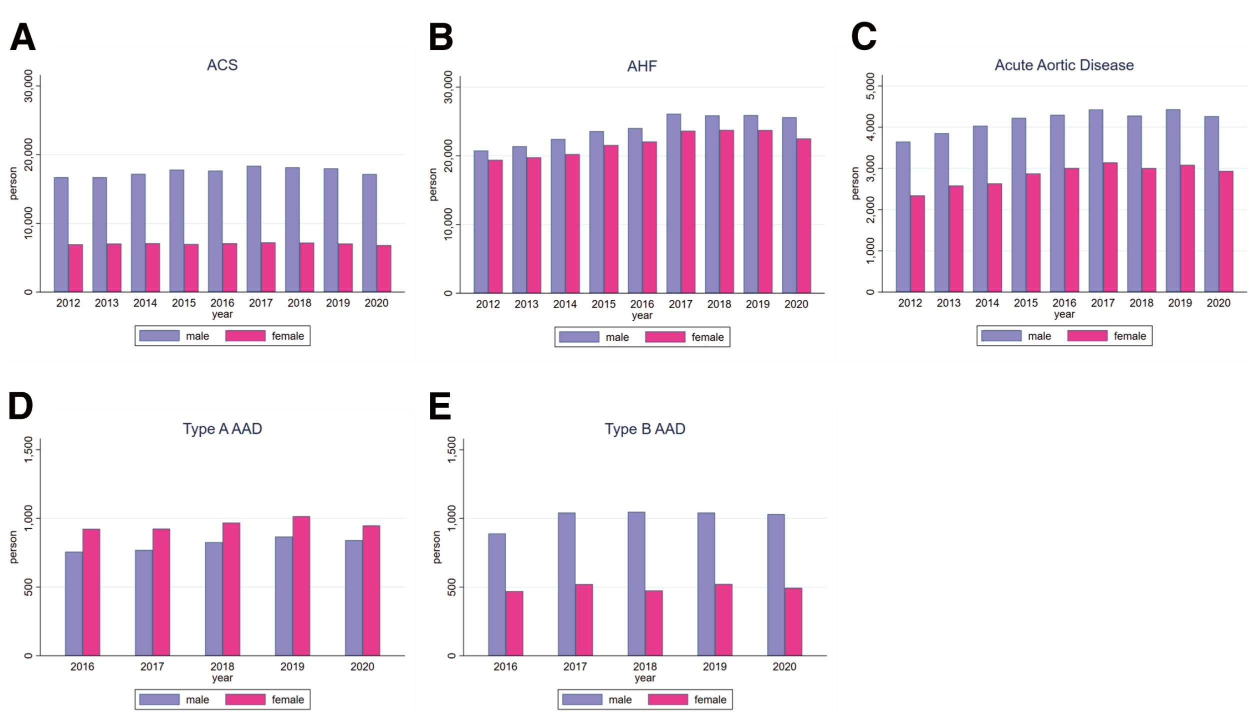

Figure 4. (**A**–**C**) Annual trends in the hospitalization of ACS, AHF, and acute aortic disease by sex: data from facilities that provided all information between 2012 and 2020. (**D**,**E**) Annual trends in the hospitalization of Type A and Type B AAD by sex: data from facilities that provided all information between 2016 and 2020. AAD, acute aortic dissection; ACS, acute coronary syndrome; AHF, acute heart failure.

Table 3. Multivariable Logistic Regression Analysis of the In-Hospital Mortality in ACS, AHF, Acute Aortic Disease, and Type A and B AAD

Variable	Multivariate OR (95% CI)	P value
ACS group (n=350,757)*		
Age, years	1.04 (1.04–1.05)	<0.001
Sex, female	1.04 (1.00–1.07)	0.028
AHF group (n=515,597)*		
Age, years	1.04 (1.041–1.043)	<0.001
Sex, female	0.90 (0.88–0.92)	<0.001
Acute aortic disease group (n=141,700)*		
Age, years	1.04 (1.04–1.05)	<0.001
Sex, female	1.16 (1.11–1.20)	<0.001
Type A AAD group (n=22,367)*		
Age, years	1.03 (1.02–1.03)	<0.001
Sex, female	0.93 (0.86–1.03)	0.164
Type B AAD group (n=20,802)*		
Age, years	1.05 (1.04–1.06)	<0.001
Sex, female	0.80 (0.62–0.95)	0.012

Variables used in the multivariable analysis were as follows: age, year, sex, BMI, HT, DL, DM, smoking, renal disease, Killip classification, PCI, and CABG in the ACS group; age, year, sex, BMI, HT, DL, DM, smoking, renal disease, and the NYHA classification in the AHF group; and age, year, sex, BMI, HT, DL, DM, smoking, renal disease, and surgery in the acute aortic disease group (Type A AAD, and Type B AAD). *Missing values removed and only complete values were analyzed. CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1,2.

or Type A and B AAD.

Sex Differences in Hospitalization

The results of this study showed similar trends to those reported from the USA,[21] considering the age distribution of male and female patients in ACS. The AHA reported that the mean age of onset for males with first-time ACS was 65.6 years,[3] and 72.0 years for females. In this study, the mean age of onset was higher than that reported by the AHA for both male and female patients, due to the aging of the Japanese population.

Large, foreign registries for AHF, such as OPTIMIZE-HF (73.1 years and 52% females),[22,23] ADHERE (72.4 years and 52% females),[24] EHFS-II (69.9 years and 39% females),[25] and ESC-HF-LT (69.4 years and 38% females),[26] have reported a lower mean age (79.7 years) than in this study and an intermediate proportion of females (48.0%). Conversely, compared with those in the large Japanese registries for AHF, such as ATTEND (73.0 years, 42% females),[8] JCARE-CARD (70.7 years, 41% females),[9,10] WET-HF (75 years, 41% females),[11] and JROAD-HF (78 years, 48% females),[12] the mean age and proportion of females in this study were comparable. The age of onset of AHF was higher in Japan than in Europe and the USA, and approximately 40% of the patients were females.

In our study, Type A AAD was observed more in female patients, deviating from prior research that predominantly reported a higher incidence in male patients.[27–29] This discrepancy could be due to earlier studies focusing on surgical cases, thus not representing true incidence, and often excluding very aging populations. For Type A AAD in the International Registry of Acute Aortic Dissection (IRAD) (n=1,078), which included patients who did not undergo surgery, the incidence in males was twice that in females in a population aged <75 years. On the other hand, in the population aged ≥75 years, the incidence was lower in males than in females.[30] The reason for the higher incidence of Type A AAD in older females compared with Type B AAD remains uncertain, but may relate to differing etiologies. Interestingly, the onset age distribution for Type B AAD mirrors that of ACS (**Figure 2A**,**E**), possibly due to shared risk factors such as atherosclerosis, influencing both conditions.[31,32] The etiology of Type A AAD is aging, which may be the reason for its prevalence in older females.

Sex Differences in In-Hospital Mortality

Previous reports indicated higher ACS mortality in female patients,[33] but our multivariate analysis found female sex not to be a risk factor for ACS in-hospital mortality. Interestingly, females aged ≥80 years showed higher mortality than males in the same age group, which may relate to post-menopausal hormonal changes affecting atherosclerosis risk.[34] In addition, an aging population may also contribute to higher female mortality rates in the older age group.[35]

The in-hospital mortality for AHF in this study was higher than in previous registries: 3.8% (OPTIMIZE-HF),[22,23] 4.2% (ADHERE),[24] 6.7% (EHFS-II),[25] 6.4% (ATTEND),[8] 5.6% (JCARE-CARD),[9,10] and 7.7% (JROAD-HF).[12] The high in-hospital mortality in our study may reflect the exclusion of outpatients and the focus of cases on "urgently admitted" patients with AHF. Our result is comparable to in-hospital mortality for AHF reported from the JROAD database between 2012 and 2021.[36] The combined in-hospital mortality for AHF and chronic HF was reported as 7.7% in another study of the JROAD-DPC database,[37] which was similar to that reported previously.[12] Notably, male patients aged ≥70 years had slightly higher mortality rates (13.0%) than female patients (12.3%) among AHF cases. A study of age–sex differences from OPTIMIZE-HF[23] reported that older age was a factor in not receiving guideline-guided treatment, and sex was irrelevant. The reasons behind higher male mortality in heart failure remain elusive.

In Type B AAD, there were no significant differences in mortality for either sex in this study, although female patients had a higher in-hospital mortality than males for Type A AAD. This result differed from that of the Tokyo Acute Aortic Super-Network Registry, a Japanese large registry, which demonstrated that females (5.3%) had a higher in-hospital mortality than males (2.7%) (P=0.002).[15] However, previous studies have shown that the IRAD is sex-dependent in Type A AAD, considering in-hospital mortality, but not sex-dependent in Type B AAD (males: 12.3% vs. females: 14.4%, P=0.56), which was consistent with the results of this study.[30] Similarly, other large-scale registries showed no significant differences in mortality for either sex in Type B AAD.[38,39]

Sex Differences in Annual Trends

Figure 4 shows that the number of hospitalizations related to all diseases increased every year except in 2020, where they decreased because of the coronavirus disease 2019 pandemic.[40,41] This may have resulted in a decrease in the number of CVD cases recorded.

Sex Differences in the Prevalence of Comorbidities

In previous large-scale studies of ACS,[8,42] AHF,[9,12] and Type A[43] and Type B[15] AAD, the comorbidity rates of HT, DL, and DM tended to be similar or slightly higher than those observed in this study. It may be a characteristic of DPC database studies that the comorbidity rate is similar or slightly lower. The smoking rate of Japanese in 2012–2019 was 30.5% in males and 8.1% in females.[44] DM was less common in acute aortic disease than in other diseases in this study. A meta-analysis also revealed DM was associated with a lower risk of AAD.[45] Clinical studies have indicated a correlation between elevated glucose levels in patients with DM and diminished metalloproteinase secretion by inflammatory cells in the aortic wall.[46,47] These factors may prevent the progression of aortic dissection by reducing the death of vascular smooth muscle cells and extracellular matrix degradation.[45]

Multivariable Analyses of Comorbidities Related to In-Hospital Mortality

Our multivariable analyses of comorbidity on in-hospital mortality revealed that female sex increased the risk in ACS, and reduced the risk in Type B AAD, which was consistent with previous studies of ACS and Type B AAD.[35,38,39] Interestingly, female sex reduced in-hospital mortality risk in older AHF patients, warranting further investigation.

Study Limitations

The JROAD-DPC database does not include information of patients with CVD in all Japanese hospitals. Therefore, we could not age-correct the data. Second, because the survey was based on hospital admission diagnoses, it did not cover diseases that resulted in cardiopulmonary arrest before arrival at the hospital. It is known that there are approximately 110,000 out-of-hospital cardiac arrests per year in Japan.[48] Third, comorbidities may have been over- or underestimated in the DPC database, particularly if comorbidities were entered for insurance purposes. Fourth, the number of surveys decreased to 252 facilities in the hospitalization related to the annual trends due to the following adjustments. We showed annual trends in hospitalizations for CVD; between 2012 and 2020, the number of JROAD-registered facilities increased every year, and hospitalization may have been added with an increase in registered facilities. There were 610 and 830 JROAD-registered facilities in 2012 and 2020, respectively. We conducted an additional analysis to select the facilities that participated in all years between 2012 and 2020 and examined the number of diseases in those facilities only. Hence, we were still able to assess the true trend.

Despite these limitations, using a large dataset from the JROAD-DPC registry is considered to accurately represent the CVD situation in Japan. We clarified sex differences in the hospitalization and mortality of CVD in Japan, which is an aging society, and allowed us to quantify the age groups requiring personalized medical care. As more CVD patients are studied, the age and sex targets for which medical care will become clearer. The findings in this study may also apply to other countries with similar aging populations.

Conclusions

Age-specific sex differences in the hospitalization and in-hospital mortality of major CVDs were studied using the national claims database JROAD-DPC. This study represents a significant milestone in medical research on sex differences in Japan. The establishment of such a comprehensive and detailed database in Japan provides a useful template for other countries, especially those with aging populations.

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Disclosures

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IRB Information

The study was conducted following the Declaration of Helsinki. It was approved by the Central Ethics Committee of Nippon Medical School (approval number: 686-4-61) and authorized for implementation by the heads of the respective research institutions. The requirement for written informed consent was waived as the data were anonymized.

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Supplementary Files

Please find supplementary file(s);
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