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Gender differences in the management of acute coronary syndrome patients: One year results from HPIAR (HP-India ACS Registry)

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ABSTRACT

Introduction: Data from high-income countries suggest that women receive less intensive diagnostic and therapeutic management than men for acute coronary syndrome (ACS). There is a paucity of such data in the Indian population, which is 69% rural and prior studies focused mostly on urban populations. The objective of the present study was to identify the gender based differences in ACS management, if any, in a predominantly rural population.

Methods: Data from 35 hospitals across Himachal Pradesh covering >90% of state population were collected for one year (July 2015–June 2016). A total of 2118 ACS subjects met inclusion criteria and baseline characteristics, in-hospital treatments and mortality rates were analyzed.

Results: Women constituted less than one-third of ACS population. Women were older compared to men and were more likely to present with NSTEMI/UA. Misinterpretation of initial symptoms and late presentation were also common in women. Fewer women received optimal guideline based treatment and PCI (0.9% vs 4.2%, $p < 0.01$). Compare to men, women more often had Killip class >1 (27.3% vs 20.4%, $p < 0.01$) and higher in-hospital mortality (8.5% vs 5.6%, $p = 0.009$). On multivariate analysis the association between female gender and mortality was attenuated (adjusted odds ratio [OR] = 1.36 [0.77–2.38]).

Conclusion: The present study from India, is the first of its kind to evaluate the gender based differences among ACS patients, in a predominantly rural population. Our analysis demonstrates a significant gender based difference between symptom awareness and delay in presentation, management and in-hospital outcome. Further studies are warranted across other parts of country to investigate this gender disparity.

1. Background

Cardiovascular disease is the leading cause of death in India and worldwide [1,2]. Ischemic heart disease accounted for 11.4% of deaths in India in 2010 [3]. Evidence of gender-related disparities in acute coronary syndrome (ACS) prognosis emerged >30 years ago [4]; but still the mechanisms behind these differences remain unclear. Data from western countries have repeatedly demonstrated that women with ACS have more atypical presentation and undergo less intensive diagnostic and therapeutic interventions than their male counterparts [5–8]. Despite this there have been no significant differences in the outcomes. A study including 78,254 patients showed that women had higher in-hospital mortality but this gender-related difference in the in-hospital mortality disappeared after adjustment for clinical factors [7]. Studies evaluating such gender-based differences in the ACS patients have been limited in India. The CREATE (Treatment and outcomes of acute coronary syndromes in India) registry of over 20,000 ACS patients across 89 centers in India did not evaluate gender based disparities [9]. The DEMAT (Detection and Management of Acute Coronary Events) registry [10]of 1565 ACS patients in India demonstrated that in-hospital management, discharge management, and 30-days outcomes did not significantly differ between genders, though consistently lower treatment rates and higher event rates in women compared to men were seen. Similarly, results from the Kerala ACS registry of 25,748 patients showed no significant differences in the in-hospital and discharge management, in-hospital mortality, or major adverse cardiovascular events between genders. However DEMAT registry consisted of only 10 urban centers across India, while the Kerala-ACS registry involved only 125 hospitals out of total 300 hospitals across the state of Kerala, who voluntarily participated in the study [11]. Overall proportion of rural population in Kerala (52.3%) is less than that of India as a whole (68.8%), so these data may not be representative of

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overall Indian population [12]. Himachal Pradesh (HP) is the state to have the highest proportion of rural population in the country with 90.2% of population living in rural areas [12]. We hypothesized that the spectrum of ACS patients in HP and the patterns of their presentation, management and outcome would best match with the Indian population as a whole. We aimed at evaluating the gender based differences in the ACS management among such a predominantly rural population, using the data from the HP-ACS Registry, involving 2118 ACS patients.

2. Methods

2.1. Study population

The present study is a retrospective analysis of 2118 ACS patients enrolled consecutively in the HP-ACS registry over a period of 1 year (July 2015–June 2016).The methods of HP-ACS registry have been previously published [13].

In brief, all the teaching and non-teaching centers in state, whether government or private, capable of managing ACS patients were invited to participate in the study. Out of 40 such hospitals, 35 agreed to participate, thus covering approximately 90% of state population. Both urban and rural populations were equally covered [13]. IGMC Shimla, equipped with cardiac catheterization facility was the central coordinating institute.

The diagnosis of ACS was made if patient presented with symptoms suggestive of ACS within preceding one week, associated with any one of the following [13]:

1. ECG changes suggestive of myocardial ischemia/infarction
2. Elevated biomarkers of myocardial necrosis (Any one of CPK-MB/Troponin-T or Troponin-I)
3. History of documented coronary artery disease in the past

ACS patients were then categorized into ST segment elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction/unstable angina (NSTEMI/UA). STEMI was diagnosed if ECG showed evidence of ST segment elevation in ≥2 contiguous leads. The rest of the cases were labeled as NSTEMI/UA based on the presence of elevated biomarkers of myocardial necrosis [13].

The case ascertainment was done at each center by the physician-in-charge. Data of ACS patients were recorded and entered by the trained data entry operators of the respective centers in consultation with the treating physicians in the pre-structured recording format (see Supplementary File 1 for Case Recording Sheet).

At each center, data related to demographics, status of urban/rural background, pre-hospital delay, cardiovascular risk factors, hemodynamic status, ACS types, treatments, and in-hospital outcomes were recorded. The primary outcome measure of interest was in-hospital mortality, which was defined as the death due to any cause during the hospital stay. The secondary outcome measures recorded were new onset heart failure, complete heart block, ventricular tachycardia/fibrillation, recurrent angina and stroke. Patients were examined on daily basis by the attending physicians. Serial ECG monitoring was done to look for development of new ischemic changes and rhythm disorders. New onset heart failure was considered to be present if the patient developed pulmonary rales and S3 gallop, or if alveolar or interstitial oedema was noted by chest radiograph. Recurrent angina was defined as the new onset of angina after initial stabilization. Stroke was defined as an acute focal neurological deficit lasting >24 h or resulting in death. Imaging was not required for the diagnosis of stroke and was performed as deemed appropriate by the treating physician. No classification into hemorrhagic or ischemic stroke types was made. The data of patients were then uploaded in the e-recording format in the HP ACS web site after discharge or death. The data manager monitored the quality of data and any missing data/discrepancies were immediately communicated to the respective registry center for corrections. The institutional review board of IGMC Shimla India approved the registry protocol, and data were collected after obtaining written informed consent from each of the eligible patients.

2.2. Statistical analysis

We present continuous variables as mean ± standard deviation or median (inter-quartile range), when skewed in distribution, and categorical variables as proportions. Differences between genders were compared using the analysis of variance for continuous variables and the chi-square test for categorical variables. Two-tailed significance at <0.05 was taken as statistically significant. Multiple logistic regression analysis was used to identify whether gender was an independent predictor of in-hospital mortality. Variables considered for inclusion were the time lapsed between symptoms and first medical contact, age, heart rate at presentation, smoking, diabetes mellitus, hypertension, reperfusion therapy, Killip class, and the presence of complete heart block. All analyses were performed using EPI INFO version 3.4.3 (Centers for Disease Control and Prevention, United States).

3. Results

3.1. Baseline characteristics

A total of 2118 patients with the diagnosis of ACS were enrolled across 35 hospitals in the state of HP. Of these, less than one-third cases were women (28.8% vs 71.2% men). The baseline characteristics of the study population are depicted in Table 1. The median age of women was significantly higher in comparison to men (65 years vs 60 years, $p < 0.001$). >90% of the ACS cases were from rural background, with no urban-rural difference among the genders (87.4% vs 90.3%, $p = 0.08$). In comparison to men with ACS, women with ACS were more likely to have history of diabetes mellitus (18% vs 12.7%, $p < 0.01$) and hypertension (39.9% vs 26.4%, $p < 0.001$), but were less likely to be tobacco users (18.6% vs 79.8%, $p < 0.001$). There were no gender-based differences in history of prior MI, prior coronary revascularization, family history and sedentary life style. 20.2% ACS patients were unaware of their initial symptoms which they wrongly attributed to non-cardiac causes. The misinterpretation of initial symptoms was more common in women as compared to men (26.3% vs 17.7%, $p < 0.001$). This was evident by the higher median delay between symptom onset and the first medical contact, among women (420 min vs 300 min, $p < 0.01$). 52.5% of women with ACS took >6 h to reach first medical contact in comparison to 43.6% men with ACS ($p < 0.001$).

A significant difference in the type of ACS was observed among the study groups. NSTEMI/UA was more common than STEMI in the overall cohort as well as in women (63.4% vs 36.6%, $p < 0.001$). On the contrary, STEMI was more common than NSTEMI/UA in men (51.7% vs 48.3%, $p < 0.001$).

In comparison to women, men more frequently presented with past history of use of aspirin (26.7% vs 20.9%), clopidogrel (24.8% vs 20.4%) and statins (22.4% vs 17.3%) ($p < 0.05$ for all).

Women at presentation were having higher heart rate than men (83.43 vs 80.66, $p < 0.001$). Proportionately more women had Killip class >1 (27.3% vs 20.4%; $p < 0.001$) random blood sugar >180 mg/dl (27.2% vs 22.3%, $p = 0.04$) and left bundle branch block on ECG (4.2% vs 1.7%, $p < 0.001$), at admission, in comparison to men. No significant gender based difference was noted in blood pressure, body mass index and baseline serum creatinine.

3.2. In-hospital management

In-hospital use of aspirin, clopidogrel, beta-blockers, ACE-I/ARBs (Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers), nitrates and heparin were high in both men and women (>90% in both groups) (Table 1). Gender difference was noted with significantly fewer

Table 1
Differences in the demographic, clinical and treatment characteristics of the patients in HP ACS Registry, stratified according to the gender type.

	Number	Total $n = 2118$	Men $n = 1508$ (71.2%)	Women $n = 610$ (28.8%)	p-Value[a]
Age	2118	61.50 ± 12.71	59.99 ± 12.67	65.26 ± 12.05	<0.001
Region					
Urban	2118	194 (9.1%)	147 (9.7%)	77 (12.6%)	0.08
Rural	2118	1924 (90.9%)	1361 (90.3%)	533 (87.4%)	
Risk factors					
Diabetes	2108	300 (14.23%)	191 (12.7%)	109 (18.0%)	<0.001
Hypertension	2108	638 (30.2%)	396 (26.4%)	242 (39.9%)	<0.001
Smoking	2108	1310 (62.2%)	1197 (79.8%)	113 (18.6%)	<0.001
Family history	2108	103 (4.9%)	77 (5.1%)	26 (4.3%)	0.24
Sedentary life	2118	349 (16.5%)	246 (16.3%)	103 (16.9%)	0.56
History of MI	2118	53 (2.5%)	40 (2.7%)	13 (2.1%)	0.29
Prior PCI/CABG	2118	23 (1.0%)	18 (1.1%)	5 (0.8%)	0.67
Delay in presentation					
Misinterpretation of initial symptoms	2118	407 (19.2%)	255 (16.9%)	152 (24/9%)	<0.001
Time >6h from symptom onset to FMC	2118	975 (46.1%)	656 (43.5%)	319 (52.3%)	<0.001
Minutes between symptom onset to first medical contact (median, interquartile range)	2118	330 (145–1080)	300 (130–1015)	420 (180–1270)	0.01
Diagnosis					
STEMI	2118	1002 (43.7%)	779 (51.7%)	223 (36.6%)	<0.001
NSTEMI/UA	2118	1116 (52.7%)	729 (48.3%)	387 (63.4%)	<0.001
Clinical features on presentation					
Heart rate, beats/min	2118	81.45 ± 17.58	80.66 ± 17.49	83.42 ± 17.67	<0.001
Systolic BP, mm of Hg	2118	130.21 ± 27.90	129.52 ± 27.81	131.91 ± 28.06	0.07
Diastolic BP, mm of Hg	2118	80.64 ± 15.06	80.70 ± 15.42	80.48 ± 14.11	0.76
Body mass index, kg/m^2	2118	24.20 + 4.50	24.26 + 4.5	24.05 + 4.4	0.35
Killip class >1	2118	475 (22.4%)	308 (20.4%)	167 (27.3%)	<0.001
Serum creatinine >1.5 mg/dl	1285	189 (14.7%)	134 (14.1%)	55 (16.3%)	0.32
RBS >180 mg/dl	1513	359 (23.72%)	243 (22.3%)	116 (27.2%)	0.04
LBBB	2118	52 (2.4%)	26 (1.7%)	26 (4.2%)	<0.001
Baseline medical therapy					
Aspirin	2118	485 (22.9%)	368 (24.4%)	117 (19.2%)	0.007
Clopidogrel	2118	455 (21.5%)	341 (22.6%)	114 (18.7%)	0.03
Statins	2118	406 (19.2%)	309 (20.5%)	97 (15.9%)	0.01
In-hospital medical therapy					
Thrombolysis (among STEMI patients)	1002	376 (37.5%)	296 (38%)	80 (35.9%)	0.56
Door-to-needle time, minutes (median)	2090	57	55	59	0.53
Aspirin	2063	2031 (98.4)	1457 (99)	574 (97)	<0.001
Clopidogrel	2066	2057 (99.6)	1467 (99.5)	590 (99.7)	0.36
Statins	2061	2049 (99.4)	1458 (99.4)	591 (99.3)	0.36
Nitrates	1755	1666 (94.9)	1198 (95.3)	468 (94)	0.12
Beta-blockers	2043	1972 (96.5)	1406 (96.6)	566 (96.4)	0.43
ACE-I/ARBs	1926	1789 (92.9)	1281 (94)	508 (90.2)	0.002
Heparin	2027	2000 (98.7)	1423 (98.3)	577 (98.5)	0.30
Key investigations					
Positive cardiac biomarkers	1763	1504 (85.3%)	1095/1245 (87.9)	409/518 (78.9)	<0.002
Coronary angiography/PCI	2118	70 (3.3%)	64 (6.1%)	6 (1.6%)	<0.001
In-hospital medical therapy					
Thrombolysis (among STEMI patients)	1002	376 (37.5%)	296 (38%)	80 (35.9%)	0.56
Door-to-needle time, minutes (median)	2090	57	55	59	0.53
Aspirin	2063	2031 (98.4)	1457 (99)	574 (97)	<0.001
Clopidogrel	2066	2057 (99.6)	1467 (99.5)	590 (99.7)	0.36
Statins	2061	2049 (99.4)	1458 (99.4)	591 (99.3)	0.36
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Heparin	2027	2000 (98.7)	1423 (98.3)	577 (98.5)	0.30
Treatment at discharge					
Aspirin	1959	1845 (94.2)	1329 (95.3)	516 (91.3)	<0.001
Clopidogrel	1960	1880 (95.9)	1345 (96.5)	535 (94.5)	0.02
Statins	1951	1862 (95.4)	1329 (96.2)	533 (93.5)	0.005
Beta blockers	1934	1825 (94.4)	1306 (95)	519 (92.8)	0.03
ACE-I/ARBs	1840	1675 (91)	1202 (92)	473 (88.6)	0.01
Nitrates	1693	1444 (85.3)	1047 (86.5)	397 (82.2)	0.01

Abbreviations: MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; STEMI = ST elevation myocardial infarction; NSTEMI/UA = non-ST elevation myocardial infarction/unstable angina; BP = blood pressure; RBS = random blood sugar; LBBB = left bundle branch block; ACE-I = Angiotensin Converting Enzyme Inhibitors; ARBs = Angiotensin II Receptor Blockers.
[a] Comparing men and women.

women receiving aspirin (97% vs 99%, $p < 0.001$) and ACE-I/ARBs (90.2% vs 94%, $p = 0.002$) in comparison to men. However, no gender-based difference was noted with other evidence based medications.

Among STEMI patients, women showed a trend towards lesser use of thrombolytic therapy (35.9% vs 38%) with a delayed door to needle time (59 vs 55 min), however difference remained statistically insignificant ($p > 0.05$) (Table 1).

The biomarkers of myocardial necrosis were elevated more commonly in men (87.9% vs 78.9%, $p \leq 0.001$) and this difference was mainly observed among NSTEMI/UA patients (78.8% vs 70.9%, $p \leq 0.001$)

Table 2
Characteristics of patients and complications according to the diagnosis at presentation.

	STEMI (1002)			NSTEMI/UA (1116)		
	Men	Women	*p*-Value[a]	Men	Women	*p*-Value[a]
Number	779 (77.7%)	223 (22.2%)		729 (65.3%)	387 (34.7%)	
Elevated biomarkers of myocardial necrosis	99.1%	96.8%	0.30	78.8%	70.9%	0.004
Death	48 (6.2)	33 (14.8)	<0.001	36 (4.9)	19 (4.9)	0.55
CHB	11 (5.3)	11 (15.3)	0.01	8 (3.0)	5 (2.8)	0.56
CHF	56 (22.6)	36 (37.5)	0.004	72 (22.4)	44 (20.4)	0.33
KILLIP class >1	152 (19.5)	79 (35.4)	<0.001	156 (21.4)	88 (22.7)	0.96

Abbreviations: STEMI = ST elevation myocardial infarction; NSTEMI/UA = non-ST elevation myocardial infarction/unstable angina; CHB = complete heart block; CHF = congestive heart failure.
[a] Comparing men and women.

(Table 2). This indirectly suggested higher proportion of unstable angina patients among women in comparison to men.

Interestingly, men were likely to undergo coronary angiography more often than women (6.1% vs 1.6%, $p < 0.001$). It is notable that overall only 70 (3.3%) patients underwent coronary angiography, which included 42 STEMI patients.

3.3. In-hospital outcome

The unadjusted in-hospital mortality rate was 8.5% in women, compared with 5.6% in men ($p < 0.001$) (Table 3). The rates of other complications like congestive heart failure, complete heart block, ventricular tachycardia/fibrillation, recurrent angina and stroke were similar in both the genders.

After stratifying the results according to the presentation diagnosis, a significant gender difference in the outcome variables was found among STEMI patients while the outcome was similar in NSTEMI/UA across genders (Table 2). Higher rates of death (14.8% vs 6.2%), complete heart block (15.3% vs 5.3%), congestive heart failure (37.5% vs 22.6%) and Killip class >1 (35.4% vs 19.4%) were seen in women with STEMI, as compared to men with STEMI.

Multivariable analysis was used to identify the independent predictors of in-hospital mortality (Table 4). These included age, gender, Killip class >1 at presentation, diagnosis of STEMI, development of complete heart block and congestive heart failure.

After adjusting for other risk determinants, the gender effect on mortality attenuated. The unadjusted odds ratio was 1.57 (95% CI = 1.10–2.26), which became 1.36 (0.77–2.38) after adjusting for other covariates (Table 4).

3.4. Discharge medication

Evidence based prescription of medications was significantly less among women at discharge with fewer women receiving aspirin (91.3% vs 95.3%), clopidogrel (94.5% vs 96.5%), statins (93.5% vs 96.2%), beta-blockers (92.8% vs 95%), ACE-I/ARBs (88.6% vs 92%) and nitrates (82.2% vs 86.5%), in comparison to men ($p < 0.05$ for all).

Table 3
In-hospital complications, stratified by sex.

	Number	Total	Men	Women	*p*-Value[a]
Average hospital stay, days	2118	4.12 + 2.65	4,08 + 2.65	4.24 + 2.64	0.20
Death	2118	136 (6.4)	84 (5.6)	52 (8.5)	0.009
CHF	2118	208 (23.6)	128 (22.5)	80 (25.6)	0.16
VT/VF	2118	18 (2.5)	15 (3.2)	3 (1.2)	0.09
CHB	2118	35 (4.8)	19 (4.0)	16 (6.3)	0.11
Recurrent angina	2118	27 (3.8)	18 (3.9)	9 (3.7)	0.55
Stroke	2118	8 (1.5)	5 (1.3)	3 (2.0)	0.93

Abbreviations: CHF = congestive heart failure; VT = ventricular tachycardia; VF = ventricular fibrillation; CHB = complete heart block; MI = myocardial infarction.
[a] Comparing men and women.

4. Discussion

4.1. Summary of results

This registry of 2118 patients with ACS from all over the state of Himachal Pradesh is the first of its kind, population representative study, regarding the gender-based differences in the presentation, management, and outcome of ACS. Results of this registry show that on presentation, women with ACS were more likely to be older and to have a history of hypertension and diabetes and were less likely to be tobacco users, than men. Women presented more commonly with NSTEMI/UA and more often misinterpreted initial symptoms of ACS resulting in delayed presentations when compared to men. Use of coronary angiography was less common in women, however interpretation should be made with caution as it was done in only 3.3% of overall study population. Fewer women received aspirin and ACE-I/ARBs during admission and optimal medical treatment at discharge. Among patients with STEMI, there was a significant gender difference with women showing increased rates of in-hospital mortality and other MACE. This was despite the fact that no significant gender difference was noted either in the proportion of patients undergoing thrombolysis, or in door-to-needle time before thrombolysis. On the contrary, there was no significant gender difference in the in-hospital outcome of NSTEMI/UA patients. Overall, the in-hospital mortality rate was higher among women. But after adjusting for confounding factors, no effect of gender on mortality was noticed.

Table 4
A. Association between gender and in-hospital mortality of HPIAR patients (reference: men) using regression analysis. B. Multivariable logistic regression model to evaluate predictors of in-hospital death.

	In-hospital death OR (95% CI)
A	
Unadjusted logistic regression model	1.57 (1.10–2.26)
Logistic regression model adjusted for age	1.30 (0.90–1.87)
B	
Multivariate logistic analysis for in-hospital death	
Gender	1.36 (0.77–2.38)
Late presentation	1.00 (0.99–1.00)
Age	1.02 (1.00–1.04)
Diabetes	0.91 (0.44–1.88)
Hypertension	0.61 (0.31–1.07)
Smoking	0.82 (0.42–1.56)
STEMI diagnosis	1.84 (1.13–2.99)
Killip class >1 at presentation	2.44 (1.32–4.49)
CHF during hospital stay	3.70 (1.87–7.33)
CHB	2.25 (0.73–6.93)
Reperfusion therapy	0.51 (0.06–4.06)

Abbreviations: OR = odds ratio; CI = confidence interval; STEMI = ST elevation myocardial infarction; CHF = congestive heart failure; CHB = complete heart block.

4.2. Comparison with ACS registries from other countries

Regarding gender differences, there are very limited data available from middle to low income countries, including India. Similar to our results, most of them have reported gender differences in the ACS management. In 2011, registry of 1204 ACS patients from5 hospitals revealed that women were less likely to receive aspirin on admission, anticoagulants and angiography during hospitalization, and aspirin and statins on discharge [14]. In 2007, a Thai registry of 3836 patients with STEMI from 17 hospitals found that beta-blockers, statins, ACE-I/ARBs, coronary angiography, thrombolysis, and PCI were used less frequently in women [15]. Similarly, in a large ACS registry of 7930 patients from 6 Arabian Gulf countries it was found that women were less likely to undergo angiography, PCI, and reperfusion therapy in comparison to men [16]. Despite these differences in the processes of care in ACS management, none of the above-mentioned registries showed a difference in in-hospital mortality between genders, after adjustment for baseline characteristics. The similar effect on in-hospital mortality was seen in our study.

The available data from high income countries also reveal differences in ACS management between men and women. The Global Registry of Acute Coronary Events (GRACE) examined 26,755 patients in 14 mostly high-income countries in Europe, the Americas, and the South Pacific and demonstrated that women were treated less aggressively than their male counterparts, and were more likely to have adverse outcomes (death, MI, stroke, rehospitalization) than men. However, no difference was seen in mortality after adjustment for baseline characteristics [5]. A database of 78,254 acute myocardial infarction 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 ≤ 30 min, door-to-balloon time ≤ 90 min) [7]. Women were also less likely to undergo cardiac catheterization and revascularization procedures after acute MI. In the overall acute MI cohort, multivariable adjustment did not reveal gender based difference in the in-hospital mortality. However, among patients with STEMI alone, women had a higher in-hospital mortality rate [7], similar to our results.

4.3. Comparison with previous ACS registries in India

As previously stated, there are limited data from previous ACS registries in India regarding the gender based differences in ACS patients. Previous large ACS registries in India including OASIS-1 and 2 [17]and CREATE [9]registries did not evaluate the gender based difference in presentation, management and outcome of ACS. The first study highlighting these differences was the DEMAT registry [10], which consisted of 1565 suspected ACS patients (21% women), from ten tertiary care centers throughout India between 2007 and 2008. Similar to HP-ACS registry, women in DEMAT registry were more likely to be older, diabetic, hypertensive and were less likely to be tobacco smokers. Similarly women presented mainly with NSTEMI/UA (61.7%) while men presented mainly with STEMI (55.2%). Overall the in-hospital management was similar, except that the use of thrombolytic therapy among STEMI patients was significantly higher among men (25.3% vs 16.2%, $p < 0.01$). Discharge treatments were largely similar except the lesser use of clopidogrel in women (87.2% vs 91.8%, $p < 0.01$). In-hospital mortality was not assessed in DEMAT registry. Instead 30 days mortality was recorded. There was a trend towards increased mortality in women (OR 1.70) but the effect attenuated after adjusting for age and other confounders (OR 1.40).

Kerala-ACS registry also provided substantial data on gender differences in ACS [11]. In this registry, 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%, $p < 0.001$). But unlike HP-ACS registry, there was no gender based difference in the presence of other risk factors, presentation and in-hospital diagnostics, management and discharge care. Similarly 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 to1.25) were seen after adjustment for possible confounding factors. Therefore, the management and outcome results of Kerala-ACS registry differed markedly from the HP-ACS registry.

Notably the DEMAT registry obtained data from 10 centers, which mainly catered to the urban population. While the Kerala-ACS registry involved 125 voluntarily participating hospitals in Kerala out of a total of 300 hospitals across the state. Therefore, none of these two registries represented a population as a whole.

Secondly only 47% of population of Kerala has the rural background which is markedly below the national distribution, consisting of 69% rural population [12]. HP is the state to have the highest percentage of rural population among all the Indian state [12]. So the results of HP-ACS registry are more likely to represent the largely rural population of India and many middle to low income countries, as a whole.

The results of this registry suggest a gender disparity in recognition and management of women patients with ACS. The possible reasons for the greater delay in presentation in women than in men include lack of awareness, misinterpretation of symptoms, social barriers to accessing care, fear, and embarrassment. Given India's history of gender relations and the gender differences that exist in the management of other diseases [18] the gender differences shown in the HP-ACS registry look realistic and may help in bridging the gaps in ACS management.

5. Limitations

The current study has several limitations. First, since the study is observational, there are chances that the potential residual confounders persist. These may influence potential associations between gender and outcomes that we did not demonstrate. Second, the sample size was relatively small and there were fewer outcome events, making gender comparisons between outcomes difficult and underpowered. Third, as the case ascertainment was done by physicians-in charge, a possibility of observer bias always persisted since the physicians were judging their own work. Fourth, post-discharge follow-up data were not captured to evaluate the adherence to secondary preventive interventions, and major adverse cardiovascular events. Caution must be exercised while extrapolating these results to the other populations, because the incidence and outcomes of ACS are influenced by socioeconomic status, access to health information, geographical characteristics, and cultural practices. Therefore, the characteristics, the treatment, and outcomes of ACS patients are likely to vary in different parts of the country. Nonetheless this population representative study is the first of its kind in India since it has been able to represent the majority of a state's population as a whole.

6. Conclusions

This study of 2118 ACS patients in the state of HP highlights the gender based differences that exist in the predominant rural population of India and other low–middle income countries. Women with ACS lack awareness regarding the symptoms, present late to the health facilities, and receive less intensive diagnostic and therapeutic interventions. This is reflected by more morbidity and mortality. These observations provide valuable information to improve the scope of treatment and outcomes through interventions at health system level.

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Contribution of authors

KM, PCN, RM and VC designed the plan and collected data. PCN and KM analyzed the data.KM and NM reviewed the literature and wrote the manuscript. SA gave conceptual advice. All the authors read and approved the final manuscript.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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