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Sex Differences in In-hospital Management and Outcomes of Patients with Acute Coronary Syndrome: Findings from the Improving Care for Cardiovascular Disease in China (CCC) Project

Running Title: *Hao et al.; Sex Differences in Management and Outcomes for ACS*

Yongchen Hao, PhD[1]; Jing Liu, MD, PhD[1]; Jun Liu, MD[1]; Na Yang, PhD[1]; Sidney C. Smith Jr, MD[2]; Yong Huo, MD[3]; Gregg C. Fonarow, MD[4]; Junbo Ge, MD, PhD[5]; Kathryn A. Taubert, PhD[6]; Louise Morgan, MSN[7]; Mengge Zhou, MD[1]; Yueyan Xing, MD[1]; Chang-Sheng Ma, MD[8]; Yaling Han, MD[9]; Dong Zhao, MD, PhD[1*]; on behalf of the CCC-ACS Investigators

[1]Department of Epidemiology, Beijing An Zhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China; [2]Division of Cardiology, University of North Carolina, Chapel Hill, NC; [3]Department of Cardiology, Peking University First Hospital, Beijing, China; [4]Division of Cardiology, Geffen School of Medicine at University of California, Los Angeles, CA; [5]Department of Cardiology, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, China; [6]Department of International Science, American Heart Association, Basel, Switzerland; [7]International Quality Improvement Department, American Heart Association, Dallas, TX; [8]Department of Cardiology, Beijing An Zhen Hospital, Capital Medical University, Beijing, China; [9]Cardiovascular Research Institute and Department of Cardiology, General Hospital of Shenyang Military Region, Shenyang, Liaoning, China

***Address for Correspondence:**
Dong Zhao, MD, PhD
Department of Epidemiology
Beijing An Zhen Hospital, Capital Medical University
Beijing Institute of Heart, Lung and Blood Vessel Diseases
No. 2 Anzhen Road, Chaoyang DistrictBeijing 100029, China
Tel: +86-10-64456524
Fax: +86-10-64419738
Email: deezhao@vip.sina.com

Abstract

Background: Coronary heart disease (CHD) 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 CHD, remains lacking in China.
Methods: The Improving Care for Cardiovascular Disease in China (CCC)-ACS project is an ongoing nationwide registry of the American Heart Association and 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 vs. 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 (DAPT), heparins during hospitalization, and reperfusion therapy for ST-segment elevation myocardial infarction (STEMI). With respect to strategies for secondary prevention, eligible women were less likely to receive DAPT, 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% vs. 1.50%, *P*< 0.001). The sex difference in in-hospital mortality was no longer observed in patients with STEMI (adjusted odds ratio [OR], 1.18; 95% confidence interval [CI], 1.00–1.41; *P*=0.057) and non-ST-segment elevation ACS (adjusted OR, 0.84; 95% CI, 0.66–1.06; *P*=0.147) after adjustment for clinical characteristics and acute treatments.
Conclusions: Women hospitalized for ACS in China less frequently received acute treatments and strategies for secondary prevention than men. The observed sex differences in in-hospital mortality were mainly due 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.
Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02306616.

Key Words: acute coronary syndrome; medical care; in-hospital mortality; women

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 less frequently received acute treatments and strategies for secondary prevention, and had higher in-hospital mortality rate than men.
- The observed sex differences in in-hospital mortality were mainly due 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.

Introduction

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

The Improving Care for Cardiovascular Disease in China (CCC)-ACS project 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 the third party 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 (AHA) and Chinese Society of Cardiology (CSC) 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. At each month, the first 20–30 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 www.ClinicalTrials.gov (number 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 CSC 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, electrocardiogram (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, USA). Data elements collected in this study included patients' demographics, medical history, symptoms on arrival, in-hospital treatments and procedures, 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: face-to-face training workshops, use of a standardized online reporting tool with automatic checks for invalid values, onsite quality control, and 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 (ACEIs)/angiotensin receptor blockers (ARBs), 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-min door-to-balloon time recommended in the American College of Cardiology/AHA 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 h, 24 h, and 72 h 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, ACEIs/ARBs 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 (Supplemental Table 1).

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), "others," or "no medical insurance". Hypertension was defined as having a history of hypertension, receiving antihypertensive therapy, or having a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg 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 A1clevel ≥6.5%. Elevated low-density lipoprotein cholesterol level (LDL-C) 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 (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation.[21] Renal insufficiency was defined as eGFR<60 mL/min per 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 prior to the current hospitalization. The transfer status indicated whether the patient was transferred in 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 (Supplemental Methods).

Statistical methods

Categorical variables were presented as frequencies and percentages, whereas continuous variables were expressed as means and standard deviations 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 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; pre-hospital 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 h, 2–12 h, and >12 h), 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, non-timely PCI, and no PCI). For each treatment and outcome, odds ratios (ORs) with 95% confidence intervals (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, USA), 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 36 936 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 Supplemental Table 2. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Two-sided *P*-values <0.05 were considered statistically significant.

Results

Patients' characteristics

Among 82 196 patients with ACS who were included in this study, 21 071 (25.6%) were women, whereas 61 125 (74.4%) were men. The clinical characteristics of the study population are summarized in Table 1. The mean age of female and male patients was 69.0±10.6 years 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 level, renal insufficiency, and a history of renal failure, heart failure, and cerebrovascular disease, whereas men more frequently presented with STEMI and had smoking habits and a history of CHD. Furthermore, women had higher systolic blood pressure, heart rate, and LDL-C level on admission than men. Women were more likely to present with severe clinical conditions, including heart failure (9.1% vs. 5.7%, *P*< 0.001) and cardiogenic shock (3.1% vs. 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 h for women and 7.7 h for men. Comparisons of clinical characteristics between men and

women among patients with STEMI and NSTE-ACS are presented in Supplemental Table 3.

Acute management

Disparities in acute management between men and women with ACS were observed (Table 2). The proportion of eligible female patients with ACS who received DAPT at arrival, 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% vs. 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 min ($P= 0.106$). Supplemental Table 4 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 h, 24 h, and 72 h 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% vs. 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).

Medical therapies for secondary prevention

Among eligible patients, women were less likely to receive DAPT at discharge (82.8% vs. 90.1%, $P < 0.001$), statins at discharge (90.7% vs. 93.2%, $P< 0.001$), β-blockers at discharge (64.8% vs. 67.8%, $P< 0.001$), ACEIs/ARBs at discharge (55.4% vs. 57.9%, $P < 0.001$), smoking cessation counseling during hospitalization (27.0% vs. 35.1%, $P< 0.001$), and cardiac

rehabilitation counseling during hospitalization (32.9% vs. 35.0%, *P*< 0.001) than men (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 1, the in-hospital mortality rate was higher in women than in men (2.60% vs. 1.50%, *P*< 0.001), especially among patients with STEMI (3.68% vs. 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 OR, 1.20; 95% CI, 1.01–1.43, *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 OR, 1.18; 95% CI, 1.00–1.41; *P*=0.057). In addition, the sex difference in in-hospital mortality was no longer observed among patients with NSTE-ACS (adjusted OR, 0.84; 95% CI, 0.66–1.06; *P* = 0.147) after adjustment for clinical characteristics and acute treatments.

In-hospital mortality rates among men and women stratified by age groups (<55years, 55–64 years, 65–74 years, 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 55–64-year, 65–74-year, and ≥75-year age groups (Supplemental Table 5). 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 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 level, diabetes, 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 55–64 years, 65–74 years, 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 (e.g., delay in hospital presentation and acute treatments). Our study revealed that women presented to hospitals for STEMI treatment 1.4 h 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 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 (NIS) 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 in the NIS study accounted for non-cardiovascular comorbidities (e.g., 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 ACEIs/ARBs 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 (e.g., 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 have still 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 non-obstructive 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.

Conclusion

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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Disclosures

Dr. Fonarow consulted for Amgen, Bayer, Janssen, and Novartis and served on the AHA's Quality Oversight Committee. The other authors have no conflicts of interest to declare.

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Table 1. Clinical characteristics of the ACS patients at admission

Variables	Total (n=82 196)	Men (n= 61 125)	Women (n= 21 071)	*P*
Age, years	63.1±12.5	61.1±12.4	69.0±10.6	<0.001
ACS type				<0.001
STEMI	50203(61.1%)	39187(64.1%)	11016(52.3%)	
NSTE-ACS	31993(38.9%)	21938(35.9%)	10055(47.7%)	
Medical insurance				<0.001
Urban insurance	44245(53.8%)	33189(54.3%)	11056(52.5%)	
Rural insurance	19344(23.5%)	13494(22.1%)	5850(27.8%)	
Other insurance	7914(9.6%)	6065(9.9%)	1849(8.8%)	
Self paid	10693(13.0%)	8377(13.7%)	2316(11.0%)	
Hospital stays, days	9 (7, 13)	9 (7, 12)	10 (7, 13)	<0.001
Time from symptom onset to admission, hour*	8.1(3.7, 27.8)	7.7(3.5, 25.6)	10.1(4.2, 41.0)	<0.001
<2 hours	5147(9.5%)	4128(10.1%)	1019(7.6%)	
2 - 12 hours	26976(49.6%)	20832(50.7%)	6144(46.1%)	
>12 hours	22298(41.0%)	16120(39.2%)	6178(46.3%)	
ECG at admission				<0.001
ST-segment elevation	40939(49.8%)	31888(52.2%)	9051(43.0%)	
Temporary ST-segment depression	14678(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	18839(22.9%)	13446(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	34223(41.6%)	24082(39.4%)	10141(48.1%)	<0.001
Hypertension	54033(65.7%)	38426(62.9%)	15607(74.1%)	<0.001
Elevated LDL-C (>= 70 mg/dL)	68940(83.9%)	50944(83.3%)	17996(85.4%)	<0.001
Smoking	34096(41.5%)	32377(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
Pre-hospital statin	14364(17.5%)	10429(17.1%)	3935(18.7%)	<0.001
Killip class				<0.001
I	60083(73.1%)	45470(74.4%)	14613(69.4%)	

II-III	19050(23.2%)	13620(22.3%)	5430(25.8%)	
IV	3063(3.7%)	2035(3.3%)	1028(4.9%)	
Renal insufficiency	13198(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	35265(42.9%)	27020(44.2%)	8245(39.1%)	<0.001

Values are mean±SD, median (interquartile range, IQ), or n (%).
ACS indicates acute coronary syndrome; ECG, electrocardiogram; LDL-C, low-density lipoprotein cholesterol; NSTE-ACS, non-ST-elevation acute coronary syndrome; and STEMI, ST-elevation myocardial infarction.
* Time from symptom onset to admission was not available for 27775 (33.8%) patients.
†Patients with cardiogenic shock were not included as heart failure.

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*
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 minutes 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-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction;

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

† Time 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*
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 minutes 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-elevation acute coronary syndrome; OR, odds ratios; PCI, percutaneous coronary intervention; STEMI, ST-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 and cerebrovascular disease, pre-hospital 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 Time were not available for 31.4%(8081/25 700) patients with STEMI who received primary PCI.

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

Table 4. Sex-based differences of in-hospital deaths

Model	STEMI patients		NSTE-ACS patients	
	Adjusted OR (95% CI) (Women vs Men)	***P***	**Adjusted OR (95% CI) (Women vs Men)**	***P***
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-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction; and OR, odds ratios.

* Model 1: age adjusted.

† Model 2: adjusted for age, medical insurance, time from symptom onset to admission (<2 hours, 2 - 12 hours and >12 hours; this variable were 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, and cerebrovascular disease, pre-hospital 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); (2) For NSTE-ACS patients, adjusted for variables in model 3 plus PCI (timely PCI, non-timely PCI and no PCI).

Figure Legend

Figure 1. In-hospital mortality rates among hospitalized women and men in the ACS overall, STEMI and NSTE-ACS populations.

ACS indicates acute coronary syndrome; NSTE-ACS, non–ST–elevation acute coronary syndrome; and STEMI, ST-elevation myocardial infarction.