Circulation

ORIGINAL RESEARCH ARTICLE

Sex Differences in In-Hospital Management and Outcomes of Patients With Acute Coronary Syndrome
Findings From the CCC Project

BACKGROUND: Coronary heart disease is a leading cause of mortality among women. Systematic evaluation of the quality of care and outcomes in women hospitalized for acute coronary syndrome (ACS), an acute manifestation of coronary heart disease, remains lacking in China.

METHODS: The CCC-ACS project (Improving Care for Cardiovascular Disease in China–Acute Coronary Syndrome) is an ongoing nationwide registry of the American Heart Association and the Chinese Society of Cardiology. Using data from the CCC-ACS project, we evaluated sex differences in acute management, medical therapies for secondary prevention, and in-hospital mortality in 82 196 patients admitted for ACS at 192 hospitals in China from 2014 to 2018.

RESULTS: Women with ACS were older than men (69.0 versus 61.1 years, $P<0.001$) and had more comorbidities. After multivariable adjustment, eligible women were less likely to receive evidence-based acute treatments for ACS than men, including early dual antiplatelet therapy, heparins during hospitalization, and reperfusion therapy for ST-segment–elevation myocardial infarction. With respect to strategies for secondary prevention, eligible women were less likely to receive dual antiplatelet therapy, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins at discharge, and smoking cessation and cardiac rehabilitation counseling during hospitalization. In-hospital mortality rate was higher in women than in men (2.60% versus 1.50%, $P<0.001$). The sex difference in in-hospital mortality was no longer observed in patients with ST-segment–elevation myocardial infarction (adjusted odds ratio, 1.18; 95% CI, 1.00 to 1.41; $P=0.057$) and non-ST–segment elevation ACS (adjusted odds ratio, 0.84; 95% CI, 0.66 to 1.06; $P=0.147$) after adjustment for clinical characteristics and acute treatments.

CONCLUSIONS: Women hospitalized for ACS in China received acute treatments and strategies for secondary prevention less frequently than men. The observed sex differences in in-hospital mortality were mainly attributable to worse clinical profiles and fewer evidence-based acute treatments provided to women with ACS. Specially targeted quality improvement programs may be warranted to narrow sex-related disparities in quality of care and outcomes in patients with ACS.

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Clinical Perspective

What Is New?

- The present study is the largest contemporary registry study that evaluated sex-related differences in in-hospital management and outcomes of patients with acute coronary syndrome (ACS) in China.
- Women hospitalized for ACS in China received less frequently acute treatments and strategies for secondary prevention and had higher in-hospital mortality rates than men.
- The observed sex differences in in-hospital mortality were mainly attributable to older age, worse clinical profiles, and fewer evidence-based acute treatments provided to women with ACS.

What Are the Clinical Implications?

- The quality of care for women hospitalized for ACS in China should be improved using evidence-based acute treatments and strategies for secondary prevention.
- Improving the application of evidence-based acute treatments in female patients with ACS may help reduce the observed sex differences in in-hospital mortality.
- Targeted quality improvement programs are required to address sex disparities in quality of care for patients with ACS.

therapies, and improve the outcomes of female patients with ACS.

The CCC-ACS project (Improving Care for Cardiovascular Disease in China–Acute Coronary Syndrome) is the largest ongoing nationwide quality improvement registry for ACS in China.[13] Using data from this project, we conducted a comprehensive analysis to investigate sex differences in clinical characteristics, acute management, medical therapies for secondary prevention, and in-hospital mortality among patients hospitalized for ACS. Furthermore, we examined whether sex-related disparities in early mortality are independent of clinical characteristics and acute management of patients with ACS.

METHODS

The data, analytic methods, and study materials will be made available for onsite audit by third parties for purposes of reproducing the results or replicating the procedure.

Study Population

The CCC-ACS project is an ongoing nationwide quality improvement registry program focusing on improving the quality of care for patients with ACS. The CCC-ACS project was launched in 2014 as a collaborative initiative of the American Heart Association and the Chinese Society of Cardiology, and collected in-hospital data of patients with ACS from 150 hospitals across China. Details on the design and methodology of the CCC-ACS project have been published elsewhere.[13] Briefly, the study included 150 tertiary hospitals from different geographic and economic regions of China. Every month, the first 20 to 30 consecutive patients with ACS in each hospital were recruited for the study. From 2017, the CCC project was extended to 42 secondary hospitals. Institutional review board approval was granted for this research with a waiver for informed consent by the ethics committee of Beijing Anzhen Hospital, Capital Medical University. This study is registered at URL: https://www.clinicaltrials.gov (Unique identifier: NCT02306616).

Based on the principal discharge diagnosis, patients with ACS were enrolled by reviewing the inpatient list. ACS was defined in accordance with the guidelines published by the Chinese Society of Cardiology for the diagnosis and management of patients with ST-segment–elevation myocardial infarction (STEMI) and non–ST-segment elevation (NSTE)–ACS.[14,15] The diagnostic criteria for ACS were based on chest pain or discomfort, ECG, and measurements of myocardial injury biomarkers. From November 2014 to June 2018, 82 196 inpatients with ACS were enrolled based on the principal discharge diagnosis.

Data Collection

Clinical data from medical charts were reported by trained data abstractors in participating hospitals via a web-based data collection platform (Oracle Clinical Remote Data Capture; Oracle Corporation, Redwood City, CA). Data elements collected in this study included patients' demographics, medical history, symptoms on arrival, in-hospital treatments and procedures,

Coronary heart disease (CHD) is one of the leading causes of death among women and men in China.[1] As an acute manifestation of CHD, acute coronary syndrome (ACS) leads to substantial morbidity and mortality. Several previous studies have reported sex differences in outcomes following ACS,[2–5] with both in-hospital mortality rate and risk of recurrent events being higher in women with ACS than in men after their first ACS.[6–11]

In China, limited studies have evaluated the quality of care and outcomes among women with ACS.[7,12] Contemporary national evidence that provides a systematic picture of in-hospital management strategies including acute treatments and secondary prevention therapies for female patients with ACS remains insufficient. Additionally, few studies have systematically compared the clinical characteristics of female and male patients with ACS in the current era. The question remains whether clinical characteristics and in-hospital quality of care account for worse short-term outcomes in women with ACS than in men in China. Filling in these information gaps will lead to significant clinical implications. This information could help identify major problems concerning quality of care, launch targeted quality improvement initiatives for acute treatments and secondary prevention

discharge medications, and secondary prevention strategies. Eligible patients for each month were consecutively entered into the online data reporting system before the middle of the following month after patients' discharge. The following four approaches were adopted to ensure the accuracy and completeness of data: (1) face-to-face training workshops, (2) use of a standardized online reporting tool with automatic checks for invalid values, (3) onsite quality control, and (4) monitoring of data completeness.

Study Variables

We calculated the proportion of ideal candidates who received acute treatments and medical therapies for secondary prevention in accordance with the updated guidelines for the diagnosis and management of patients with ACS.[14–19] Acute treatment measures for patients with ACS included dual antiplatelet therapy (DAPT); angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, and statins within 24 h of arrival; and heparin during hospitalization. For patients with STEMI, acute treatment measures also included acute reperfusion therapy and primary percutaneous coronary intervention (PCI) within the 90-minute door-to-balloon time recommended in the American College of Cardiology/American Heart Association guidelines.[17] For patients with NSTE-ACS, acute treatment measures also included timely PCI for eligible patients, as recommended in the European Society of Cardiology guidelines (within 2, 24, and 72 hours of admission for groups with very high risk, high risk, and moderate risk, respectively).[18] Medical therapies for secondary prevention included DAPT at discharge, β-blockers at discharge, statins at discharge, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers at discharge, smoking cessation counseling, and cardiac rehabilitation counseling. For each treatment, specialized inclusion and exclusion criteria were used, and only appropriate eligible patients with no contraindications were counted as denominators (Table I in the online-only Data Supplement).

The medical insurance status of patients was categorized as "urban" (Urban Employee Basic Medical Insurance and Urban Resident Basic Medical Insurance), "rural" (New Rural Cooperative Medical Insurance), "other," or "no medical insurance." Hypertension was defined as having a history of hypertension, receiving antihypertensive therapy, or having a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on admission. Diabetes mellitus was defined as having a previous or new diagnosis of diabetes mellitus, receiving oral hypoglycemic drug therapy or insulin therapy, or having a fasting blood glucose level ≥7.0 mmol/L (126 mg/dL) or hemoglobin A1c level ≥6.5%. Elevated low-density lipoprotein cholesterol (LDL-C) level was defined as having a serum LDL-C level ≥1.8 mmol/L (70 mg/dL). Current smoking was defined as smoking within the preceding 1 year based on information in medical records.[20] Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Study equation.[21] Renal insufficiency was defined as estimated glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2}. A history of CHD was specified if patients had a clinical history of myocardial infarction or underwent PCI or coronary artery bypass grafting before the current hospitalization. The transfer status indicated whether the patient was transferred from another hospital. Acute heart failure, cardiogenic shock, and cardiac arrest at admission were defined based on the corresponding documentation of the clinical condition at hospital arrival in medical records (Methods in the online-only Data Supplement).

Statistical Methods

Categorical variables were presented as frequencies and percentages, whereas continuous variables were expressed as means and SDs or medians and interquartile ranges. Unpaired t test or Mann-Whitney U test was used to assess the statistical significance of differences between means or medians, where appropriate. The significance of differences for categorical variables was analyzed using the chi-squared test. To examine the association between patients' sex and care pattern, logistic regression models were used to adjust for patients' clinical characteristics, including age; medical insurance status; acute heart failure, cardiogenic shock, and cardiac arrest at admission; heart rate and systolic blood pressure; diabetes mellitus; smoking; history of CHD, heart failure, renal failure, and cerebrovascular disease; prehospital statin use; renal insufficiency; and transfer status. To evaluate the relationship between sex and in-hospital mortality, logistic regression analyses were performed separately in STEMI and NSTE-ACS populations. Moreover, in patients with STEMI, we adjusted for time from symptom onset to admission (<2, 2 to 12, and >12 hours), DAPT at arrival, PCI use (primary PCI, delayed PCI, and no PCI), and fibrinolytic therapy in addition to the clinical characteristics mentioned above. In patients with NSTE-ACS, we additionally adjusted for DAPT at arrival and PCI use (timely PCI, nontimely PCI, and no PCI). For each treatment and outcome, odds ratios with 95% CIs were reported for women versus men. For variables with missing data, we imputed the missing values of clinical variables using the sequential regression multiple imputation method implemented by IVEware software version 0.2 (Survey Research Center, University of Michigan, Ann Arbor, MI), except for the time from symptom onset to admission (missing data, 33.8%). Imputation was separately performed in patients with STEMI and NSTE-ACS. For the time from symptom onset to admission, Pearson's chi-squared test revealed that this variable was significantly associated with in-hospital mortality in patients with STEMI, but not in patients with NSTE-ACS. We included this variable in the logistic regression model (using complete case analysis based on data from 36936 patients) for patients with STEMI, but not for patients with NSTE-ACS. Missing rates of variables and strategies for the management of missing data are presented in Table II in the online-only Data Supplement. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). Two-sided P values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Among 82196 patients with ACS who were included in this study, 21071 (25.6%) were women, whereas 61125 (74.4%) were men. The clinical characteristics of the study population are summarized in Table 1.

Table 1. Clinical Characteristics of the ACS Patients at Admission

Variables	Total (n=82 196)	Men (n=61 125)	Women (n=21 071)	P Value
Age, y	63.1±12.5	61.1±12.4	69.0±10.6	<0.001
ACS type				<0.001
STEMI (%)	50 203 (61.1)	39 187 (64.1)	11 016 (52.3)	
NSTE-ACS (%)	31 993 (38.9)	21 938 (35.9)	10 055 (47.7)	
Medical insurance				<0.001
Urban insurance (%)	44 245 (53.8)	33 189 (54.3)	11 056 (52.5)	
Rural insurance (%)	19 344 (23.5)	13 494 (22.1)	5850 (27.8)	
Other insurance (%)	7914 (9.6)	6065 (9.9)	1849 (8.8)	
Self-paid (%)	10 693 (13.0)	8377 (13.7)	2316 (11.0)	
Hospital stays, d	9 (7, 13)	9 (7, 12)	10 (7, 13)	<0.001
Time from symptom onset to admission, h*	8.1 (3.7, 27.8)	7.7 (3.5, 25.6)	10.1 (4.2, 41.0)	<0.001
<2 h (%)	5147 (9.5)	4128 (10.1)	1019 (7.6)	
2–12 h (%)	26 976 (49.6)	20 832 (50.7)	6144 (46.1)	
>12 h (%)	22 298 (41.0)	16 120 (39.2)	6178 (46.3)	
ECG at admission				<0.001
ST-segment elevation (%)	40 939 (49.8)	31 888 (52.2)	9051 (43.0)	
Temporary ST-segment depression (%)	14 678 (17.9)	9683 (15.8)	4995 (23.7)	
Pathological Q wave (%)	7237 (8.8)	5771 (9.4)	1466 (7.0)	
Left bundle-branch block (%)	503 (0.6)	337 (0.6)	166 (0.8)	
Others (%)	18 839 (22.9)	13 446 (22.0)	5393 (25.6)	
Severe clinical conditions at admission				
Heart failure† (%)	5393 (6.6)	3481 (5.7)	1912 (9.1)	<0.001
Cardiogenic shock (%)	2349 (2.9)	1687 (2.8)	662 (3.1)	0.004
Cardiac arrest (%)	1392 (1.7)	1043 (1.7)	349 (1.7)	0.627
Medical history				
Diabetes mellitus (%)	34 223 (41.6)	24 082 (39.4)	10 141 (48.1)	<0.001
Hypertension (%)	54 033 (65.7)	38 426 (62.9)	15 607 (74.1)	<0.001
Elevated LDL-C (≥70 mg/dL) (%)	68 940 (83.9)	50 944 (83.3)	17 996 (85.4)	<0.001
Smoking (%)	34 096 (41.5)	32 377 (53.0)	1719 (8.2)	<0.001
Renal failure history (%)	1405 (1.7)	945 (1.5)	460 (2.2)	<0.001
Coronary heart disease history (%)	9399 (11.4)	7177 (11.7)	2222 (10.5)	<0.001
Heart failure history (%)	1775 (2.2)	1057 (1.7)	718 (3.4)	<0.001
Cerebrovascular disease history (%)	7643 (9.3)	5311 (8.7)	2332 (11.1)	<0.001
Prehospital statin (%)	14 364 (17.5)	10 429 (17.1)	3935 (18.7)	<0.001
Killip class (%)				<0.001
I	60 083 (73.1)	45 470 (74.4)	14 613 (69.4)	
II–III	19 050 (23.2)	13 620 (22.3)	5430 (25.8)	
IV	3063 (3.7)	2035 (3.3)	1028 (4.9)	
Renal insufficiency (%)	13 198 (16.1)	8150 (13.3)	5048 (24.0)	<0.001
Heart rate, bpm	77.5±16.2	77.2±16.0	78.2±16.8	<0.001
Systolic blood pressure, mm Hg	130.5±23.5	129.4±23.0	133.6±24.7	<0.001
Glucose, mmol/L	6.1 (5.1, 8.2)	6.0 (5.1, 8.0)	6.4 (5.3, 8.8)	<0.001
LDL-C, mmol/L	2.74±0.99	2.71±0.98	2.83±1.03	<0.001
Transferred (%)	35 265 (42.9)	27 020 (44.2)	8245 (39.1)	<0.001

The values are means±SD, median (interquartile range), or n (%). ACS indicates acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; and STEMI, ST-segment–elevation myocardial infarction.

*Time from symptom onset to admission was not available for 27 775 (33.8%) patients.

†Patients with cardiogenic shock were not included as heart failure.

The mean ages of female and male patients were 69.0±10.6 and 61.1±12.4 years, respectively; 32.6% of women were older than 75 years, whereas 15.4% of men were older than 75 years. Women had a higher prevalence of diabetes mellitus, hypertension, elevated LDL-C levels, renal insufficiency, and a history of renal failure, heart failure, and cerebrovascular disease; whereas men more frequently presented with STEMI and had a smoking habit and a history of CHD. Furthermore, women had higher systolic blood pressure, heart rate, and LDL-C levels on admission than men. Women were more likely to present with severe clinical conditions, including heart failure (9.1% versus 5.7%, P<0.001) and cardiogenic shock (3.1% versus 2.8%, P=0.004), and took a longer time from symptom onset to hospital arrival than men (P<0.001). The median delay time from the onset of ACS symptoms to hospital arrival was 10.1 hours for women and 7.7 hours for men. Comparisons of clinical characteristics between men and women among patients with STEMI and NSTE-ACS are presented in Table III in the online-only Data Supplement.

Acute Management

Disparities in acute management between men and women with ACS were observed (Table 2). The pro-portion of eligible female patients with ACS who received DAPT at arrival and statins and heparin during hospitalization was lower than that of male patients (all P<0.001). Among patients with STEMI, 57.4% received acute reperfusion therapy, 49.8% underwent primary PCI alone, 6.2% received fibrinolytic therapy alone, and 1.4% were treated with a combination of fibrinolytic therapy and PCI. Women with STEMI were less likely to receive acute reperfusion therapy than men (50.2% versus 59.5%, P<0.001). Overall, 71.0% and 71.9% of female and male patients who underwent primary PCI achieved a door-to-balloon time of <90 minutes (P=0.106). Table IV in the online-only Data Supplement presents the risk-relevant characteristics of patients with NSTE-ACS by risk stratification according to sex. Among patients with NSTE-ACS, 53.3% underwent PCI during hospitalization; 33.2% of these patients with NSTE-ACS who were treated with PCI had this procedure within the timing specified in the guidelines (within 2, 24, and 72 hours of admission for groups with very high risk, high risk, and moderate risk, respectively). Eligible women with NSTE-ACS were less likely to undergo timely PCI than men (30.5% versus 34.2%, P<0.001). These sex differences in acute management persisted after multivariable adjustment for DAPT at arrival, heparin during hospitalization, and reperfusion therapy for STEMI (Table 3).

Table 2. Sex-Based Differences in Acute Managements and Medical Therapies for Secondary Prevention

Treatment	Total (n=82 196)	Men (n=61 125)	Women (n=21 071)	P Value
Acute treatments				
DAPT at arrival, %	92.3	93.5	89.0	<0.001
ACEIs/ARBs, %	50.9	50.9	50.9	0.963
β-Blockers, %	63.1	63.3	62.6	0.075
Statins, %	95.1	95.4	94.3	<0.001
Heparin during hospitalization, %	70.0	71.2	66.7	<0.001
Reperfusion therapy for STEMI, %	57.4	59.5	50.2	<0.001
Primary PCI, %	49.8	51.4	44.1	<0.001
Fibrinolysis, %	6.2	6.6	4.9	<0.001
Fibrinolysis+PCI, %	1.4	1.6	1.1	<0.001
DTB within 90 min for STEMI,* %	71.7	71.9	71.0	0.106
Timely PCI for eligible NSTE-ACS,† %	33.2	34.2	30.5	< 0.001
Medical therapies for secondary prevention				
DAPT at discharge, %	88.3	90.1	82.8	<0.001
Statins at discharge, %	92.6	93.2	90.7	<0.001
β-Blockers at discharge, %	67.0	67.8	64.8	<0.001
ACEI/ARB at discharge, %	57.2	57.9	55.4	<0.001
Smoking cessation counseling, %	34.7	35.1	27.0	<0.001
Cardiac rehabilitation counseling, %	34.5	35.0	32.9	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; DTB, door-to-balloon; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*DTB times were not available for 31.4% (8081/25 700) patients with STEMI who received primary PCI.

†Times from hospital arrival to PCI were not available for 16.7% (2843/17 049) patients with NSTE-ACS who received PCI.

Table 3. Adjusted Odds Ratios for Acute Management, Medical Therapies for Secondary Prevention in Women Compared With Men

Treatment	Adjusted OR* (95% CI) (Women vs Men)	P Value
Acute treatments		
DAPT at arrival	0.81 (0.77, 0.86)	<0.001
ACEIs/ARBs	0.97 (0.94, 1.01)	0.151
β-Blockers	1.04 (1.00, 1.08)	0.070
Statins	0.93 (0.86, 1.01)	0.080
Heparin during hospitalization	0.94 (0.91, 0.98)	0.001
Reperfusion therapy for STEMI	0.92 (0.88, 0.97)	<0.001
DTB within 90 min for STEMI†	1.02 (0.93, 1.12)	0.679
Timely PCI for eligible NSTE-ACS‡	0.92 (0.83, 1.01)	0.071
Medical therapies for secondary prevention		
DAPT at discharge	0.72 (0.69, 0.76)	<0.001
Statins at discharge	0.86 (0.81, 0.92)	<0.001
β-Blockers at discharge	0.99 (0.96, 1.03)	0.767
ACEI/ARB at discharge	0.94 (0.90, 0.97)	<0.001
Smoking cessation counseling	0.68 (0.61, 0.76)	<0.001
Cardiac rehabilitation counseling	0.91 (0.88, 0.94)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; DTB, door-to-balloon; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; OR, odds ratios; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*ORs (women vs men) were adjusted for age, medical insurance, acute heart failure at admission, cardiogenic shock at admission, cardiac arrest at admission, heart rate, systolic blood pressure, diabetes mellitus, smoking, history of coronary heart disease, heart failure, renal failure, cerebrovascular disease, prehospital statin use, renal insufficiency, and transfer status. Smoking was not included in the multivariate analysis for the association between sex of patients and smoking cessation counseling.

†DTB times were not available for 31.4% (8081/25 700) patients with STEMI who received primary PCI.

‡Times from hospital arrival to PCI were not available for 16.7% (2843/17 049) patients with NSTE-ACS who received PCI.

Medical Therapies for Secondary Prevention

Among eligible patients, women were less likely than men to receive DAPT at discharge (82.8% versus 90.1%, P<0.001), statins at discharge (90.7% versus 93.2%, P<0.001), β-blockers at discharge (64.8% versus 67.8%, P<0.001), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers at discharge (55.4% versus 57.9%, P<0.001), smoking cessation counseling during hospitalization (27.0% versus 35.1%, P<0.001), and cardiac rehabilitation counseling during hospitalization (32.9% versus 35.0%, P<0.001) (Table 2). These sex differences in medical therapies for secondary prevention persisted after multivariable adjustment except for β-blockers at discharge (Table 3).

In-Hospital Mortality

As shown in Figure, the in-hospital mortality rate was higher in women than in men (2.60% versus 1.50%,

P<0.001), especially among patients with STEMI (3.68% versus 1.71%, P<0.001). After adjustment for age and other clinical characteristics, the sex difference in in-hospital mortality was attenuated in the STEMI population, and women had a 20% higher risk of in-hospital mortality than men (adjusted odds ratio, 1.20; 95% CI, 1.01 to 1.43, P=0.035; Table 4). To evaluate whether the residual sex difference in early mortality could be explained by disparities in the acute management of STEMI, we further adjusted for the use of DAPT at arrival, fibrinolytic therapy, and PCI. After additional adjustment for acute treatments, the sex difference in in-hospital mortality was no longer statistically significant in patients with STEMI (adjusted odds ratio, 1.18; 95% confidence interval, 1.00 to 1.41; P=0.057). In addition, the sex difference in in-hospital mortality was no longer observed among patients with NSTE-ACS (adjusted odds ratio, 0.84; 95% CI, 0.66 to 1.06; P=0.147) after adjustment for clinical characteristics and acute treatments.

In-hospital mortality rates among men and women stratified by age groups (<55, 55 to 64, 65 to 74, and ≥75 years) were estimated. In patients with STEMI, the differences in in-hospital mortality rates between women and men were statistically significant in the 55 to 64-, 65 to 74-, and ≥75-year age groups (Table V in the online-only Data Supplement). Multivariable analyses indicated no significant interaction between sex and age with respect to in-hospital mortality (P for interaction = 0.07 in patients with STEMI and P for interaction = 0.64 in patients with NSTE-ACS).

DISCUSSION

In this large, hospital-based registry for male and female patients hospitalized for ACS in China, we observed that women were less likely to receive acute treatments and
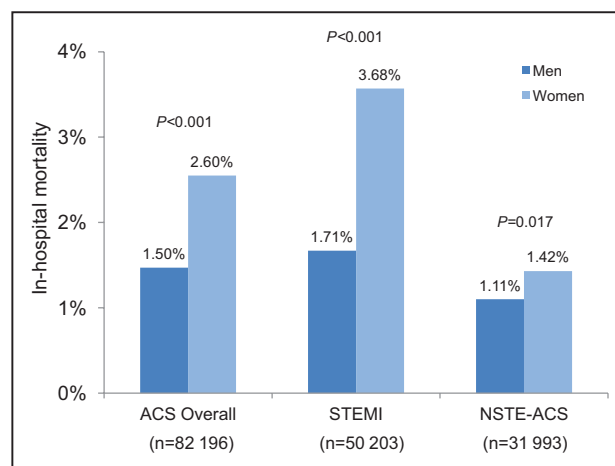

Figure. In-hospital mortality rates among hospitalized women and men in the acute coronary syndrome (ACS) overall, ST-segment–elevation myocardial infarction (STEMI), and non–ST-segment–elevation acute coronary syndrome (NSTE-ACS) populations.

Table 4. Sex-Based Differences of In-Hospital Deaths

Model	STEMI Patients		NSTE-ACS Patients	
	Adjusted OR (95% CI) (Women vs Men)	P Value	Adjusted OR (95% CI) (Women vs Men)	P Value
Unadjusted	2.26 (1.97, 2.60)	<0.001	1.29 (1.05, 1.59)	0.017
Model 1*	1.42 (1.22, 1.65)	<0.001	0.90 (0.73, 1.11)	0.337
Model 2†	1.20 (1.01, 1.43)	0.035	0.87 (0.69, 1.11)	0.263
Model 3‡	1.20 (1.01, 1.43)	0.035	0.87 (0.68, 1.10)	0.230
Model 4§	1.18 (1.00, 1.41)	0.057	0.84 (0.66, 1.06)	0.147

NSTE-ACS indicates non–ST-segment–elevation acute coronary syndrome; OR, odds ratio; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Model 1: age adjusted.

†Model 2: adjusted for age, medical insurance, time from symptom onset to admission (<2 h, 2–12 h, and >12 h; this variable was not included in the model for patients with NSTE-ACS), acute heart failure at admission, cardiogenic shock at admission, cardiac arrest at admission, heart rate, systolic blood pressure, diabetes mellitus, smoking, history of coronary heart disease, heart failure, renal failure, cerebrovascular disease, prehospital statin use, renal insufficiency, and transfer status.

‡Model 3: adjusted for variables in model 2 plus DAPT at arrival.

§Model 4: (1) for STEMI patients, adjusted for variables in model 3 plus fibrinolysis therapy and PCI (primary PCI, delayed PCI, and no PCI); and (2) for NSTE-ACS patients, adjusted for variables in model 3 plus PCI (timely PCI, nontimely PCI, and no PCI).

medical therapies for secondary prevention than men. After multivariable adjustment, sex-related disparities in in-hospital management of patients with ACS persisted. Moreover, women had higher crude in-hospital mortality rates than men. After adjustment for clinical characteristics and early management, sex-related disparities in early mortality were no longer observed.

Consistent with previous reports, we observed a higher unadjusted in-hospital mortality rate in women hospitalized for ACS than in men, and the difference in mortality rate was more pronounced in patients with STEMI.[22–25] Similar to those in previous studies, women in the present study were older and had more comorbidities, including hypertension, elevated LDL-C levels, diabetes mellitus, and heart failure, than men.[10,11] Previous studies have shown that sex differences in early mortality after ACS are largely explained by these clinical differences at presentation.[26,27] In our study, the increased mortality risk in women attenuated largely after adjustment for age and other clinical characteristics in patients with STEMI. Previous studies have reported excess early mortality after STEMI in younger women[7,28,29] and detected interaction between sex and age.[7] In the present study, the in-hospital mortality rate was observed to be higher in women aged 55 to 64, 65 to 74, and ≥75 years than in men. No significant interactions between age categories and sex with respect to the risk of in-hospital mortality were noted after adjustment for clinical profiles and acute treatments. These inconsistent results in subgroup and sex-age interaction analyses may be attributed to different overall in-hospital mortality rates, definitions of age categories, and covariates used across studies.

In addition to differences in clinical profiles, other factors may contribute to the observed sex difference in mortality after STEMI (eg, delay in hospital presentation and acute treatments). Our study revealed that women presented to hospitals for STEMI treatment 1.4 hours later than men. This delay in presentation has been reported to be associated with an increased risk of death and recurrent events in patients with STEMI.[30] This prolonged delay in presentation to the hospital in women compared with men may be attributed to the misinterpretation of symptoms, lack of awareness, and barriers to accessing care.[31,32] Moreover, women were less likely to receive acute treatments including DAPT at arrival and reperfusion therapy than men. These disparities in acute treatments also contributed to the difference in mortality rate between men and women. A meta-analysis that investigated sex differences in mortality among patients treated with primary PCI concluded that the increased mortality in women was likely confounded by differences in baseline cardiovascular risk factors and clinical profiles.[33] In the present study, sex-related disparities in early mortality were no longer observed after additional adjustment for acute management (DAPT at arrival, fibrinolytic therapy, and PCI). Addressing the sex-related disparities in evidence-based treatments may improve the outcomes of female patients with STEMI.

Furthermore, previous studies have reported that women with NSTE-ACS (NSTE myocardial infarction and unstable angina) experience higher absolute in-hospital mortality than men.[34–36] The higher risk of early mortality in women with NSTE-ACS was no longer apparent after adjustment for clinical characteristics.[35,36] A recent study using data from the National Inpatient Sample database in the United States has indicated that women had lower risk-adjusted in-hospital mortality than men after accounting for differences in age and comorbidities between sexes.[34] In our study, women with NSTE-ACS had higher crude in-hospital mortality rates than men, and this difference was no longer significant after adjustment for age and clinical characteristics. It is worth noting that the multivariable analysis

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in the National Inpatient Sample study accounted for noncardiovascular comorbidities (eg, depression and chronic pulmonary diseases), which were not included in most previous studies and in the present study.

Although evidence-based medications and invasive procedures are similarly effective in male and female patients with ACS, women with ACS are less likely to undergo invasive interventions and receive fewer evidence-based medications than men. With respect to reperfusion therapy for patients with STEMI, women were less likely to receive reperfusion therapy with fibrinolytic therapy or primary PCI than their male counterparts in our study. This disparity persisted after adjustment for clinical factors. Multiple studies have also documented such sex-specific differences in reperfusion therapies for STEMI.[9,10] The prolonged delay between symptom onset and hospital arrival in women compared with that in men may partly explain the lower proportion of reperfusion therapy observed in women.[37]

With respect to pharmacological therapies for secondary prevention, women received fewer guideline-recommended therapies, including DAPT, statins, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers at discharge, as well as smoking cessation and cardiac rehabilitation counseling during hospitalization, than men. Despite the modest absolute treatment differences between women and men, women were less likely to receive evidence-based treatments than men. The disparity in medical insurance reimbursement is a barrier to accessing care that cannot be ignored. However, after adjustment for medical insurance status, women were still less likely to receive evidence-based treatments than men.

Although sex differences in the clinical management of patients with ACS have been reported over the last 3 decades, the reasons for these disparities remain largely unknown.[3,5] Potential explanations include sex differences in eligibility for therapy, clinical contraindications, and other clinical factors.[10] As expected in our study, women with ACS were older and had worse clinical profiles than men. These worse clinical profiles contribute to an increased risk of adverse outcomes, thus signifying greater absolute treatment benefits. These characteristics are always associated with undertreatment, partly for fear of complications (eg, higher risk of bleeding) and partly because of the lack of evidence from randomized clinical trials in these groups.[35] In the present study, we focused on eligible patients with treatment indications and adjusted for clinical patient characteristics to minimize the effect of potential confounders mentioned above.

The results of this study should be interpreted in consideration of several limitations. The CCC-ACS project recruited only patients with ACS who were admitted to the hospital, and there was no information on patients who died before arrival to the hospital. This may have led to potential selection bias. Women had worse clinical profiles than men. We adjusted for these clinical profiles in the regression model; nonetheless, residual measured and unmeasured confounding may still have contributed to some of these findings. In particular, cardiac troponin elevation and changes in ECG parameters may be attributed to an exacerbation of heart failure, which was more common in women. Such residual confounding may have contributed to undertreatment with PCI and DAPT among women. Moreover, the angiographic severity of coronary lesions, which may also contribute to the sex difference in early mortality after ACS, was not adjusted in the present study. A previous study reported no significant differences in 30-day mortality among women and men, regardless of ACS type, after adjusting for angiographic disease severity and clinical covariates.[23] Another study revealed that the higher risk of in-hospital mortality in women than in men was restricted to patients with myocardial infarction who had obstructive coronary artery disease, but was not observed in patients with myocardial infarction who had nonobstructive coronary artery disease.[22] The present study focused on data during hospitalization. Future studies that track patients after discharge will help examine the effect of sex-related disparities in quality of care on the long-term outcomes of patients with ACS. Moreover, the clinical characteristics, in-hospital management, and outcomes in the CCC-ACS project, being a hospital-based registry, were defined based on the information abstracted from inpatient records. The quality of documentation could have affected the present study.

CONCLUSIONS

The present study is the largest registry study that evaluated sex-related differences in in-hospital management and outcomes of patients with ACS in China, with 82 196 patients with ACS from 192 hospitals. Women with ACS showed a higher unadjusted risk of in-hospital mortality than men. The sex difference in in-hospital mortality was attenuated after adjustment for clinical characteristics and was no longer significant after additional adjustment for acute treatments. Women were less likely to receive acute treatments and medical therapies for secondary prevention than men. However, the reasons for these sex-based differences in the clinical management of ACS remain largely unknown. The sex differences in quality of care and in-hospital mortality emphasize the need for further investigation and a specially targeted quality improvement program to reduce or even eliminate the disparities in care.

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