Sex Differences in the Presentation, Diagnosis, and Management of Acute Coronary Syndromes

Findings From the Kerala-India ACS Registry

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ABSTRACT

Background: Previous literature from high-income countries has repeatedly shown sex differences in the presentation, diagnosis, and management of acute coronary syndromes (ACS), with women having atypical presentations and undergoing less aggressive diagnostic and therapeutic measures. However, much less data exist evaluating sex differences in ACS in India.

Objectives: This study sought to evaluate sex differences in the diagnosis, management, and treatment of patients with ACS in Kerala, India.

Methods: The Kerala ACS Registry collected data from 25,748 consecutive ACS admissions (19,923 men and 5,825 women) from 125 hospitals in the Indian state of Kerala from 2007 to 2009. This study evaluated the association between sex differences in presentation, in-hospital management, and discharge care with in-hospital mortality and in-hospital major adverse cardiovascular events (defined as death, reinfarction, stroke, heart failure, or cardiogenic shock).

Results: Women with ACS were older than men with ACS (64 vs. 59, $p < 0.001$) and were more likely to have a history of previous myocardial infarction (16% vs. 14%, $p < 0.001$). Inpatient diagnostics and management and discharge care were similar between sexes. No significant differences between men and women in the outcome of death (odds ratio [OR]: 1.05, 95% confidence interval [CI]: 0.80 to 1.38) or in the composite outcome of death, reinfarction, stroke, heart failure, or cardiogenic shock (OR: 0.99, 95% CI: 0.79 to 1.25) were seen after adjustment for possible confounding factors.

Conclusions: In Kerala, even though women with ACS were older and more likely to have previous myocardial infarction, there were no significant differences in in-hospital and discharge management, in-hospital mortality, or major adverse cardiovascular events between sexes. Whether these results apply to other parts of India or acute presentations of other chronic diseases in low- and middle-income countries warrants further study.

Cardiovascular disease (CVD) is the number one cause of death in India and accounted for approximately 21% of deaths in 2010, with 11.4% of these deaths due to ischemic heart disease [1]. In India, previous surveillance studies evaluating sex differences in tobacco use and other CVD risk factors have provided useful data on community-level exposures. However, Indian studies exploring sex differences in cardiovascular health service delivery have been limited and can provide complementary information [2]. In pre-existing large acute coronary syndromes (ACS) registries in India (CREATE [Treatment and Outcomes of Acute Coronary Syndromes in India] and OASIS-2 [Organization to Assess Strategies for Ischemic Syndromes Trial]), little has been described regarding sex differences in these patients [3,4]. The DEMAT (Detection and Management of Acute Coronary Events) registry of 1,565 ACS patients from 10 tertiary care centers in India demonstrated that after adjustment for age, education, history of coronary heart disease, ST-segment elevation myocardial infarction (STEMI) presentation, or reperfusion of any type, there was no evidence of an effect of increased risk of death at 30 days among women compared with men, nor was there any difference between death, rehospitalization, and cardiac arrest at 30 days [5]. However, literature from high-income countries (HIC) has repeatedly shown that sex differences do exist in the presentation, diagnostics, and therapeutic management of ACS patients [6–10]. Specifically, women with ACS tend to be older than their male counterparts, are more likely to have a history of hypertension, and more often have atypical

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presenting symptoms [10]. Data from the ACC-NCDR (American College of Cardiology's National Cardiovascular Data Registry) has shown that women are more likely to present with unstable angina/non−STEMI than STEMI, less likely to receive aspirin or glycoprotein IIb/IIIa inhibitors on admission, and are less likely to be prescribed aspirin or statins on discharge [7]. Additionally, women have been seen to have fewer high-risk angiographic features than men (left main disease, 3-vessel disease, bifurcation lesions), despite having higher levels of comorbidities [7]. Long term, women tend to have higher mortality rates than men do 5 and 10 years after an ACS, but these differences are largely accounted for by differences in baseline age, comorbidities, and treatment utilization [11].

Currently, there are limited data regarding sex differences in the presentation, management, and outcomes of acute manifestations of noncommunicable, chronic diseases in India, particularly CVD. To address this gap, we aimed to evaluate whether such differences exist using the Kerala ACS Registry, the largest prospective ACS registry in India containing 25,748 ACS admissions.

METHODS

The methods of the Kerala ACS Registry have been previously published [12]. In brief, we invited representatives from 185 hospitals that admitted patients with ACS (out of an estimated 300 acute care hospitals in Kerala at the time) to participate. Of the 185 hospitals invited, 140 hospitals responded to this invitation, and 125 hospitals participated. We collected data from 25,748 consecutive ACS admissions from 125 hospitals from May 2007 to May 2009. We included patients if they were >18 years old and presented with chest pain and ≥1 of the following: ST-segment elevation in 2 contiguous leads with or without reciprocal ST-segment depression; troponin or creatine kinase-myocardial band elevation; or ST-segment depression or T-wave inversion in 2 contiguous leads with a history of coronary heart disease. We captured data from patients in coronary care units.

We waived consent for in-hospital data collected, based on the Common Rule. Trained medical personnel abstracted in-hospital data regarding patient demographics, education level, self-reported medical history, previous medications, anthropometry, vital signs, diagnostics, treatment, and outcomes from the medical record. We supplemented data by using patient interviews, when necessary. We entered data into a central database for storage and subsequent analysis.

Statistical analysis

We present continuous variables as mean ± SD or median (interquartile range [IQR]), when skewed in distribution, and categorical variables as proportions. We made sex-based comparisons via analysis of variance for continuous variables and chi-square for categorical variables. We used a 2-sided p value of <0.05 to define statistical significance. We created univariate and random effects multivariable logistic regression models to adjust standard errors for the clustering of patients within hospitals to assess the association between sex and in-hospital mortality and in-hospital major adverse cardiovascular events (defined as death, reinfarction, stroke, heart failure, or cardiogenic shock). Previous analyses of the Kerala ACS Registry have shown a large degree of heterogeneity in the data [13]. In addition to age and sex, we created models that included covariates from the GRACE (Global Registry of Acute Coronary Events) risk model [14] to serve as the basis of our investigation into potential pre- and in-hospital targets for intervention. The previous work we have done leading to improvements in symptom-to-door time and door-to-needle time [15] led us to model the impact of these variables on outcomes. We used Stata (version 11.0, College Station, TX, USA) for our analyses.

The Institutional Ethics Committee of Sree Chithra Institute of Medical Sciences and Technology in Trivandrum and Westfort Hi-tech Hospital in Thrissur approved the study.

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RESULTS

Demographics, medical history, and clinical presentation

The hospitals included within this study enrolled between 1 and 3,531 patients (IQR: 33, 222). The mean age of participants was 60.4 ± 12.1 years and more than three-fourths were men (Table 1). The mean age of women (64.4 years) was older than men (59.3 years, $p < 0.001$). Women were less likely to be employed (32%) than were men (56%, $p < 0.001$). Previous history of myocardial infarction (MI) was more common in women (16%) than in men (14%, $p < 0.001$), whereas history of hypertension was slightly more common in men (52%) than in women (50%, $p = 0.02$). There were no sex-based differences in history of diabetes or stroke. Heart rate, systolic and diastolic blood pressure, body mass index, and hemoglobin were similar across the sexes. Women were slightly more likely than men to present with previous aspirin (18% vs. 16%), clopidogrel (16% vs. 15%), beta-blocker (13% vs. 12%), statin (12% vs. 11%), angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker (9% vs. 7%), or nitrate (11 vs. 10%) use ($p < 0.05$ for all), but these rates were largely similar. Men and women were also similarly likely to present with chest pain (86% vs. 85%, $p = 0.006$) and dyspnea (11% vs. 12%, $p = 0.006$). Women and men had similar rates of presenting with left bundle branch block (3% vs. 2%, $p = 0.03$).

TABLE 1. Patient-level characteristics on presentation, by sex

	n	Total (N = 25,748)	Men (n = 19,923)	Women (n = 5,825)	p Value
Age, yrs	25,745	60.4 ± 12.1	59.3 ± 11.9	64.4 ± 11.7	<0.001
Nonresident Indian	25,748	1,176 (6.7)	1,322 (6.6)	394 (6.8)	0.730
Education level	25,748				0.146
Illiterate	25,748	14,412 (56.0)	11,176 (56.1)	3,236 (55.6)	
Lower primary	25,748	1,123 (4.4)	888 (4.5)	235 (4.0)	
Upper primary	25,748	1,695 (6.6)	1,272 (6.4)	423 (7.3)	
Secondary	25,748	5,740 (22.3)	4,455 (22.4)	1,285 (22.1)	
Higher secondary	25,748	2,766 (10.7)	2,123 (10.7)	643 (11.0)	
Degree	25,748	12 (0.05)	9 (0.05)	9 (0.05)	
Occupation	25,517				<0.001
Unemployed	25,517	9,762 (38.3)	6,691 (33.9)	3,071 (53.4)	
Agriculture	25,517	2,223 (8.7)	1,892 (9.6)	331 (5.8)	
Government	25,517	2,064 (8.1)	1,685 (8.5)	379 (6.6)	
Professional	25,517	137 (0.5)	122 (0.6)	15 (0.3)	
Business	25,517	1,603 (6.3)	1,530 (7.7)	73 (1.3)	
Private sector	25,517	1,589 (6.2)	1,345 (6.8)	244 (4.2)	
Skilled worker	25,517	1,843 (7.2)	1,659 (8.4)	184 (3.2)	
Unskilled worker	25,517	2,449 (9.6)	2,125 (10.8)	324 (5.6)	
Pensioners	25,517	786 (3.1)	665 (3.4)	121 (2.1)	
Homemaker	25,517	1,577 (6.2)	921 (4.7)	656 (11.4)	
Others	25,517	1,067 (4.2)	771 (3.9)	296 (5.2)	
Key risk factors					
History of diabetes	25,748	9,683 (37.6)	7,462 (37.5)	2,221 (38.1)	0.350
History of hypertension	25,748	13,280 (51.6)	10,354 (52.0)	2,926 (50.2)	0.020
History of myocardial infarction	25,748	3,655 (14.2)	2,712 (13.6)	943 (16.2)	<0.001
History of stroke	25,748	646 (2.5)	514 (2.6)	132 (2.3)	0.178
History of PCI/CABG	25,748	73 (0.3)	63 (0.3)	10 (0.2)	0.068
Clinical features on presentation					
Transfer	25,748	5,597 (21.7)	4,149 (20.8)	1,448 (24.9)	<0.001
Chest pain	25,748	22,037 (85.6)	17,116 (85.9)	4,921 (84.5)	0.006
Dyspnea	25,748	2,843 (11.0)	2,142 (10.8)	701 (12.0)	0.006
Heart rate, beats/min	25,195	80.1 ± 19.5	80.1 ± 19.6	79.9 ± 19.2	
Systolic blood pressure, mm Hg	25,126	140.8 ± 30.0	140.9 ± 30.2	140.6 ± 29.6	
Diastolic blood pressure, mm Hg	25,123	86.6 ± 15.3	86.5 ± 15.3	86.6 ± 15.0	
Body mass index, kg/m^2	25,671	23.1 ± 3.6	23.1 ± 3.5	23.0 ± 3.9	
Hemoglobin, mg/dl	21,545	12.6 ± 1.9	12.6 ± 1.9	12.6 ± 1.9	
Creatinine >2	21,557	911 (4.2)	720 (4.4)	191 (3.8)	0.378
Killip class >1	13,793	2,996 (21.7)	2,364 (21.7)	632 (21.7)	0.988
Ejection fraction <30%	17.084	260 (1.5)	199 (1.5)	61 (1.5)	0.593
Presence of left bundle branch block	25,748	588 (2.3)	433 (2.2)	155 (2.7)	0.028
New diagnosis of STEMI	25,748	9,569 (37.2)	7,400 (37.1)	2,169 (37.2)	0.897
Baseline medical therapy					
Aspirin	25,748	4,106 (16.0)	3,084 (15.5)	1,022 (17.6)	<0.001
Clopidogrel	25,748	3,934 (15.3)	2,978 (15.0)	956 (16.4)	0.006
Beta-blocker	25,748	3,090 (12.0)	2,340 (11.8)	750 (12.9)	0.020
Statin	25,748	2,941 (11.4)	2,222 (11.2)	719 (12.3)	0.012
ACE-I or ARB	25,748	1,977 (7.7)	1,472 (7.4)	505 (8.7)	0.001
Nitrates	25,748	2640 (10.3)	1,991 (10.0)	649 (11.1)	0.011
Calcium channel blocker	25,748	1,079 (4.2)	809 (4.1)	270 (4.6)	0.054

Values are mean ± SD or n (%) unless otherwise indicated.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

TABLE 2. In-hospital diagnostic evaluations and medical/surgical treatments, by sex

	n	Total (N = 25,748)	Men (n = 19,923)	Women (n = 5,825)	p Value
Key investigations					
Positive cardiac enzyme	25,748	14,845 (57.7)	11,367 (57.1)	3,478 (59.7)	<0.001
Coronary angiography	25,748	2,955 (11.5)	2,172 (10.9)	783 (13.4)	<0.001
In-hospital medical therapy					
Thrombolysis	9,569	3,964 (41.4)	2,994 (31.3)	970 (10.1)	<0.001
Door-to-needle time >30 min, STEMI only	17,995	12,966 (72.1)	10,031 (72.1)	2,935 (72.0)	0.986
Symptom-to-door time >6 h	25,527	9,937 (38.9)	7,708 (39.0)	2,229 (38.7)	0.633
Aspirin	25,748	23,944 (93.0)	18,562 (93.2)	5,382 (92.4)	0.042
Clopidogrel	25,748	24,476 (95.1)	18,971 (95.2)	5,505 (94.5)	0.027
Beta-blockers	25,748	16,948 (65.8)	13,277 (66.6)	3,671 (63.0)	<0.001
Statins	25,748	20,280 (78.8)	15,555 (78.1)	4,725 (81.1)	<0.001
ACE-I/ARB	25,748	7,166 (27.8)	5,316 (26.7)	1,850 (31.8)	<0.001
Nitrates	25,748	22,297 (86.6)	17,338 (87.0)	4,959 (85.1)	<0.001
Calcium channel blockers	25,748	2,917 (11.3)	2,234 (11.2)	683 (11.7)	0.278
Any heparin	25,748	18,018 (70.0)	14,188 (71.2)	3,830 (65.8)	<0.001
Glycoprotein IIb/IIIa inhibitors	25,748	759 (3.0)	556 (2.8)	203 (3.5)	0.006
Optimal in-hospital care	25,748	10,307 (40.0)	8,009 (40.2)	2,298 (39.5)	0.305
In-hospital reperfusion/other therapy					
PCI	25,748	3,060 (11.9)	2,340 (11.8)	720 (12.4)	0.202
CABG	25,748	347 (1.4)	268 (1.4)	79 (1.4)	0.949
Reperfusion—thrombolysis, PCI, or CABG	25,748	8,432 (32.8)	6,368 (32.0)	2,064 (35.4)	<0.001
Temporary pacemaker	25,748	200 (0.8)	169 (0.9)	31 (0.5)	0.016
Permanent pacemaker	25,748	102 (0.4)	88 (0.4)	14 (0.2)	0.031
Intra-aortic balloon pump	25, 748	71 (0.3)	54 (0.3)	17 (0.3)	0.790

Values are n (%) unless otherwise indicated.
Abbreviations as in Table 1.

In-hospital and discharge diagnostics and management

Women had positive cardiac biomarkers more often than did men (60% vs. 57%, p < 0.001) and were also more likely to undergo coronary angiography (13% vs. 11%, p < 0.001) (Table 2), but these differences were modest. In-hospital aspirin and clopidogrel was given in >90% of patients in both sexes (p = 0.04 and 0.02, respectively). Nitrates were the next commonly used class of medications in the hospital (87% in men vs. 85% in women, p < 0.001), whereas beta-blockers (67% in men vs. 63% in women, p < 0.001), statins (78% in men vs. 81% in women, p < 0.001), and heparin (71% in men vs. 66% in women, p < 0.001) were used less commonly overall. A similar, but lower, trend was seen in post-discharge prescription medication rates (Table 3).

TABLE 3. Discharge medical therapy prescriptions, by sex

	n	Total (N = 25,748)	Men (n = 19,923)	Women (n = 5,825)	p Value
Aspirin	25,748	19,669 (76.4)	15,150 (76.0)	4,519 (77.6)	0.015
Clopidogrel	25,748	20,443 (79.4)	15,739 (79.0)	4,694 (80.6)	0.009
Beta-blockers	25,748	16,133 (62.7)	12,646 (63.5)	3,487 (59.9)	<0.001
Statins	25,748	18,057 (70.1)	13,879 (69.7)	4,178 (71.7)	0.002
ACE-I/ARB	25,748	6,553 (25.5)	4,872 (24.5)	1,681 (28.9)	<0.001
Nitrates	25,748	19,323 (75.1)	15,104 (75.8)	4,219 (72.4)	<0.001
Calcium channel blockers	25,748	2,969 (11.5)	2,278 (11.4)	691 (11.9)	0.368
Optimal discharge care	24,750	11,397 (46.1)	8,790 (45.9)	2,607 (46.7)	0.289

Values are n (%) unless otherwise indicated.
Abbreviations as in Table 1.

In-hospital outcomes and predictors of outcomes

The unadjusted in-hospital mortality rate was 3.8% in men, compared with 4.1% in women (p = 0.31) (Table 4). Rates of stroke, though low overall, were twice as high in women as in men (n = 43 vs. 23, or 0.4% vs. 0.2%, p = 0.02). Among men and women, rates of reinfarction (0.5% vs. 0.4%, p = 0.37), and heart failure or cardiogenic shock (1.9% vs. 2.0%, p = 0.85) were similar.

Table 5 demonstrates the patient and process-of-care variables that are associated with in-hospital mortality before and after adjustment. With men used as the reference group, there was no significant sex difference in unadjusted in-hospital death (OR: 1.08, 95% CI: 0.80 to 1.38), or the combined endpoint of in-hospital death,

TABLE 4. In-hospital event rates, by sex

	n	Total (N = 25,748)	Men (n = 19,923)	Women (n = 5,825)	p Value
Death	25,748	998 (3.9)	759 (3.8)	239 (4.1)	0.308
Reinfarction	25,748	115 (0.5)	93 (0.5)	22 (0.4)	0.370
Stroke—any type	25,748	66 (0.3)	43 (0.2)	23 (0.4)	0.017
Heart failure/cardiogenic shock	25,748	496 (1.9)	382 (1.9)	114 (2.0)	0.846
Death, reinfarction, stroke, heart failure, or cardiogenic shock	25,748	1,470 (5.7)	1,132 (5.7)	338 (5.8)	0.727

Values are n (%) unless otherwise indicated. Event rates are unadjusted.

reinfarction, stroke, heart failure, or cardiogenic shock (OR: 1.02, 95% CI: 0.90 to 1.16). After adjustment for age, sex, socioeconomic position (measured by education), modified-GRACE risk score variables, and within-hospital clustering, sex was not associated with in-hospital death (OR: 1.05, 95% CI: 0.80 to 1.38) or the combined endpoint of in-hospital death, reinfarction, stroke, heart failure, or cardiogenic shock (OR: 0.99, 95% CI: 0.79 to 1.25).

DISCUSSION

Summary of findings

In this registry of 25,748 patients with ACS from 125 hospitals in Kerala, we present data regarding sex-based differences in the presentation, management, and outcome of ACS. Our results show that on presentation, women were approximately 5 years older than were men, had moderately higher rates of previous MI, but were otherwise largely similar. In-hospital medical therapy was similar in both groups, though women were slightly more likely to receive reperfusion therapy than were men. Discharge medication rates also showed similar trends among sexes. Even after adjustment for possible confounding factors, there were no significant differences between men and women in the outcome of death or in the composite outcome of death, reinfarction, stroke, heart failure, or cardiogenic shock.

Comparison with previous ACS registries

There are limited data available comparing ACS outcomes data between men and women from other ACS registries in low- and middle-income countries (LMIC). The INTERHEART (A Global Study of Risk Factors for Acute Myocardial Infarction) of modifiable risk factors associated with MI in 29,972 individuals from 52 countries demonstrated that the median age of presentation with acute MI in South Asia was higher in women than in men (60 years [IQR: 50, 66] vs. 52 years [IQR: 45, 60]), which is similar to our results [16]. However, in contrast to our results, smaller ACS registries in LMIC have reported differences in ACS processes of care between men and women [17–20]. The CRACE (Chinese Registry of Acute Coronary Events), which consisted of 1,301 patients from 12 medical centers in China, found that female patients less often received reperfusion therapies and more often had recurrent

TABLE 5. Multivariable logistic regression model to evaluate predictors of in-hospital death and combined outcomes

	In-Hospital Death OR (95% CI)	In-Hospital Death, Reinfarction, Stroke, Heart Failure, or Cardiogenic Shock OR (95% CI)
Unadjusted		
Sex—men as reference group	1.08 (0.93–1.25)	1.02 (0.90–1.16)
Age, yrs	1.00 (0.99–1.00)	1.00 (0.99–1.00)
Education	1.25 (1.20–1.30)	1.19 (1.16–1.23)
Heart rate, beats/min	1.01 (1.01–1.01)	1.01 (1.01–1.01)
Systolic blood pressure, mm Hg	1.00 (0.99–1.00)	0.99 (0.99–0.99)
Serum creatinine, mg/dl	1.11 (1.02–1.20)	1.09 (1.02–1.17)
Killip class 1 (reference) vs. >1	1.60 (1.46–1.75)	1.73 (1.60–1.87)
Positive cardiac enzyme	3.12 (2.66–3.65)	2.08 (1.85–2.34)
Any ST-segment change	7.14 (5.70–8.94)	3.68 (3.17–4.23)
Adjusted		
Sex—men as reference group	1.05 (0.80–1.38)	0.99 (0.79–1.25)
Age, yrs	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Education	1.34 (1.26–1.43)	1.26 (1.19–1.33)
Heart rate, beats/min	1.00 (1.00–1.01)	1.00 (1.00–1.01)
Systolic blood pressure, mm Hg	1.00 (1.00–1.00)	1.00 (0.99–1.00)
Serum creatinine, mg/dl	1.13 (1.02–1.26)	1.08 (0.98–1.20)
Killip class 1 (reference) vs. >1		
Positive cardiac enzyme	2.75 (1.83–4.14)	2.20 (1.56–3.10)
Any ST-segment change	2.54 (1.69–3.83)	1.92 (1.41–2.60)

This unadjusted univariate and random effects multivariable logistic regression model was developed to evaluate predictors of in-hospital death and combined outcome of in-hospital death, reinfarction, stroke, heart failure, or cardiogenic shock. It has been adjusted for within-center clustering, GRACE risk score variables (age, heart rate, systolic blood pressure, serum creatinine, Killip class, cardiac enzyme [positive vs. negative], and ST-segment deviation [cardiac arrest at presentation was excluded as those data were not collected]), and quality-of-care measures.
CI, confidence interval; GRACE, Global Registry of Acute Coronary Events; OR, odds ratio.

angina [17]. In Egypt, a 2011 ACS registry of 1,204 patients from 5 hospitals showed that women were less likely to receive aspirin on admission, angiography during hospitalization, and aspirin and statins on discharge [18]. The GULF RACE-2 (2nd Gulf Registry of Acute Coronary Events) of 7,930 patients from 6 Arabian Gulf countries with ACS found that women were less likely to undergo angiography, percutaneous coronary intervention (PCI), and reperfusion therapy [19]. Finally, a 2007 Thai registry of 1,223 patients demonstrated that beta-blockers, statins, angiotensin-converting enzyme inhibitor therapy, angiotensin-receptor blocker therapy, coronary angiography, thrombolysis, and PCI were all used less frequently in women [20].

Despite these differences in process-of-care measures, reports from LMIC do not consistently demonstrate differences in in-hospital mortality. The above-mentioned registries from China, Egypt, and Thailand showed no difference in in-hospital mortality after adjustment for baseline characteristics. In GULF RACE-2, the differences seen in management were associated with higher 1-month and 1-year mortality rates in women (11.0% in women vs. 7.4% in men, $p < 0.001$ at 1 month and 17.3% in women vs. 11.4% in men, $p < 0.001$ at 1 year) [18]. These differences were no longer seen after adjustment for age, country, diagnosis, body mass index, Killip class, tobacco smoking, predominant presenting symptoms, medical history, invasive procedures (reperfusion, PCI, coronary artery bypass grafting), and medications at discharge [19]. In India, the DEMAT registry has demonstrated that after adjustment for age, education, history of coronary heart disease, STEMI presentation, or reperfusion of any type, there was no evidence of an effect of increased risk of death at 30 days among women versus men (OR: 1.4, 95% CI: 0.62 to 3.16) nor were there any differences among death, rehospitalization, and cardiac arrest at 30 days (OR: 1.0, 95% CI: 0.67 to 1.48) [5].

In comparison, multiple studies from HIC have shown differences in ACS management between men and women. In the ACC-NCDR of 199,690 patients with ACS, women received aspirin and glycoprotein IIb/IIIa inhibitors and were discharged on aspirin and statin therapy less often than men were [7]. Even though women had fewer comorbidities than men did and fewer high-risk features on angiography, they were more likely to experience in-hospital complications including heart failure, cardiogenic shock, vascular complications, and bleeding when compared with men [7]. GRACE examined 26,755 patients in 14 mostly HIC in Europe, the Americas, and the South Pacific and demonstrated that after adjustment for age and extent of disease, women were more likely to have adverse outcomes (death, MI, stroke, and rehospitalization) at 6 months than were men. However, sex differences in mortality were no longer seen after adjustment for age and extent of disease [21]. The American Heart Association's Get With the Guidelines Coronary Artery Disease database of 78,254 patients from 420 hospitals in the United States showed that compared with men, women were less likely to receive early aspirin or beta-blocker treatment, reperfusion therapy, or timely reperfusion (door-to-needle time $\leq$30 min, door-to-balloon time $\leq$90 min). Women also experienced lower use of cardiac catheterization and revascularization procedures after acute MI [9]. Though sex differences in in-hospital mortality rates were not observed after multivariable adjustment in the overall acute MI cohort, in-hospital mortality was higher in female patients with STEMI [9] (Figure 1). This difference appears to be explained by clinical covariates, like age, clinical presentation, and treatment utilization, as outlined in a 2014 systematic review by Bucholz et al. [11].

In contrast to the above-mentioned studies both in LMIC and in HIC, our registry showed no significant differences in in-hospital management of ACS in women. However, our data are consistent with many of the above-mentioned studies that have found no mortality difference between sexes after adjustment, both in the short and long term [11], despite differences in process-of-care measures.

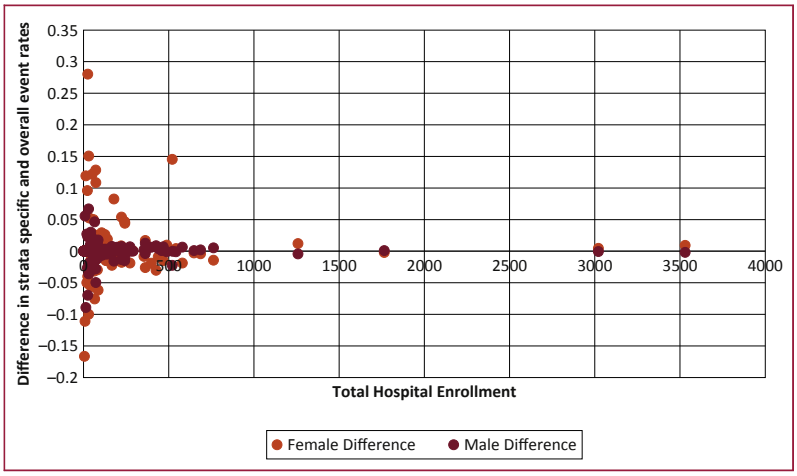

FIGURE 1. Differences between male and female event rates with overall hospital event rate.

Comparison with other disease states in South Asia

Sex differences have been described in the initiation of highly active antiretroviral therapy in a human immunodeficiency virus (HIV) population in rural South India, with women more likely to experience lactic acidosis (2.8% in women vs. 0.7% in men, $p < 0.001$) and nausea (27% in women vs. 19% in men, $p < 0.001$), and men more likely to develop immune reconstitution syndrome (6% in men vs. 2% in women, $p < 0.001$) 1 year after the initiation of highly active antiretroviral therapy [22]. However, there are few studies about sex differences in chronic diseases. Small observational studies have shown some differences in the diagnosis and treatment of diabetes mellitus and epilepsy in Nepal and India, respectively, but not in the acute setting [23,24]. This highlights the need for further study in the management and outcomes of acute

manifestations of noncommunicable, chronic diseases in India.

Strengths and limitations

Our study has several strengths. First, our data are derived from the largest ACS registry in India. Second, our results are being linked to action through our ACS QUIK (Acute Coronary Syndromes Quality Improvement in Kerala) clinical trial, which aims to develop, implement, and evaluate the effect of a locally developed quality improvement toolkit on 30-day major adverse cardiovascular events.

However, our study also has several limitations. First, due to the observational nature of our data, potential residual confounding exists, which may influence potential associations between sex and outcomes that we did not demonstrate. However, we used a validated risk model to adjust for potential confounders. Second, our data are limited to voluntary participation among hospitals in the state of Kerala, which may limit our study's external validity to other states in India. Third, the social, economic, and educational norms in Kerala are not likely to be representative of the rest of the country, given that Kerala has the highest literacy rate in India and is among the wealthier states in India by gross domestic product and per capita income [25]. Finally, post-discharge follow-up data to study event rates, medication and lifestyle modification adherence, economic costs, and health-related quality of life were not captured, though these are all important metrics for quality of care that are areas of active investigation within our group.

CONCLUSIONS

This study of 25,748 patients with ACS from 125 hospitals in Kerala, India, is the largest to examine sex-based differences in ACS presentation, management, and outcomes in India. Though women with ACS were older and more likely to have previous MI, we found no significant differences in process-of-care measures of in-hospital mortality, reinfarction, heart failure, or cardiogenic shock between sexes after adjustment for potential confounders. The information provided through the Kerala ACS registry provides useful insights when addressing ACS management in both sexes and suggests that process-of-care quality improvement measures in Kerala need not be sex-specific. On a broader scale, our study highlights that sex-based differences in acute presentations of chronic diseases in LMIC, and India in particular, are understudied. Even though there is a suggestion of sex-based differences in diseases such as HIV, these research gaps warrant further investigation.

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