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ORIGINAL ARTICLE

Sex Differences in Characteristics, Treatments, and Outcomes Among Patients Hospitalized for Non–ST-Segment–Elevation Myocardial Infarction in China: 2006 to 2015

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BACKGROUND: Sex differences in clinical characteristics and in-hospital outcomes among patients with non–ST-segment–elevation myocardial infarction have been described in Western countries, but whether these differences exist in China is unknown.

METHODS: We used a 2-stage random sampling design to create a nationally representative sample of patients admitted to 151 Chinese hospitals for non–ST-segment–elevation myocardial infarction in 2006, 2011, and 2015 and examined sex differences in clinical profiles, treatments, and in-hospital outcomes over this time. Multivariable logistic regression models adjusting for age or other potentially confounding clinical covariates were used to estimate these sex-specific differences.

RESULTS: Among 4611 patients, the proportion of women (39.8%) was unchanged between 2006 and 2015. Women were older with higher rates of hypertension, diabetes, and dyslipidemia. Among patients without contraindications, women were less likely to receive treatments than men, with significant differences for aspirin in 2015 (90.3% versus 93.9%) and for invasive strategy in 2011 (28.7% versus 45.7%) and 2015 (34.0% versus 48.4%). After adjusting for age, such differences in aspirin and invasive strategy in 2015 were not significant, but the difference in invasive strategy in 2011 persisted. The sex gaps in the use of invasive strategy did not narrow. From 2006 to 2015, a significant decrease in in-hospital mortality was observed in men (from 16.9% to 8.7%), but not in women (from 11.8% to 12.0%), with significant interaction between sex and study year (P=0.023). After adjustment, in-hospital mortality in women was significantly lower than men in 2006, but not in 2011 or 2015.

CONCLUSIONS: Sex differences in cardiovascular risk factors and invasive strategy after non–ST-segment–elevation myocardial infarction were observed between 2011 and 2015 in China. Although sex gaps in in-hospital mortality were largely explained by age differences, efforts to narrow sex-related disparities in quality of care should remain a focus.

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Key Words: mortality ■ myocardial infarction ■ quality of health care ■ risk factors ■ sex characteristics ■ women

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WHAT IS KNOWN

- Sex differences in patient characteristics and outcomes among the patients hospitalized for non–ST-segment–elevation myocardial infarction have been well described in the United States and European countries.

WHAT THE STUDY ADDS

- It is the first nationally representative study to examine sex differences in characteristics, treatment, and outcomes among patients with non–ST-segment–elevation myocardial infarction in China.
- Women consistently had a higher burden of cardiovascular risk factors than men from 2011 to 2015.
- Although the quality of care has improved for both sexes, women had lower use rates of aspirin in 2015 and received less invasive strategy in 2011 and 2015 among patients without contraindications.
- The observed higher in-hospital mortality in women than men was mainly due to older age.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blocker
CAMI	China Acute Myocardial Infarction
China PEACE-Retrospective AMI	China Patient-Centered Evaluative Assessment of Cardiac Events Retrospective Study of Acute Myocardial Infarction
eGFR	estimated glomerular filtration rate
GRACE	Global Registry of Acute Coronary Events
NSTEMI	non–ST-segment–elevation myocardial infarction
PCI	percutaneous coronary intervention

Studies from 2 decades ago in Europe and the United States found that women with non–ST-segment–elevation acute coronary syndrome had worse clinical profiles and in-hospital outcomes and were less likely to receive evidence-based treatments.[1,2] Since 2007, the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines made clear that treatments for non–ST-segment–elevation myocardial infarction (NSTEMI) should not vary by patient sex.[3,4] Subsequent studies from Western countries have shown decreasing in-hospital mortality of NSTEMI[5,6]; this favorable trend appeared equally in both sexes,[7] or even more prominently in women.[8] Nevertheless, more recent studies have highlighted persistent sex differences in NSTEMI therapies in the 2010s[9] but reporting conflicting in-hospital outcomes.[10–12]

In China, the increased number of NSTEMI is occurring in women, while a large-scale assessment on sex differences and trends in NSTEMI is still lacking.[13] Contemporary data from the CAMI (China Acute Myocardial Infarction) registry found that women with NSTEMI were less likely to receive guideline-based treatments and had higher in-hospital mortality than men.[14] In addition, an epidemiological study conducted in Beijing observed no significant improvement in in-hospital mortality in women from 2007 to 2012.[15] Given that previous studies have primarily derived data from single sites or single time points, a national assessment about sex differences in treatments and outcomes among patients with NSTEMI is needed. Moreover, an understanding of how these sex-based differences have evolved over time may help implement targeted quality improvement initiatives for women.

Hence, we analyzed data from the China PEACE-Retrospective AMI study (China Patient-Centered Evaluative Assessment of Cardiac Events Retrospective Study of Acute Myocardial Infarction), which included a random nationally representative sample of patients with NSTEMI from 62 urban and 89 rural hospitals across China in 2006, 2011, and 2015. Our primary aim is to investigate the trends of sex differences in characteristics, treatments, and outcomes of patients hospitalized for NSTEMI.

METHODS

The data are not available to be shared at this time.

Study Design

The China PEACE-Retrospective AMI study is a cross-sectional assessment that has been described previously, from which we included a nationally representative sample of patients for AMI in China between 2006 and 2011.[16] We also included a more recent sample of patients admitted in 2015 using the same 2-stage random sampling process. Briefly, we first stratified our sample of hospitals by economic-geographic regions using a simple random sampling procedure. Based on differences in per capita income and health service capacity across urban and rural areas, as well as 3 official economic-geographic regions (Eastern, Central, and Western), we divided mainland China into 5 study strata: eastern-rural, central-rural, western-rural, eastern-urban, and central/western-urban. We sampled representative hospitals from 2011 to reflect current practices and used the same cohort of hospitals for 2006 and 2015 to describe trends. Then, we adopted a systematic random sampling method to select cases from the local hospital database of each sampled hospital for each study year (2006, 2011, and 2015). We screened for AMI cases based on the *International Classification of Diseases* versions 9 and 10 (if

available) or through primary discharge diagnosis. The diagnosis of NSTEMI was determined by the combination of clinical discharge diagnosis terms and ECG results and validated by a review of ECGs from randomly selected records by a cardiologist not involved in data abstraction. To verify the accuracy of AMI type (STEMI or NSTEMI), we examined the concordance between the discharge diagnosis of medical records and ECG randomly selected, and there was a 94.7% concordance.[16]

We collected data by central abstraction of medical charts using standardized data definitions and used rigorous monitoring at each stage to ensure data quality. Data abstraction quality was monitored by random auditing of 5% of the medical records, with overall variable accuracy exceeding 98%. This retrospective project was reviewed and approved by the central ethics committee of the National Center for Cardiovascular Diseases and cooperative hospitals. The requirement to obtain written informed consent was waived.

Study Sample

For this analysis, our study was limited to patients with a discharge diagnosis of NSTEMI. We excluded all patients whose NSTEMI occurred during hospitalization and those who were transferred in, transferred out, or were discharged alive in the first 24 hours of admission (Figure S1).

Data Collection and Variables

We abstracted the data for patient- and hospital-level characteristics. The indications for oral anticoagulants were defined as documented atrial fibrillation, pulmonary embolism, deep vein thrombosis, or venous thromboembolism. We assessed clinical severity at admission by calculating the mini-Global Registry of Acute Coronary Events (mini-GRACE) risk score—a modified version of the GRACE risk score, including age, systolic blood pressure, ST-segment deviation, cardiac arrest at admission, elevated cardiac enzymes, and heart rate, which has been validated to predict 6-month mortality for AMI.[17]

We assessed the use of treatments recommended by the 2016 Chinese Guideline for the management of patients with non–ST-segment–elevation acute coronary syndrome, which was consistent with those recommended in European Society of Cardiology and American Heart Association guidelines.[18] These recommendations included the use of aspirin, clopidogrel/ticagrelor, dual antiplatelet therapy, β-blocker, ACE (angiotensin-converting enzyme) inhibitor/ARB (angiotensin receptor blocker), statin and parenteral anticoagulant during hospitalization, as well as an invasive strategy (defined as invasive coronary angiography or percutaneous coronary intervention [PCI]) and PCI. The use rates for each treatment were assessed only in eligible patients, defined as patients without documented contraindications (Supplemental Methods). When assessing the sex differences in using invasive coronary catheterization, we restricted this analysis to the patients admitted to hospitals capable of performing PCI.

We compared in-hospital outcomes, including mortality, a composite outcome of complications (including mortality, reinfarction, cardiogenic shock, ischemic stroke, or congestive heart failure) and major bleeding, between women and men. In-hospital mortality was defined as a composite outcome of death or withdrawal from treatment due to a terminal condition. Withdrawing treatment is common in China as many patients would like to die at home when in terminal conditions. Major bleeding included any intracranial hemorrhage or drop in hemoglobin of at least 5 g/dL or hypovolemic shock caused by bleeding, or lethal bleeding (defined as bleeding resulting in death within 7 days).

Statistical Analysis

We compared the baseline characteristics, treatments, and outcomes between both sexes in the overall study period and each study year (2006, 2011, and 2015). The categorical variables were presented as percentages and analyzed using χ^2 tests. The continuous variables were reported as medians (interquartile range) and analyzed using the Kruskal-Wallis test. To analyze the 10-year trend, we used the Mann-Kendall trend test for continuous variables and the Cochran-Armitage trend test for categorical variables. All trend tests were based on the 3 time points (2006, 2011, and 2015). We adjusted for age in logistic regression models to investigate the association between sex and the prevalence of cardiovascular risk factors. The relationship between sex and treatment received was examined using logistic regression models adjusted for age. Additionally, we included a sex × year interaction term in multivariable models to determine whether sex differences in treatments and outcomes changed over time. To account for the clustering of patients within hospitals, we used a mixed model with hospitals as the random effect. To explore the factors potentially accounting for sex differences in invasive strategy in women and men, we conducted multivariable logistic regression models stratified by sex and also tested for interactions between each variable and sex. To evaluate the incremental contribution of important confounders in explaining any sex differences in patient outcomes, logistic regression analyses were performed adjusting for explanatory variables step by step, including unadjusted model, model 1 (adjusting for age), model 2 (adjusting for model 1 and hypertension, diabetes, dyslipidemia, and current smoking), and model 3 (adjusting for model 2 and indication for oral anticoagulants, mini-GRACE risk score, and estimated glomerular filtration rate [eGFR]) in the complete sample and stratified by year. In these models, variables like age, eGFR, and mini-GRACE risk score were included as continuous variables. Due to a higher proportion of missing data on eGFR (11% of the entire sample), we used the multiple imputation method to impute the variable. For each outcome, odds ratios with 95% CIs were reported (men as the reference group). All data analyses were performed using SAS 9.4 version. A 2-sided *P* level <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

We identified 4611 participants hospitalized for NSTEMI (39.8% women) at 151 hospitals across China. Over time, the proportion of women has remained relatively stable (39.3% in 2015). Women were older than men (median age 73 versus 67 years). The median age of both sexes did not change significantly over time (*P* value for trend >0.05).

Except for smoking, the prevalence of cardiovascular risk factors remained constant over time in both sexes

(*P* value for trend >0.05 for all; Figure 1). Compared with men, women more often had hypertension, diabetes, and dyslipidemia since 2011 (*P* value<0.001 for all comparisons). Similar findings were found in the age-adjusted results (Figure S2). In contrast, men more often had a history of coronary heart disease, and the difference between the sexes persisted between 2011 and 2015. Furthermore, women were less likely to have chest discomfort in 2006 and 2011, but this sex difference disappeared in 2015 (*P* value for interaction <0.05). Overall, more women were classified as high ischemic risk (27.2% versus 20.7%) according to the mini-GRACE risk score, and such disparities persisted in each study year (*P* value for interaction >0.05). Although no sex difference existed in median ejection fraction in each year, women had lower eGFR, mean corpuscular hemoglobin concentration, median troponin concentration than men, and the difference in eGFR persisted over time. The proportion of both sexes admitted to hospitals capable of performing PCI was increasing over the past decade (*P* value for trend <0.001). Length of hospital stay did not differ by sex, and the median and interquartile range of hospital stays was 10 (7–14) days in both sexes (Table 1).

In-Hospital Treatments

Among patients without contraindications, women were less likely to receive invasive strategy (31.8% versus 46.8%) and PCI (22.4% versus 35.3%) than men. Although the invasive strategy was performed increasingly in both sexes, sex differences did not narrow (*P* value for interaction=0.323; Figure 2). After adjustment for age, the sex difference disappeared in 2015 but remained significant in 2011 (adjusted odds ratio, 0.62 [95% CI, 0.46–0.84]; Table S1).

Additionally, we explored potential factors influencing sex-based differences in utilization of invasive strategy (Table S2). We found a significant interaction between sex and the factors of increased age, hypertension, increased mini-GRACE risk score, and eGFR. Compared with men, women with older age, higher GRACE risk score, and hypertension were relatively less likely to undergo invasive strategy. Women with higher eGFR levels were more likely to undergo invasive strategy than men.

Trends in the pharmacotherapies were similar between sexes except for parenteral anticoagulants (Table 2). Women were less likely to receive aspirin in 2015 (90.3% versus 93.9%) than men. However, after adjustment for age, such difference disappeared. From 2006 to 2015, sex differences in using parenteral anticoagulants and statin diminished. No significant sex differences were observed in the administration of clopidogrel/ticagrelor, β-blocker, ACE inhibitor/ARB, and oral anticoagulants over the study period.

In-Hospital Outcomes

From 2006 to 2015, there were absolute declines in crude in-hospital mortality and composite complications among

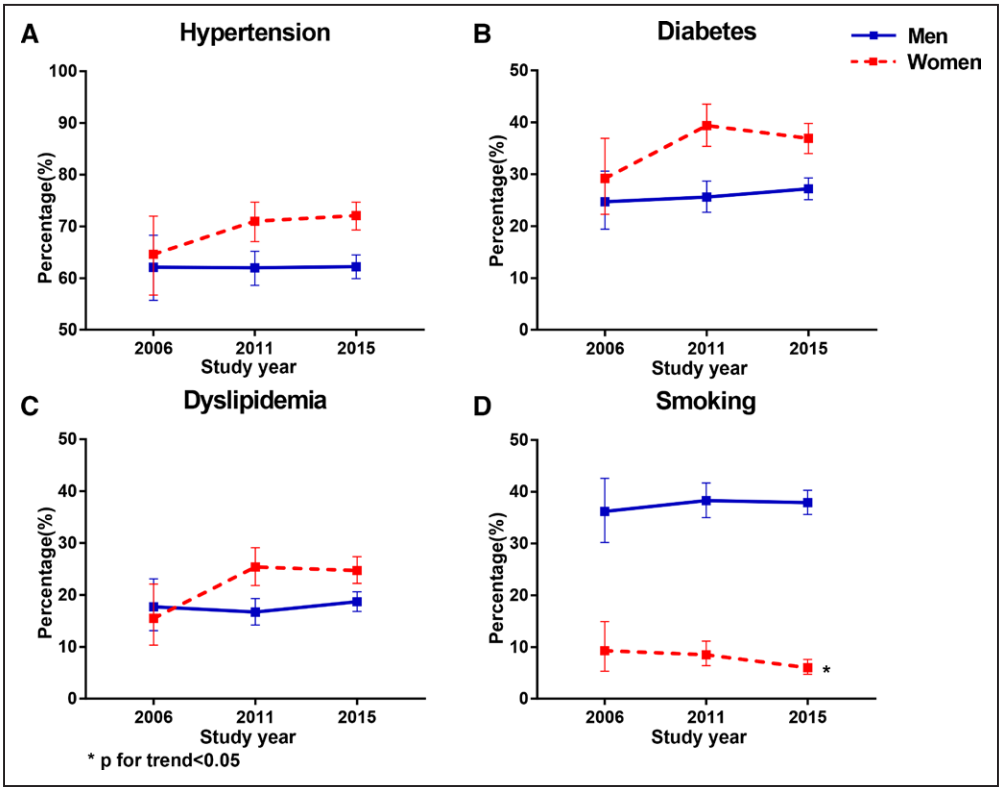

Figure 1. Temporal trends in cardiovascular risk factors by sex.

Table 1. Patient Characteristics According to Sex and Study Year

Characteristics	Men (n=2778)	Women (n=1833)	*P* value	Men			*P* value for trend	Women			*P* value for trend
				2006 (n=243)	2011 (n=841)	2015 (n=1694)		2006 (n=161)	2011 (n=576)	2015 (n=1096)	
Age, y	67 (58–76)	73 (66–80)	<0.001	68 (57–76)	67 (57–76)	67 (58–76)	0.534	72 (65–77)	73 (66–80)	74 (66–80)	0.058
Length of stay, d	10 (7–14)	10 (7–14)	0.042	10 (5–15)	10 (7–14)	10 (7–13)	<0.001	9 (6–15)	11 (7–15)	10 (7–14)	0.325
Cardiovascular risk factors											
Hypertension	1726 (62.1)	1303 (71.1)	<0.001	151 (62.1)	521 (62.0)	1054 (62.2)	0.929	104 (64.6)	409 (71.0)	790 (72.1)	0.092
Diabetes	735 (26.5)	678 (37.0)	<0.001	60 (24.7)	215 (25.6)	460 (27.2)	0.288	47 (29.2)	227 (39.4)	404 (36.9)	0.408
Dyslipidemia*	499 (18.0)	442 (24.1)	<0.001	43 (17.7)	140 (16.6)	316 (18.7)	0.402	25 (15.5)	146 (25.3)	271 (24.7)	0.248
Current smoking	1052 (37.9)	130 (7.1)	<0.001	88 (36.2)	322 (38.3)	642 (37.9)	0.786	15 (9.3)	49 (8.5)	66 (6.0)	0.033
No. of risk factors ≥1	2375 (85.5)	1549 (84.5)	0.357	198 (81.5)	710 (84.4)	1467 (86.6)	0.019	126 (78.3)	494 (85.8)	929 (84.8)	0.203
Medical history											
Coronary heart disease	498 (17.9)	264 (14.4)	0.002	34 (14.0)	148 (17.6)	316 (18.7)	0.097	20 (12.4)	77 (13.4)	167 (15.2)	0.208
Stroke	396 (14.3)	293 (16.0)	0.107	20 (8.2)	125 (14.9)	251 (14.8)	0.044	23 (14.3)	91 (15.8)	179 (16.3)	0.523
Heart failure	114 (4.1)	92 (5.0)	0.141	3 (1.2)	23 (2.7)	88 (5.2)	<0.001	3 (1.9)	23 (4.0)	66 (6.0)	0.008
Chronic renal failure	220 (7.9)	138 (7.5)	0.628	14 (5.8)	59 (7.0)	147 (8.7)	0.051	8 (5.0)	40 (6.9)	90 (8.2)	0.115
Indication for OAC	91 (3.3)	73 (4.0)	0.205	3 (1.2)	26 (3.0)	63 (3.7)	0.041	7 (4.4)	13 (2.3)	53 (4.8)	0.109
Clinical characteristics											
Duration from symptom onset to admission, h†	29 (6–120)	48 (8–120)	0.055	24 (4–72)	24 (4–96)	48 (12–168)	<0.001	24 (4–72)	24 (6–96)	72 (14–168)	<0.001
Unknown	655 (23.6)	442 (24.1)	0.676	0 (0.0)	0 (0.0)	655 (38.7)	<0.001	0 (0.0)	0 (0.0)	442 (40.3)	<0.001
Chest discomfort	2432 (87.5)	1553 (84.7)	0.006	217 (89.3)	742 (88.2)	1473 (87.0)	0.208	132 (82.0)	476 (82.6)	945 (86.2)	0.038
Cardiac arrest	18 (0.6)	14 (0.8)	0.643	3 (1.2)	1 (0.1)	14 (0.8)	0.562	0 (0.0)	6 (1.0)	8 (0.7)	0.724
Cardiogenic shock	107 (3.9)	91 (5.0)	0.068	8 (3.4)	25 (3.0)	70 (4.1)	0.749	9 (5.6)	19 (3.3)	63 (5.7)	0.211
Acute stroke	87 (3.1)	66 (3.6)	0.384	6 (2.6)	15 (1.8)	66 (3.9)	0.015	0 (0.0)	10 (1.7)	56 (5.1)	<0.001
Heart failure	1385 (49.9)	1045 (57.0)	<0.001	124 (51.0)	405 (48.2)	856 (50.5)	0.617	88 (54.7)	341 (59.2)	616 (56.2)	0.715
Heart rate (beats per min)	78 (68–92)	81 (70–97)	<0.001	80 (68–98)	77 (67–90)	78 (68–92)	0.445	80 (72–100)	80 (68–96)	82 (70–98)	0.315
Systolic blood pressure, mm Hg	133 (118–150)	139 (120–157)	<0.001	130 (120–153)	130 (116–154)	134 (119–150)	0.474	136 (117–150)	139 (120–157)	140 (120–158)	0.090
Mini-GRACE risk score	115 (97–137)	124 (108–142)	<0.001	124 (99–142)	118 (98–141)	114 (94–132)	<0.001	128 (112–147)	129 (110–147)	122 (105–139)	<0.001
Mini-GRACE risk score category											
Low risk (<109)	1155 (41.6)	511 (27.9)	<0.001	82 (33.7)	321 (38.2)	752 (44.4)	<0.001	36 (22.4)	134 (23.3)	341 (31.1)	<0.001
Intermediate risk (109–140)	1047 (37.7)	824 (45.0)		92 (37.9)	301 (35.8)	654 (38.6)	0.363	73 (45.3)	251 (43.6)	500 (45.6)	0.631
High risk (>140)	576 (20.7)	498 (27.2)		69 (28.4)	219 (26.0)	288 (17.0)	<0.001	52 (32.3)	191 (33.2)	255 (23.3)	<0.001
Tests during admission											
Troponin assessment	2072 (74.6)	1284 (70.0)	<0.001	138 (56.8)	566 (67.3)	1368 (80.8)	<0.001	67 (41.6)	369 (64.1)	848 (77.4)	<0.001
Troponin concentration (multiple of upper limit of normal)†	21.7 (4.3–84.9)	16.1 (4.5–67.2)	0.020	24.8 (5.6–75.3)	20.0 (4.1–77.8)	22.6 (4.3–91.3)	0.139	7.9 (4.2–30.8)	13.5 (4.6–66.7)	18.8 (4.5–68.9)	0.177
Hematocrit (%)†	40.9 (36.7–44.0)	36.9 (33.0–40.0)	<0.001	40 (35.1–4.75)	40.6 (36.1–44.0)	41.0 (37.2–44.2)	<0.001	36.0 (33.0–38.0)	36.3 (33.0–40.0)	37.2 (33.4–40.2)	0.028
Hemoglobin, g/L†	138 (123–149)	122 (109–132)	<0.001	135 (120–147)	137 (123–148.5)	139 (124–150)	0.007	119 (110–127)	121 (107–132)	123 (110–133)	0.248
MCHC, g/dL†	33.6 (32.6–34.7)	33.0 (32.0–33.9)	<0.001	33.8 (32.7–35.0)	33.6 (32.4–34.8)	33.6 (32.6–34.6)	0.016	33.3 (32.5–34.7)	33.0 (32.0–34.1)	32.9 (31.9–33.8)	<0.001
eGFR, mL/min per 1.73 m²†	81.7 (59.9–101.9)	71.3 (48.0–94.9)	<0.001	71.4 (49.6–90.8)	82.1 (59.9–101.9)	82.9 (61.4–102.9)	0.022	62.3 (43.1–83.2)	68.1 (46.0–91.8)	73.9 (50.6–97.8)	<0.001
Echocardiogram measurement	1937 (69.7)	1182 (64.5)	<0.001	108 (44.4)	545 (64.8)	1284 (75.8)	<0.001	73 (45.3)	341 (59.2)	768 (70.1)	<0.001

(*Continued*)

Table 1. Continued

Characteristics	Men (n=2778)	Women (n=1833)	*P* value	Men			*P* value for trend	Women			*P* value for trend
				2006 (n=243)	2011 (n=841)	2015 (n=1694)		2006 (n=161)	2011 (n=576)	2015 (n=1096)	
Left ventricular ejection fraction†	58 (50–64)	57 (49–63)	0.073	56 (49–64)	58 (49–64)	59 (51–64)	0.351	55 (45–63)	56 (49–63)	58 (50–64)	0.018
Hospital characteristics											
Teaching hospital	2347 (84.5)	1552 (84.7)	0.865	200 (82.3)	701 (83.4)	1446 (85.4)	0.106	140 (87.0)	468 (81.3)	944 (86.1)	0.220
PCI-capable hospital	2315 (83.3)	1521 (83.0)	0.752	148 (60.9)	669 (79.5)	1498 (88.4)	<0.001	99 (61.5)	469 (81.4)	953 (87.0)	<0.001
Hospital with CCU	458 (16.5)	305 (16.6)	0.891	42 (17.3)	112 (13.3)	304 (17.9)	0.072	29 (18.0)	74 (12.8)	202 (18.4)	0.094
Economic-geographic region											
Western	517 (18.6)	300 (16.4)	0.008	35 (14.4)	170 (20.2)	312 (18.4)	0.602	21 (13.0)	82 (14.2)	197 (18.0)	0.026
Central	608 (21.9)	359 (19.6)		37 (15.2)	183 (21.8)	388 (22.9)	0.019	29 (18.0)	106 (18.4)	224 (20.4)	0.284
Eastern	1653 (59.5)	1174 (64.0)		171 (70.4)	488 (58.0)	994 (58.7)	0.017	111 (68.9)	388 (67.4)	675 (61.6)	0.009
Urban/rural											
Urban	1845 (66.4)	1166 (63.6)	0.050	159 (65.4)	593 (70.5)	1093 (64.5)	0.067	105 (65.2)	398 (69.1)	663 (60.5)	0.006
Rural	933 (33.6)	667 (36.4)	0.050	84 (34.6)	248 (29.5)	601 (35.5)	0.067	56 (34.8)	178 (30.9)	433 (39.5)	0.006

Data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables. CCU indicates cardiac care unit; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; LDL-C, low-density lipoprotein cholesterol; MCHC, mean corpuscular hemoglobin concentration; OAC, oral anticoagulants; and PCI, percutaneous coronary intervention.

*Dyslipidemia is defined as LDL-C≥130 mg/dL or recorded history of dyslipidemia.

†Among patients with measurements available.

men (*P* value for trend <0.001) but not among women (Table 2). Thus, women had significantly higher crude rates of mortality (12.0% versus 8.7%) and composite complications in 2015 (23.1% versus 18.3%) than men. Table 3 shows that after adjustment, compared with men, women had a lower risk of death in 2006 (odds ratio, 0.40 [95% CI, 0.22–0.72]) and had a not significantly different risk of death since 2011. Women had a similar risk of composite complications with men in each year after sequential adjustments. Trends in and the rates of major bleeding were both similar between sexes from 2006 to 2015.

DISCUSSION

In this study, we identified sex differences in the characteristics, treatment, and outcomes of patients admitted with NSTEMI in China. Among eligible patients, lower utilization of aspirin in 2015 and invasive strategy in 2011 and 2015 were observed in women relative to men. Notably, the sex disparity in invasive strategy did not narrow over time. Moreover, women had higher crude in-hospital mortality, and the increased risk was substantially attenuated by age.

Women with NSTEMI were more likely to have cardiovascular risk factors except smoking, which was largely consistent with prior studies.[9–11,14,19] Although trends in such sex differences have been assessed in the United States and Europe, limited data are available in China.[20,21] We observed in women, the prevalence of all these risk factors did not decline across 10 years, except smoking which decreased more recently. However, the persistent differences in the risk factors did not translate into measurable differences in in-hospital outcomes. Some studies observed that these risk factors may not independently influence in-hospital mortality but have an important influence on long-term mortality.[22–25] Additionally, it is particularly noted that, although age explained much of the difference in in-hospital mortality, accounting for cardiovascular risk factors resulted in a decrease in the magnitude of difference in mortality for 2006, 2011, and 2015. It is possible that if the prevalence of these risk factors had been lower among women, women might tend to have a significantly lower risk of mortality.

Consistent with previous studies, we observed that women less often presented with chest discomfort than men.[26–28] However, others reported inconsistent results. A prospective study found that women with NSTEMI were more likely to present with chest pain than men.[29] Another study reported that the proportion of patients with chest discomfort was similar in both sexes.[30] Considering the lack of standardization for characterizing AMI presentation, data collection, and reporting on women's symptoms among these studies, it is difficult to provide direct comparisons. Even so, the differences in the approaches of obtaining collecting symptoms between the studies may potentially explain the controversial results. Our study used symptoms abstracted from medical records, which is different from using direct patient interviews during which patients might be led to elaborate on their descriptions of their presenting symptoms, or interviewers were more diligent and complete than clinicians in recording symptoms.[27] More importantly, our finding implies that physicians should consider the possible diagnosis of AMI even in the absence of chest discomfort, particularly in women. As the first step in AMI care is recognizing any significant new symptoms, it is possible that some women were not diagnosed as AMI in the first place because they did not present with chest pain, and the following treatments were delayed. In particular, we found that the use of invasive strategies was lower in women.

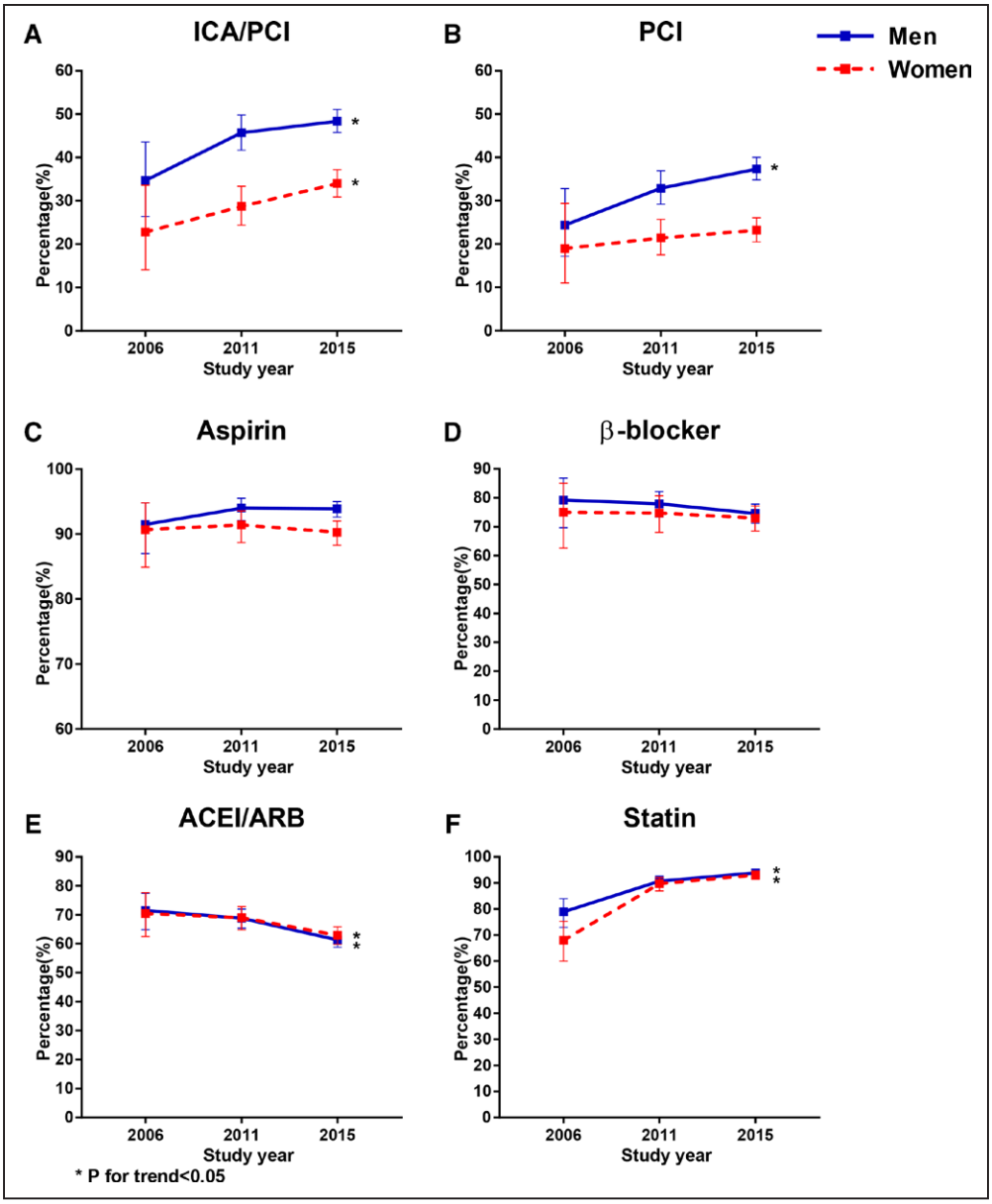

Figure 2. Temporal trends of sex differences in treatments among eligible patients.
ACE inhibitor indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICA, invasive coronary angiography; and PCI, percutaneous coronary intervention.

Despite a similar increasing trend in using invasive strategies for both sexes in the past decade, sex gaps persisted. The reasons for women less often undergoing an invasive strategy may relate to the differences in baseline characteristics and physician recognition of NSTEMI in women, with a conservative approach in decisions for invasive coronary angiography/PCI. Prior studies have confirmed that NSTEMI patients with high-risk features were less likely to undergo invasive strategy.[14] In our study, advanced age was a major factor limiting their utilization. A lower eGFR level in women than men may also partly explain the sex differences. Such a risk-treatment paradox seemed more strongly in women compared with men as demonstrated by significant interaction terms. The factors other than those analyzed in this study might explain the undertreatment in women, such as sociodemographic circumstances, type of NSTEMI, and rates of nonobstructive coronary artery disease.[31,32] However, a recent study suggested that socioeconomic and health system factors did not contribute to the sex differences in invasive strategy for ischemic heart disease in China.[33] Notably, only one-third of women underwent invasive strategy in 2015, which was much lower than that reported from developed countries (eg, 50.2% in the United States,[11] 74.5% in Switzerland,[7] 46.7% in the United Kingdom[34]) and similar with the results from CAMI study in China (35.4%).[14] The gap in quality of care with the underuse of invasive strategy

Table 2. In-Hospital Treatments and Outcomes According to Sex and Year

	Men	Women	*P* value	Men			*P* value for trend	Women			*P* value for trend
				2006	2011	2015		2006	2011	2015	
Treatments,* N (%)											
Aspirin	2449 (93.7)	1562 (90.7)	<0.001	204 (91.5)	748 (94.0)	1497 (93.9)	0.345	137 (90.7)	497 (91.4)	928 (90.3)	0.607
Clopidogrel/ ticagrelor	2279 (86.6)	1451 (83.9)	0.014	129 (57.8)	674 (84.7)	1476 (91.5)	<0.001	73 (48.3)	454 (83.5)	924 (89.4)	<0.001
DAPT	2191 (83.8)	1366 (79.3)	<0.001	124 (55.6)	651 (81.8)	1416 (88.8)	<0.001	70 (46.4)	430 (79.2)	866 (84.2)	<0.001
β-blocker	863 (76.0)	504 (73.7)	0.261	76 (79.2)	279 (77.9)	508 (74.6)	0.169	48 (75.0)	145 (74.7)	311 (73.0)	0.623
Statin	2473 (91.7)	1595 (89.9)	0.036	179 (78.9)	745 (90.7)	1549 (93.9)	<0.001	104 (68.0)	497 (89.7)	994 (93.1)	<0.001
ACE inhibitor/ARB	1614 (64.5)	1080 (65.5)	0.515	153 (71.5)	539 (68.8)	922 (61.3)	<0.001	105 (70.5)	360 (69.0)	615 (62.9)	0.009
Parenteral anticoagulant	2458 (88.7)	1571 (85.8)	0.004	204 (84.0)	757 (90.1)	1497 (88.7)	0.302	125 (77.6)	497 (86.3)	949 (86.8)	0.014
UFH	773 (32.5)	386 (25.1)	<0.001	46 (24.5)	197 (26.9)	530 (36.4)	<0.001	12 (11.4)	89 (17.5)	285 (30.7)	<0.001
LMWH	2163 (80.6)	1402 (79.5)	0.338	186 (77.8)	678 (83.0)	1299 (79.9)	0.676	119 (75.8)	445 (79.7)	838 (79.9)	0.365
Fondaparinux	88 (3.6)	62 (4.0)	0.558	0 (0.0)	39 (5.1)	49 (3.4)	0.568	0 (0.0)	28 (5.4)	34 (3.7)	0.651
Oral anticoagulant†	26 (0.9)	21 (1.1)	0.488	5 (2.1)	1 (0.1)	20 (1.2)	0.668	0 (0.0)	2 (0.3)	19 (1.7)	0.005
ICA/PCI‡	1002 (46.8)	441 (31.8)	<0.001	44 (34.6)	272 (45.7)	686 (48.4)	0.006	18 (22.8)	118 (28.7)	305 (34.0)	0.009
PCI‡	756 (35.3)	311 (22.4)	<0.001	31 (24.4)	196 (32.9)	529 (37.3)	0.002	15 (19.0)	88 (21.4)	208 (23.2)	0.301
Outcomes, N (%)											
Mortality	267 (9.6)	214 (11.7)	0.025	41 (16.9)	79 (9.4)	147 (8.7)	<0.001	19 (11.8)	64 (11.1)	131 (12.0)	0.752
Composite complications	574 (20.7)	433 (23.6)	0.017	70 (28.8)	194 (23.1)	310 (18.3)	<0.001	38 (23.6)	142 (24.7)	253 (23.1)	0.621
Major bleeding	21 (0.8)	13 (0.7)	0.856	3 (1.2)	7 (0.8)	11 (0.6)	0.318	1 (0.6)	2 (0.3)	10 (0.9)	0.312

Composite complications include mortality, reinfarction, cardiogenic shock, ischemic stroke, or congestive heart failure. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy, indicates aspirin plus $P2Y_{12}$ receptor inhibitor; ICA, invasive coronary angiography; LMWH, low molecular weight heparin and fondaparinux; PCI, percutaneous coronary intervention; and UFH, parenteral anticoagulant include unfractionated heparin.

*Among eligible patients.

†Among all patients.

‡Only among patients admitted into a hospital capable of PCI.

between China and developed countries may result from lagging system-wide quality improvement programs for cardiovascular diseases care.[35] Implementing a program based on quality indicators might facilitate reducing the gap in care between evidence and practice, and mitigating the sex differences in management.[36]

Similar to previous studies in China, we observed a decline in crude in-hospital mortality in men, but not in women.[15] By contrast, a decline in crude in-hospital mortality among women was observed in the United States and Switzerland.[7,8] Despite the different trends, both our and prior studies consistently suggested that overall women were at increased risk of in-hospital mortality after NSTEMI compared with men, with inconsistent results after adjustments across studies.[2,10–12] The controversy in the literature may partly stem from differences in the populations studied and methodological variations, including differences in adjustment analyses. Also, the national socioeconomic

Table 3. Trends of Sex Differences in In-Hospital Outcomes (Mortality, Composite Complications)

In-hospital outcomes (men=reference group)	Model	Adjusted odds ratios (95% CI)				*P* value for interaction
		Overall	2006	2011	2015	
Mortality	Unadjusted	1.25 (1.04–1.50)	0.66 (0.38–1.13)	1.20 (0.85–1.68)	1.42 (1.11–1.80)	0.023
	Model 1	1.00 (0.82–1.21)	0.57 (0.33–1.00)	0.93 (0.65–1.32)	1.14 (0.89–1.46)	0.030
	Model 2	0.93 (0.76–1.13)	0.48 (0.27–0.85)	0.90 (0.61–1.31)	1.06 (0.83–1.37)	0.025
	Model 3	0.89 (0.72–1.10)	0.40 (0.22–0.72)	0.81 (0.55–1.20)	1.10 (0.84–1.44)	0.011
Composite complications*	Unadjusted	1.21 (1.05–1.40)	0.82 (0.52–1.29)	1.10 (0.86–1.42)	1.33 (1.11–1.61)	0.019
	Model 1	1.02 (0.88–1.18)	0.73 (0.46–1.16)	0.98 (0.76–1.26)	1.08 (0.89–1.31)	0.024
	Model 2	0.94 (0.81–1.10)	0.71 (0.44–1.16)	0.92 (0.70–1.20)	0.98 (0.81–1.20)	0.020
	Model 3	0.94 (0.80–1.10)	0.69 (0.42–1.14)	0.89 (0.68–1.17)	1.02 (0.82–1.26)	0.009

Model 1: adjusted for age. Model 2: adjusted for age, hypertension, diabetes, dyslipidemia, and current smoking. Model 3: adjusted for variables in model 2 plus indication for oral anticoagulants, mini-Global Registry of Acute Coronary Events risk score, and estimated glomerular filtration rate.

*Composite complications include mortality, reinfarction, cardiogenic shock, ischemic stroke, or congestive heart failure.

backgrounds across countries may partly be a contributor. A large international cohort study showed that after adjustment for confounders, the sex differences in the postdischarge mortality risk after acute coronary syndrome was more evident as country wealth increased and income inequality decreased.[37] Our study suggested that excess risk in mortality observed among women versus men was primarily explained by differences in age, largely consistent with other studies.[2,11,38] Nevertheless, the lower utilization of invasive strategy did not affect mortality risks in women, which seems to be counterintuitive. One potential reason might be that the benefit of invasive strategies becomes more apparent over time after hospital discharge.[39] NSTEMI guidelines' recommendation of an invasive strategy is based on several studies demonstrating significant reductions in adverse long-term outcomes.[40] A population-based cohort study in Sweden also reported that excess mortality risk was observed at 5 years after NSTEMI among women but did not differ by sex at earlier time points.[22]

Several limitations apply to our study. First, because this is a retrospective observational study, unmeasured confounders might affect the observed results, including laboratory data such as platelet count, which may help explain the differences in anticoagulant/antiplatelet therapy. Other uncollected data, like coronary angiographic characteristics, might have modified the relationship between sex and in-hospital mortality. However, a prior study found that women had similar 30-day mortality with men after accounting for angiographic disease severity.[19] Second, our study did not collect information about the type of NSTEMI, which may influence sex differences in treatment patterns and mortality. Third, the mortality was low in 2006, thus we had low statistical power to detect the difference in mortality between the sexes—and, therefore, could only adjust a limited number of variables. Fourth, some variables like eGFR might be over-adjusted in multivariable models as age and sex are also taken into account for their estimation. Fifth, our most recent data were from 2015. Nevertheless, the observed increasing trend in sex differences in invasive strategy is much more concerning and requires further efforts for better understanding and mitigation. Also, additional research is needed to track whether these differences attenuate in the future.

CONCLUSIONS

We observed significant sex differences in cardiovascular risk factors and treatment patterns since 2011 among patients with NSTEMI in a nationally representative cohort in China. There is a need for national strategies to ensure that women have the same quality care as men.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Methods
Figures S1–S2
Tables S1–S2

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