Sex Differences in Acute Coronary Syndrome in a Multiethnic Asian Population

Results of the Malaysian National Cardiovascular Disease Database—Acute Coronary Syndrome (NCVD-ACS) Registry

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ABSTRACT

Background: Sex differences in acute coronary syndrome (ACS) have been well studied in major registries and clinical trials in Western populations. Limited studies have examined the sex differences in ACS using a large number of Asian women as the subjects.

Objectives: The aim was to study the sex differences in ACS using the NCVD-ACS (National Cardiovascular Disease Database—Acute Coronary Syndrome) registry.

Methods: We analyzed 13,591 ACS patients, of which 75.8% were men and 24.2% were women, from March 2006 to February 2010. Data were collected on demographic characteristics, risk factors, anthropometrics, treatments, procedures, mortalities, and complications. The results were compared among 3 cohorts of ACS (ST-segment elevation myocardial infarction [STEMI], non−STEMI, and unstable angina).

Results: Women were older and more likely to have diabetes, hypertension, previous heart failure, and cerebral vascular accidents than men were. Women were less likely to receive in-hospital administration of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, and they were less likely to undergo angiography and percutaneous coronary intervention. In STEMI, a significantly lower proportion of women than men received primary percutaneous coronary intervention (6.2% vs. 6.7%, respectively, $p = 0.000$) and fibrinolysis (64.4% vs. 74.6%, respectively, $p = 0.000$). In addition, with regard to STEMI, women had a significantly higher unadjusted in-hospital mortality rate than men did (15.0% vs. 8.1%, respectively, $p < 0.000$). There was no statistically significant in-hospital mortality difference between sexes for non-STEMI and unstable angina. After adjustment for age and other covariates, a multivariate analysis showed no sex differences in the in-hospital mortality in all spectrums of ACS.

Conclusions: Our study showed significant sex differences in the demographic characteristics, risk factors, treatments, and outcomes of ACS. More importantly, in ACS patients, we found evidence of suboptimal treatments and interventions in women versus men. Our findings provide an opportunity to narrow the sex gap in the care of women with ACS in Malaysia.

Cardiovascular disease (CVD) is the most common cause of death in women worldwide [1]. CVD is on the rise in Asian-Pacific countries that are currently undergoing rapid urbanization, industrialization, and lifestyle changes; in parallel with increasing life expectancies, the proportion of women with CVD is also increasing and constitutes an increased percentage of patients hospitalized for acute coronary syndrome (ACS).

Recently, knowledge regarding sex differences in CVD has evolved as the volume of literature has expanded and clinical studies have included more women [2]. During the past 3 decades, numerous and remarkably consistent studies have reported sex differences in the epidemiology, clinical manifestations, risk factors, diagnoses, outcomes and prevention of ACS [3−6]. Many ACS studies have shown women to be older and with higher incidences of comorbidities at presentation [4,6,7]. Women were usually under-represented in clinical trials and were less likely to receive procedures such as coronary angiography, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG) surgeries [4,6]. The role of sex in ACS outcomes remains controversial. Many studies reported higher ACS mortalities in women than in men [6,8−10]. However, when comorbidities and other confounding

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factors were taken into account, there were no mortality differences between sexes [4,11].

These sex differences in ACS have been well-studied in major registries and clinical trials in developed countries that consist mainly of Western populations and in which men constitute the majority of the study cohort. It may not be appropriate to apply the findings of studies conducted mainly on men to the management of CVD in women [12,13]. A better understanding of sex differences will improve the current management of ACS, especially in women.

Currently, limited numbers of ACS studies have examined sex differences in Asians. We aim to study the differences and similarities between men and women diagnosed with ACS using the NCVD-ACS (National Cardiovascular Disease Database—Acute Coronary Syndrome) registry. The NCVD-ACS registry is a joint effort of physicians and nurses in public, private, and academic medical institutions; is supported by the National Heart Association, the Malaysia National Heart Foundation, and the Ministry of Health; and is also among the pioneer projects for the treatment and prevention CVD in Malaysia [14].

METHODS

The NCVD-ACS registry is the first prospective, multicenter, observational registry that involves 15 tertiary (public) hospitals nationwide, 1 academic teaching hospital (University Malaya Medical Centre), and the National Heart Institute (*Institut Jantung Negara*). These centers were selected on the basis of their willingness to participate in the registry. Since its establishment in 2006, all registry centers have attempted to enroll a complete spectrum of patients with ACS. An overview of the NCVD-ACS registry [14], methods, and annual reports have been published elsewhere [15]. The NCVD-ACS registry provides a detailed and comprehensive description of patients with ACS by collecting data on patients presenting with ST-segment elevation myocardial infarction (STEMI), non−ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA).

Entry criteria include patients who are at least 18 years of age and who present with clinical features consistent with ACS accompanied by clinical, electrocardiographic, and biochemical features. The data were extracted from the medical records and recorded on a standardized case report form [15] by trained study coordinators. Standardized definitions were used for all patient-related variables such as demographic characteristics (age, sex, and ethnicity), coronary risk factors (cigarette smoking, diabetes mellitus [DM], hypertension, and dyslipidemia), and other comorbidities (previous myocardial infarction [MI], heart failure, or renal failure; cerebrovascular accident; and body mass index). The vital signs at presentation, time-to-treatment (door-to-needle time and door-to-balloon time), in-hospital medical and invasive treatments, disease severities (culprit artery and number of diseased vessels), and in-hospital outcomes (all-cause mortality, hospitalization days [coronary care unit days and total days], and complications [bleeding rate]) were captured [15]. The final diagnosis of ACS is made by the responsible physician according to the standardized criteria [16,17].

The data were entered into a web-based centralized database with security password encryption according to individual centers. Each center's investigator was given a password to ensure that only key personnel were able to access or edit the data. Regular data checks and audits were performed, and queries were generated for corrections to ensure accuracy. Patients were stratified according to sex, demographic characteristics, risk factors, anthropometrics, treatments, procedures, hospitalization days, outcomes, and complications. These variables were analyzed and compared among the 3 groups of ACS (STEMI, NSTEMI, and UA) patients.

Ethics Approval

The NCVD-ACS registry is registered with the National Medical Research Register of Malaysia and was approved by the Medical Review and Ethics Committee, Ministry of Health Malaysia in 2007 (approval code: NMRR-07-20-250). The Medical Review and Ethics Committee also waived the need for informed consent.

Statistical Analysis

Descriptive statistics and baseline variables are presented as numbers and percentages, means ± SD, or medians (interquartile ranges [IQR]). A chi-square test was used to assess differences between categorical variables; an independent *t* test (parametric analysis) or Mann-Whitney *U* test (nonparametric analysis) was used to test differences between numerical variables. For multivariate analyses, simple binary and multiple logistic regressions were used to model the dichotomous outcomes of STEMI, NSTEMI, and UA in-hospital mortalities between sexes with adjustments for other covariates based on 5 models. The following steps were used to model in-hospital mortalities (dependent, outcome variable) and sex (independent, predictor variable): in model 1, only sex was entered as the unadjusted predictor variable for in-hospital mortality. In model 2, the following covariates were adjusted based on a stepwise approach: age, admission heart rate, admission systolic blood pressure, Killip class IV at presentation and elevated creatinine kinase. In model 3, additional covariates (coronary risk factors) were entered: cigarette smoking, DM, hypertension, and ethnicity. In model 4, hospital management factors were added to the existing covariates: PCI, CABG, and in-hospital use of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors (ACE-I), and statins. Finally, in model 5, the participating centers (institutional factor) were added to the covariates.

The results were reported as odds ratios (OR) with 95% confidence intervals (CI) for sex differences. A p value of <0.05 was considered statistically significant. All

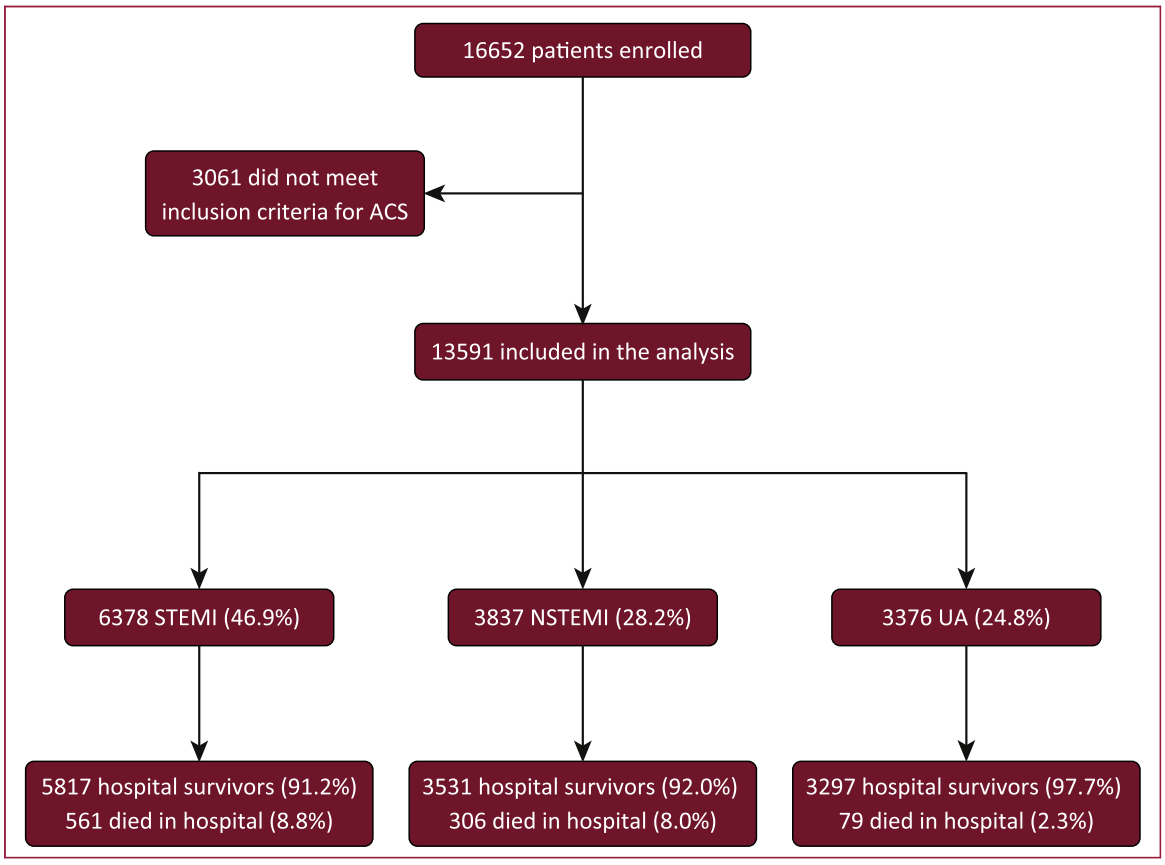

FIGURE 1. NCVD-ACS Registry flowchart. NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

statistical calculations were performed using the SPSS statistics software (version 20, IBM, Armonk, New York).

RESULTS

Baseline Characteristics and Risk Factors

A total of 13,591 patients were included in the analysis between March 2006 and February 2010 (Fig. 1). Of these patients, 75.8% were men and 24.2% were women with a men-to-women ratio of 3:1 (Fig. 2). With regard to presenting diagnoses, more men than women were observed in all ACS groups. However, in STEMI compared with the NSTEMI and UA groups, men were disproportionately outnumbered by women.

The baseline characteristics and risk factors according to sex and ACS stratum are listed in Table 1. Across the ACS groups of STEMI, NSTEMI, and UA patients, women were generally older and more likely to have DM, hypertension, previous heart failure, and cerebrovascular accident than men were.

Women were less likely than men to be current or former smokers. Likewise, in the NSTEMI and UA groups, women were less likely to have a previous history of MI than men were. At presentation, women in all ACS groups had higher heart rates and higher systolic blood pressures than men did, and in the STEMI and NSTEMI groups, women had higher Killip classes at presentation than men did.

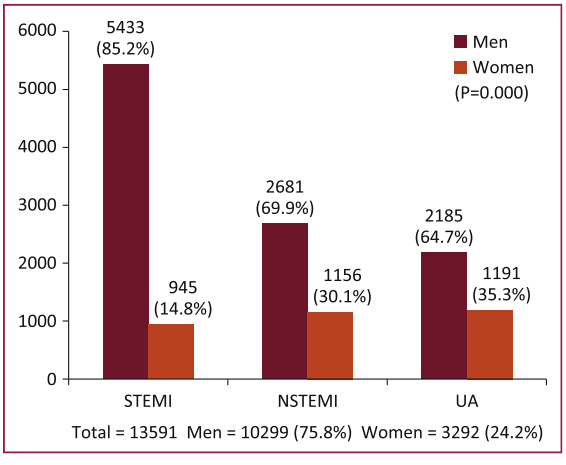

FIGURE 2. Acute coronary syndrome by sex. Abbreviations as in Figure 1.

TABLE 1. Baseline characteristics and risk factors for NCVD-ACS (N = 13,591)

	STEMI			NSTEMI			UA		
	Men	Women	p Value	Men	Women	p Value	Men	Women	p Value
Age, yrs	55.1 ± 11.4	62.4 ± 11.5	0.000*	59.6 ± 11.2	67.0 ± 10.5	0.000*	59.3 ± 11.5	63.7 ± 11.3	0.000*
Ethnic group									
Malay	55.2	47.5	0.000	46.8	43.8	0.083	44.9	39.8	0.004
Non-Malay†	44.8	52.5		53.2	56.2		55.1	60.2	
Current, former smoker	79.3	11.2	0.000	69.8	11.0	0.000	68.8	8.7	0.000
Diabetes	41.9	63.3	0.000	52.1	67.8	0.000	51.0	60.1	0.000
Hypertension	56.2	78.7	0.000	73.3	88.2	0.000	78.5	86.5	0.000
Dyslipidemia	39.4	42.4	0.178	54.0	58.0	0.054	58.3	57.4	0.654
Previous MI	14.4	13.0	0.305	33.7	26.1	0.000	35.6	25.1	0.000
Previous heart failure	3.8	5.4	0.034	12.5	17.4	0.000	10.1	10.4	0.787
Previous renal failure	3.4	7.5	0.000	13.3	17.0	0.006	9.1	9.1	0.948
CVA	2.9	5.5	0.000	4.6	6.9	0.007	5.4	5.2	0.855
PVD	0.5	0.3	0.384	1.5	1.9	0.368	0.9	1.3	0.320
Heart rate, beats/min	82 ± 22	88 ± 22	0.000*	85 ± 22	90 ± 22	0.000*	80 ± 18	85 ± 20	0.000*
SBP, mm Hg	134 ± 28	138 ± 30	0.001*	140 ± 29	148 ± 31	0.000*	141 ± 26	149 ± 28	0.000*
BMI, kg/m^2	25.6 ± 4.0	25.6 ± 4.6	0.876*	25.7 ± 4.2	25.5 ± 4.8	0.422*	25.7 ± 4.5	26.2 ± 4.8	0.034*
Killip class									
I (no heart failure)	66.7	56.7	0.000	64.0	56.7	0.002	83.0	79.9	0.210
II (heart failure)	22.8	28.4		24.5	28.0		14.2	17.5	
III (pulmonary edema)	4.1	7.4		7.8	11.1		1.8	1.7	
IV (cardiogenic shock)	6.4	7.5		3.7	4.2		1.0	0.9	

Values are mean ± SD or %.

BMI, body mass index; CVA, cerebral vascular accident; MI, myocardial infarction; NCVD-ACS, National Cardiovascular Disease Database—Acute Coronary Syndrome; NSTEMI, non—ST-segment elevation myocardial infarction; PVD, peripheral vascular disease; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

*Independent *t* test for differences between 2 means. All categorical variables are expressed as percentages. Chi-square test for 2 x 2 table (using Fisher exact test) for categorical variables.

†Non-Malay: Chinese, Indian, Indigenous (Orang Asli), and minor ethnic groups.

In-Hospital Medications Received

On admission, antiplatelets (aspirin), adenosine diphosphate antagonists, beta-blockers, ACE-I, and statins were commonly prescribed to both sexes (Table 2). More than 90% of patients in each group were taking aspirin at baseline. However, the in-hospital use of aspirin was slightly lower among women than among men, particularly in the NSTEMI and UA groups (90.1% vs. 93.0%, p = 0.000, and 91.5% vs. 93.7%, p = 0.018, respectively). In the NSTEMI group, women were less likely than men to receive beta-blockers and ACE-I. Similarly, in the STEMI group, women were less likely to receive statins than men were. On the contrary, the in-hospital use of oral hypoglycemic agents, insulin, low molecular-weight heparin, and diuretics was significantly higher in women than men among all ACS groups.

Invasive Therapeutic Procedures, Culprit Arteries, and Numbers of Diseased Vessels

In each of the 3 ACS groups (STEMI, NSTEMI, and UA), women were less likely to undergo angiography (18.7% vs. 22.3%, p = 0.018; 20.1% vs. 26.4%, p = 0.000; 6.6% vs. 11.2%, p = 0.000, respectively) and PCI (16.6% vs. 19.7%, p = 0.027; 11.9% vs. 15.7%, p = 0.003; 4.5% vs. 7.6% p = 0.000, respectively) than men during hospitalization (Table 3). Statistically, there were no differences between sexes in the rates of CABG and angiographic characteristics, such as culprit arteries and numbers of diseased vessels. More than 50% of patients of both sexes had >2 diseased vessels. Among all ACS groups, the left anterior descending artery accounted for >55% of the culprit vessels for both sexes.

Treatment of STEMI

The majority of patients (≥70%) of both sexes received some form of reperfusion either by fibrinolysis or primary PCI, although many more patients received fibrinolysis than primary PCI (Table 4). Our results indicate that a higher proportion of women with STEMI received no reperfusion therapy (29.4% vs. 18.7%, respectively, p = 0.000), and a significantly lower proportion of women versus men received primary PCI (6.2% vs. 6.7%, respectively, p = 0.000) or fibrinolysis (64.4% vs. 74.6%, respectively, p = 0.000). The median door-to-needle time was longer in women than in men (60.8 min [IQR: 87.9] vs. 49.7 min [IQR: 74.2], respectively, p = 0.000). The

TABLE 2. In-hospital medications

	STEMI			NSTEMI			UA		
	Men	Women	P Value*	Men	Women	P Value*	Men	Women	P Value*
Antiplatelets									
Aspirin	5,069 (96.1)	866 (95.4)	0.269	2,435 (93.9)	1,005 (90.1)	0.000	1,959 (93.7)	1,038 (91.5)	0.018
Other antiplatelets	3,814 (75.0)	667 (75.9)	0.560	1,842 (72.2)	750 (68.8)	0.041	1,384 (67.2)	706 (62.8)	0.012
Anticoagulants									
Heparin	533 (11.2)	92 (11.2)	0.991	312 (12.5)	129 (12.0)	0.691	254 (12.5)	125 (11.2)	0.294
LMWH	2,010 (41.0)	404 (47.1)	0.001	1,951 (76.3)	841 (75.6)	0.647	1,574 (76.2)	917 (81.3)	0.001
Antihypertensives									
Beta-blockers	3,440 (68.7)	556 (64.1)	0.006	1,753 (68.7)	714 (64.9)	0.023	1,521 (73.1)	801 (70.8)	0.170
ACE-I	3,049 (61.1)	480 (56.3)	0.008	1,505 (59.2)	554 (50.5)	0.000	1,405 (67.8)	731 (64.7)	0.079
ARB	283 (5.9)	63 (7.7)	0.049	263 (10.5)	171 (15.9)	0.000	187 (9.2)	107 (9.6)	0.693
Diuretics	1,227 (25.2)	312 (36.9)	0.000	961 (37.8)	525 (47.9)	0.000	526 (25.6)	349 (31.1)	0.001
CCB	356 (7.5)	74 (9.0)	0.128	478 (19.0)	322 (29.5)	0.000	392 (19.2)	275 (24.6)	0.000
Antidiabetic agents									
OHA	1,153 (23.8)	277 (33.0)	0.000	724 (28.7)	391 (35.9)	0.000	619 (30.3)	418 (37.4)	0.000
Insulin	1,155 (23.7)	363 (42.1)	0.000	615 (24.3)	386 (35.4)	0.000	392 (19.2)	279 (25.0)	0.000
Statins									
Statins	4,856 (92.8)	819 (90.7)	0.029	2,310 (89.2)	992 (89.2)	0.989	1,921 (92.4)	1,029 (90.7)	0.111

Values are n (%).

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; LMWH, low molecular weight heparin; OHA, oral hypoglycemic agents; other abbreviations as in Table 1.

*Chi-square test for 2 x 2 table (using Fisher exact test) for categorical variables. All categorical variables are expressed as number (%).

median door-to-balloon time was not statistically significant between sexes (121.0 min [IQR: 109.0] vs. 110.0 [IQR: 104.5], respectively, p = 0.244).

In-Hospital Clinical Outcomes and Mortality

As illustrated in Figure 3, the proportion of in-hospital mortality increases with age, and sex differences appear to exist in all age groups. The sex discrepancy was most evident in the younger patients (<40 years old). Overall, women demonstrated a significantly higher risk of in-hospital mortality than did men. The unadjusted in-hospital mortality rates of both sexes were higher in the STEMI group than in the NSTEMI and UA groups (Table 3).

In the STEMI group, women had higher unadjusted in-hospital mortality rates than men did (15.0% vs. 8.1%, respectively, p < 0.000; unadjusted OR: 2.02, 95% CI: 1.64 to 2.48). The in-hospital mortality rates were not statistically significantly different between women and men in the NSTEMI (9.5% vs. 7.6%, respectively, p = 0.052; unadjusted OR: 1.28, 95% CI: 0.99 to 1.23) and UA groups (2.2% vs. 2.5%, respectively, p = 0.526; unadjusted OR: 0.86, 95% CI: 0.53 to 1.38) (Tables 3 and 5). After adjustment for all of the covariates, a multivariate analysis for in-hospital mortality revealed that the female sex was not associated with an increased in-hospital mortality compared with that of men in the STEMI (adjusted OR: 1.06, 95% CI: 0.67 to 1.70), NSTEMI (adjusted OR: 0.77, 95% CI: 0.47 to 1.26), and UA (adjusted OR: 0.55, 95% CI: 0.22 to 1.39) groups (Table 5).

Women had longer coronary care unit and total hospitalization days than did men in both the STEMI (3.7 vs. 3.4 days, respectively, p = 0.018) and NSTEMI (4.1 vs. 3.3 days, respectively, p = 0.000) groups (Table 3). The rates of major bleeding were generally low (0.1% to 0.9%) among all ACS groups and both sexes. Overall, there were no statistically significant differences in major or minor bleeding complications according to the TIMI (Thrombolysis In Myocardial Infarction) criteria for bleeding [18] in all ACS groups and both sexes.

DISCUSSION

Our study design is unique in that we compared the sex-based differences in each type of ACS, which enabled us to determine outcomes in a well-defined population. Our study showed significant sex differences in the baseline characteristics, risk factors, treatments, and outcomes of ACS in Malaysia.

Baseline Characteristics and Risk Factors

Similar to many ACS trials and registries [4,9,19,20], more men than women were enrolled in this study. Atypical presentations and less predictive ischemic screening tests for women are the factors that most likely limit the enrollment of women in trials [21]. Regarding the type of ACS diagnoses at presentation, the proportion of women

TABLE 3. In-hospital procedures, culprit artery, number of disease vessels, and outcomes

	STEMI			NSTEMI			UA		
	Men	Women	p Value	Men	Women	p Value	Men	Women	p Value
Angiography	1,214 (22.3)	177 (18.7)	0.018	708 (26.4)	232 (20.1)	0.000	245 (11.2)	79 (6.6)	0.000
PCI	1,069 (19.7)	157 (16.6)	0.027	420 (15.7)	138 (11.9)	0.003	167 (7.6)	53 (4.5)	0.000
CABG	29 (0.5)	3 (0.3)	0.385	81 (3.0)	18 (1.6)	0.009	29 (1.3)	10 (0.8)	0.205
Culprit artery									
LAD	669 (57.6)	96 (56.1)	0.860	316 (55.0)	103 (57.2)	0.018	110 (58.2)	32 (57.1)	0.998
RCA	385 (33.2)	56 (32.9)		138 (24.0)	39 (21.7)		44 (23.3)	13 (23.2)	
LCX	90 (7.8)	16 (9.4)		82 (14.2)	24 (13.3)		22 (11.6)	7 (12.5)	
LMA	12 (1.0)	2 (1.2)		9 (1.6)	10 (5.6)		3 (1.6)	1 (1.8)	
Bypass graft	5 (0.4)	0 (0.0)		30 (5.2)	4 (2.2)		10 (5.3)	3 (5.4)	
No. of diseased vessels									
0	62 (5.0)	8 (4.4)	0.442	32 (5.0)	5 (2.5)	0.396	15 (7.0)	10 (14.2)	0.308
1	492 (39.5)	62 (34.3)		143 (22.1)	46 (23.0)		57 (26.5)	16 (22.5)	
2	348 (28.0)	52 (28.7)		189 (29.3)	54 (27.0)		58 (27.0)	17 (23.9)	
3	343 (27.5)	59 (36.6)		281 (43.6)	95 (47.5)		85 (39.5)	28 (39.4)	
Outcomes									
CCU days	3.4 ± 2.5	3.7 ± 3.0	0.018*	3.3 ± 2.7	4.1 ± 4.2	0.000*	3.2 ± 2.9	3.3 ± 3.4	0.617*
Total days	5.0 ± 3.0	5.9 ± 4.2	0.000*	5.2 ± 4.2	5.6 ± 4.2	0.008*	3.8 ± 3.1	3.9 ± 3.4	0.234*
Bleeding (TIMI†)									
Major	41 (0.9)	5 (0.6)	0.509	10 (0.4)	5 (0.5)	0.356	7 (0.4)	1 (0.1)	0.271
Minor	135 (2.8)	30 (3.7)		38 (1.6)	24 (2.4)		17 (0.9)	6 (0.6)	
Minimal	6 (0.1)	1 (0.1)		1 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
None	4,634 (96.2)	781 (95.6)		2,318 (97.9)	952 (97.0)		1,900 (98.8)	1,030 (99.3)	
In-hospital mortality‡	424 (8.1)	137 (15.0)	0.000	199 (7.6)	107 (9.5)	0.052	54 (2.5)	25 (2.2)	0.526

Values are n (%) or mean ± SD.

CABG, coronary artery bypass graft; CCU, coronary care unit; LAD, left anterior descending artery; LCX, left circumflex artery; LMA, left main artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

*Independent *t* test for differences between 2 means. Chi-square test for 2 x 2 table (using Fisher exact test) for categorical variables. All categorical variables are expressed as n (%).

†TIMI major bleeding involves a hemoglobin drop >5 g/dl (with or without an identified site) or intracranial hemorrhage or cardiac tamponade.

‡Unadjusted in-hospital all-cause mortality rate.

with STEMI was significantly lower than that of men. It seems that women are less likely to present with STEMI than men are. The results from other trials concurred with this finding [9,20,22].

Our study showed that women were older and had a higher prevalence of risk factors, such as DM, hypertension, previous heart failure, and cerebrovascular accident than men. Women were less likely to be smokers and less likely to have previous MI. These findings were consistent with previous clinical trials and registries [4,6,7,22,23].

The onset of coronary artery disease (CAD) exhibits a delay of approximately 10 years' delay in women than in men [24]. An earlier study explained why women were older at presentation: it was attributed to the fact that aging is associated with progressive endothelial dysfunction, which appears to occur earlier in men than in women. In women, however, a steep decline of endothelial function commences at menopause. This is consistent with a protective effect of estrogens on the arterial walls [25]. An earlier study in Malaysia showed that ACS is rare in women of reproductive age [26].

In-Hospital Medications Received

A previous study showed that women with ACS benefit from medical treatment and intervention as much as men do. For example, thrombolytic therapy has been shown to reduce mortality equally in both sexes [27]. Consistent with previous studies [22,28,29], the NCVD-ACS registry showed that women were less likely than men to receive evidence-based treatment such as antiplatelets, beta-blockers, ACE-I, and angiotensin receptor blockers. Several explanations exist for such differences. For example, older age may be among the factors responsible for the lower use of evidence-based treatment in women [29]. It is possible that the physician's awareness of evidence-based treatment, fear of adverse effects, and socioeconomic resources may contribute to this prescribing pattern, which needs revision. On the contrary, more women were taking oral hypoglycemic agents and insulin, and these results reflect their higher prevalence of DM. Our study showed that women were more frequently afflicted with comorbidities, such as hypertension, DM, and heart

failure. In light of these findings, it is essential to advocate for the use of evidence-based therapies that are likely to result in greater benefit and outcomes, as recommended by the American College of Cardiology/American Heart Association's clinical practice guidelines [16,17].

Invasive Therapeutic Procedures, Culprit Arteries, and Numbers of Diseased Vessels

Our study was in agreement with previous studies [4,8,22,28–30] that women were less likely to receive invasive investigations and reperfusion procedures. This difference appears to be multifactorial and has a few possible explanations. First, women with ACS are more likely to be treated conservatively, possibly due to underestimation of the patients' risks related to the perception that CAD is mainly a disease observed in men [6,29,31]. Second, the evaluation of CAD in women is complicated by atypical presentations [3,21]. Furthermore, traditional screening tests for ischemia are less capable of detecting CAD in women [3,27,32]. In addition, the ethnicity of a patient may also influence the physician's decision to refer or to perform coronary angiography [31]. Additionally, women were less willing to undergo procedures [33]. Patients with lower education levels were less inclined to undergo cardiac catheterization [34]; this may be true for elderly women in Malaysia. It has been found that women benefit from an invasive approach despite advanced age [27,35]. Thus, our findings provide an important opportunity to implement measures to ensure the optimal utilization of therapeutic procedures in women.

An ACS registry with a large number of patients reported that women, despite having more comorbidities, had fewer high-risk angiographic features and higher prevalences of single-vessel disease than men did [13]. However, in the present NCVD-ACS registry, >50% of men and women had >2 diseased vessels, suggesting a more severe disease pattern among the present cohort of ACS patients, regardless of sex.

Treatment of STEMI

For the reasons previously described, women were more likely to be treated conservatively, as evidenced by the lower rate of primary PCI and higher rate of fibrinolysis; these findings were similar to those of previous studies on the management of ACS in developing countries [20,36]. The finding of the underuse of PCI in women with STEMI was also reported elsewhere [8].

In-Hospital Clinical Outcomes and Mortality

There are conflicting evidence and unconvincing explanations regarding the effect of sex on mortality following ACS. Generally, unadjusted comparisons of mortality after ACS have shown that women have worse outcomes than men do [7,23].

In the NCVD-ACS registry, women with STEMI had higher unadjusted in-hospital mortalities than men did.

TABLE 4. Treatment of STEMI

	Men	Women	Chi-square*	df	p Value
Primary PCI†	362 (6.7)	60 (6.2)	71.10	2	0.000
Fibrinolysis†	4,032 (74.6)	625 (64.4)			
No revascularization†‡	1,011 (18.7)	285 (29.4)			
Total†	5,405 (100.0)	970 (100.0)			
Fibrinolysis subgroup					
Type of fibrinolytic drug used†					
Streptokinase	3,019 (97.1)	481 (97.4)	0.11	1	0.744
Other fibrinolytic drugs	90 (2.9)	13 (2.6)			
Door-to-needle time,§ min	49.7 (25.7, 99.9)	60.8 (32.0, 119.9)			0.000‖
Door-to-balloon time,§ min	110.0 (74.2, 178.6)	121.0 (80.0, 189.0)			0.244‖

Values are n (%) or median (IQR).
df, degrees of freedom; IQR, interquartile range; other abbreviations as in Tables 1 and 3.
*Pearson chi-square.
†All categorical variables are expressed as n (%).
‡Reason for no revascularization includes refusal, missed fibrinolysis, and contraindication.
§Median (IQR).
‖Mann-Whitney *U* test.

However, after adjusting for differences in age and other covariates, the STEMI group's in-hospital mortality OR was not significantly different between women and men (adjusted OR: 1.06, 95% CI: 0.67 to 1.70, p = 0.769). Our study concluded that sex was not an independent predictor of in-hospital mortality after STEMI. Similar findings were found in the NSTEMI and UA groups. In agreement with our study, other ACS studies reported that differences in mortalities between sexes were due largely to the different age structure of these populations. Women do not have worse outcomes than men after acute MI when age and other factors are taken into account [4,11,23,37]. In contrast, many studies on Western, Middle Eastern, and Asian patients found that women had a significantly higher rate of in-hospital mortality even after adjusting for age and other comorbidities [6,8–10]. Nevertheless, other researchers found that the sex difference in ACS mortality was dependent on the clinical presentation and severity of angiographically documented disease [23,37]. Some studies have suggested a link to the less aggressive hospital care of women, including the underuse of reperfusion, as an explanation for their increased mortality [10,30]. It is possible that other factors, including ethnicity, culture, psychosocial, educational, and socioeconomic statuses contribute to the sex differences in ACS mortality [38–40].

In the NCVD-ACS registry, the in-hospital mortality sex discrepancy seems to be evident for the younger age groups (<40 years old) (Fig. 3). Previous studies reported a higher risk of in-hospital mortality in younger women than in younger men that was more evident in patients

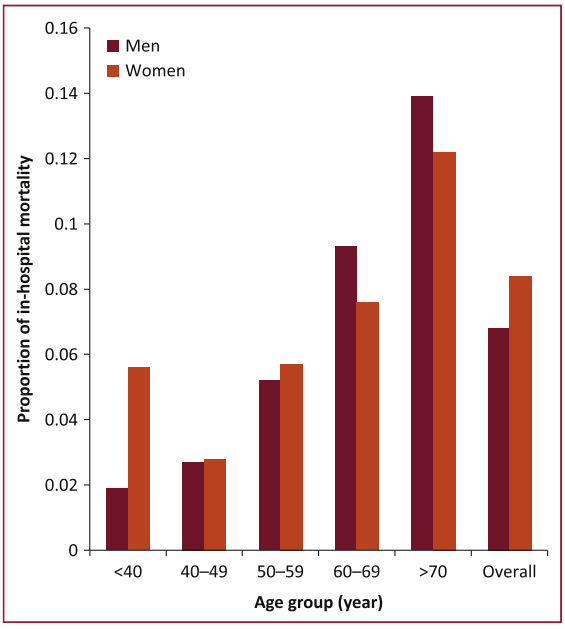

FIGURE 3. Proportion of ACS (STEMI, NSTEMI, and UA) in-hospital mortality according to age groups and sex (n = 13,591). Proportion of in-hospital mortality increased with age (OR: 1.06; 95% CI: 1.05 to 1.06; p = 0.000). Overall, women demonstrated significantly higher risk of in-hospital mortality compared to men (OR: 1.29; 95% CI: 1.06 to 1.59; p = 0.012). The interaction between sex and age is not significant (p = 0.390).

with STEMI [38,41]. An earlier publication using the NCVD-ACS registry reported that the prevalence of ACS in reproductive-age women was low, but their prognosis was worse than that of older women or same-aged men. The explanation was probably related to the higher incidence of STEMI in this group [26]. The contributory factors toward these outcomes are pending further studies.

As with most previous studies, there are limitations in the analysis of mortality outcomes when comparing sexes. The NCVD-ACS registry is a hospital-based, rather than population-based study that captures data from patients who survived to seek medical treatment in a hospital after the onset of ACS; it is not known how the outcomes would be affected by sex differences because patients may not survive to reach a hospital or may simply refuse treatment. For instance, a population-based study showed that the women have higher probability of surviving and reaching a hospital, and men are more likely to die before hospitalization after acute MI [11], leaving a sicker, surviving population of women at the hospital door. Individuals who die of out-of-hospital cardiac death were not represented in the NCVD-ACS registry. Therefore, the in-hospital mortality may not reflect the true sex difference in outcomes because we excluded the nonhospitalized patients with ACS. Furthermore, we used in-hospital, all-cause mortality as an endpoint to minimize event misclassification. The results for cardiac-specific mortality might be different from the present results.

Women with ACS had longer coronary care unit and total days of hospitalization than men did. This could be explained by older age and more comorbidities at presentation. A clinical trial that studied the efficacy of various antithrombotic therapies in ACS patients showed that women had a higher risk of bleeding than men did [3,42], but this difference was not observed in the NCVD-ACS registry.

Strengths

The NCVD-ACS registry enrolls patients from multiple centers representing a complete and unselected group of patients in a real-world setting. Unlike randomized controlled trials, which tend to exclude high-risk and elderly patients, the NCVD-ACS registry collects data on the full spectrum of ACS patients from a nationwide perspective. We used a standardized method for defining ACS, thereby gaining insight into ACS patients who were not included in randomized controlled trials. Our study

TABLE 5. Result of multiple logistic regression analyses of in-hospital mortality

	STEMI	p Value	NSTEMI	p Value	UA	p Value
Model 1	2.02 (1.64–2.48)	0.000	1.28 (0.99–1.63)	0.053	0.86 (0.53–1.38)	0.526
Model 2	1.43 (1.08–1.90)	0.012	1.03 (0.72–1.47)	0.878	0.82 (0.44–1.52)	0.519
Model 3	1.35 (0.92–1.97)	0.128	0.79 (0.50–1.25)	0.793	0.89 (0.42–1.87)	0.596
Model 4	1.18 (0.76–1.84)	0.459	0.79 (0.49–1.27)	0.333	0.66 (0.27–1.60)	0.356
Model 5	1.06 (0.67–1.70)	0.769	0.77 (0.47–1.26)	0.300	0.55 (0.22–1.39)	0.205

Values are OR (95% CI). Estimate for sex (women) was adjusted for other covariates.
Model 1: Unadjusted logistic regression analysis including sex only (men as reference).
Model 2: Logistic regression analysis adjusted for age, admission HR, admission SBP, Killip class IV at presentation, elevated creatinine kinase (adapted from Steg et al. [19]).
Model 3: Model 2 plus cigarette smoking, DM, hypertension, ethnicity (coronary risk factors).
Model 4: Model 3 plus PCI, CABG, in-hospital use of aspirin, beta-blockers, ACE-I, statins (hospital management).
Model 5: Model 4 plus participating centers (institutions).
CI, confidence interval; DM, diabetes mellitus; HR, heart rate; OR, odds ratio; other abbreviations as in Tables 1 to 3.

focused on 3 different ACS groups with large numbers of patients. Hence, the NCVD-ACS registry should reflect true sex differences in the population. Our findings have identified areas requiring further educational efforts and improved patient care and are useful to healthcare planners. The findings also help provide clinicians insights for managing ACS in accordance with the principles of evidence-based medicine.

Limitations

First, women could have been under-represented in the NCVD-ACS registry as a result of selection bias owing to educational and psychosocial factors as well as cultural influences. This more commonly occurred among elderly women with ACS who tend to delay seeking medical treatment [43]. Second, as a nonrandomized observational study, the NCVD-ACS registry is subject to a selection bias despite our attempt to include hospitals from different regions of the country. Third, there are many private hospitals in Malaysia with significant numbers of ACS patients who do not participate in this registry. In Malaysia, health care in private hospitals is mostly "self-paying" (i.e., covered by personal or company insurance), in contrast to public hospitals or institutions with government funding (partial or full). As a result, the NCVD-ACS registry may not reflect a wide range of patients with different socioeconomic statuses, educations, and occupations who could present with different cardiovascular risk factors and disease spectrums. Furthermore, errors in data entry cannot be completely ruled out and may result in unrecognized biases despite periodic audits at the participating centers.

CONCLUSIONS

We conclude that the NCVD-ACS registry results strongly confirm the sex differences published in previous studies. There are 2 major implications of our study. First, we show differences in terms of demographics, risk profiles, presenting diagnoses, treatments, and outcomes of ACS between both sexes. Similar to clinical trials and registries worldwide, Malaysian women with ACS were older at presentation, with more comorbidities and higher Killip classes, and were more likely to be treated conservatively. After adjustments for age and other variables, their in-hospital mortality was not different from that of men.

Second, the NCVD-ACS registry establishes a critical understanding of the overall quality of care provided to ACS patients of both sexes. The major concern of our study is that there appeared to be continuing evidence of suboptimal treatment and intervention in women with ACS in current practice. Though further research is needed to fully understand the reasons for the sex difference in ACS, there is a need to narrow the sex gap in the care of women with ACS in Malaysia.

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