ORIGINAL ARTICLE

IMPACT OF GENDER ON THE CLINICAL FEATURES, ANGIOGRAPHIC FINDINGS, AND OUTCOMES OF YOUNG PATIENTS PRESENTED WITH ACUTE CORONARY SYNDROME

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Objectives: Acute coronary syndrome (ACS) at a younger age is now becoming a crucial problem. This study determined the effect of gender on the clinical findings and outcomes of young patients (≤ 45 years) with ACS.

Methodology: In this descriptive cross sectional study, young patients (≤45 years) who presented with ACS and underwent coronary angiography were recruited. The comparison of clinical profile, angiographic findings, in-hospital, and 90-days mortality between genders were made.

Results: A total of 335 young patients with ACS were included, 80.6% of whom were men. A significant difference was found between men and women in terms of mean age: 38±6 vs. 40±5 (p=0.014), hypertension: 37.8% vs. 58.5% (p=0.002), diabetes: 17.4% vs. 35.4% (p=0.001), smoking: 50.4% vs. 6.2% (p≤0.001), use of smokeless tobacco: 14.1% vs. 4.6% (p=0.037), median time from symptom onset to first medical contact: 270 [420–165] minutes vs. 346 [499.5–240] minutes (p=0.047), ST-segment elevation myocardial infarction (STEMI) 89.6% vs. 78.5% (p=0.015), non-ST-elevation myocardial infarction (NSTEMI) 8.5% vs. 18.5% (p=0.019), and three-vessel disease (3VD) 10.7% vs. 21.5% (p=0.019), respectively. In-hospital and 90-day mortality rates were 0.4% vs. 3.1% (p=0.097) and 1.5% vs. 4.6% (p=0.136) for men and women, respectively.

Conclusion: Women tended to have a higher age at presentation, more frequent traditional risk factors, late presentation after symptom onset, frequent NSTEMI, and 3VD, whereas men were distinct with frequent STEMI and higher tobacco use. In addition, women trended to have a higher in-hospital as well as short-term mortality than men did.

Keywords: STEMI, premature CAD, gender, outcomes, young

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INTRODUCTION

Acute coronary syndrome (ACS) predominantly occurs in individuals over 50 years of age, but this does not imply that younger adults are spared.[1] The cut-off age for young individuals varies from 40 to 55 years old.[2, 3] However, several studies have suggested that the cut-off age of 45 years be defined as young with respect to ACS and have used it as the upper limit to define young age.[4]

Limited studies have looked into gender differences in ACS patients with respect to clinical features, angiographic findings, and outcomes. Some data have suggested that men have higher mortality rates than women, whereas other studies have failed to show gender as a contributory factor in the presentation and mortality of ACS patients.[5] A study has shown better long-term survival of women than men.[6]

Cardiovascular disease tends to manifest in women almost a decade later than in men, but it remains a predominant cause of death after 65 years of age. The risk of coronary artery disease (CAD) is considered low due to the misperception that women are relatively protected from ischemic heart disease. However, the National Health and Nutrition Examination Surveys have reported that the rate of myocardial infarction has increased in women falling in the age range of 35–45 years.[7]

The few studies that looked into gender differences among ACS patients showed that women had an atypical presentation and that they often took longer to seek medical care, both of which act as contributory factors in delaying appropriate management.[8] Qinghua et al. reported a higher incidence of unstable angina and thrombolysis in myocardial infarction (TIMI) III flow in women but with a higher mortality both in-hospital and in the long-term follow-up.[9] The Gulf

RACE-I study, which was conducted in 2007, including six Middle Eastern countries, showed that mortality among women with ACS was higher than among men.[10]

After a robust literature search, we found variable and conflicting evidence of the effect of gender on the presentation, clinical features, and overall outcome in ACS patients in other parts of the world but could not find any study specifically on the effect of gender on the clinical profile, angiographic findings, and overall outcomes in the young population who presented with ACS in our region. This provided a strong rationale for conducting such a study to ascertain the variation in the clinical profile, angiographic findings, and overall outcome based on gender among the young population that presented with ACS.

METHODOLOGY

This work was designed as a descriptive cross sectional study and was conducted at the National Institute of Cardiovascular Diseases, a large tertiary care cardiac hospital in the southern part of Pakistan. Among all adult patients with ACS (n = 2,035) who underwent coronary angiogram between August 2020 to January 2021, those who were in the age range of 20–45 years (n = 335) were enrolled in the study with their written and informed consent after obtaining approval from the institutional ethical committee. All recruited patients were divided into two groups based on gender. The primary endpoint was the variation in their clinical profile, including demographics, comorbidities, and angiographic findings. The secondary endpoint was the difference in the composite major adverse cardiovascular events (MACE) in-hospital and at 90 days. All the studied patients were followed up to three months post-discharge.

The diagnosis of ACS was established as unstable angina pectoris (USAP) in patients with anginal pain with no ST-segment elevation myocardial infarction (STEMI) and a negative cardiac marker, Troponin I (Trop I) < 0.05 ng/ml, non-ST-segment elevation myocardial infarction (NSTEMI) with Trop I level of > 0.05 ng/ml, and STEMI in patients with chest discomfort with at least 1 mm elevation in the ST-segment in contiguous leads or with a presumably new onset of left bundle branch block.

Patients with non-cardiac chest pain, cardiomyopathies, pericarditis, and congenital heart diseases, or those who refused to participate were excluded.

Data related to demographics and clinical profile, including age, sex, diabetes, hypertension, dyslipidemia, body mass index (BMI), history of smoking, use of smokeless tobacco like gutka (a form of flavored tobacco combined with catechu, minced areca nut, and paraffin wax), naswar (powdered moist tobacco), paan (combination of betel leaf, areca nut, and tobacco), or plain tobacco, family history of premature CAD, drug abuse, alcohol use, and previous history of CAD were noted through self-report. BMI was described according to the World Health Organization, with 25–29.9 classified as overweight and > 30 as obese.[11]

Dyslipidemia was defined as having a total serum cholesterol of ≥ 200 mg/dl, low density lipoprotein of > 130 mg/dl, high density lipoprotein of < 40 mg/dl in men or < 50 mg/dl in women, and triglycerides of > 150 mg/dl. All patients were subjected to complete baseline biochemical and hematological investigations. The left ventricular ejection fraction (LVEF) was documented as assessed by echocardiography performed at the one-month follow-up by an experienced echocardiographer blinded to the studied population.

All patients underwent a coronary angiogram via the femoral or radial route after a positive Barbeau test using a standard technique. Angiographic severity of coronary disease was evaluated visually by at least two experienced cardiologists in at least two orthogonal views. Lesions with narrowing of ≥ 70% in epicardial coronaries, including the left anterior descending artery, left circumflex artery, right coronary artery or their major branches, and ≥ 50% in the left main coronary artery (LMCA) were defined as obstructive. Other lesions were categorized as non-obstructive. Based on the number of diseased vessels, CAD was further divided into single-vessel disease (SVD), two-vessel disease (2VD), and three-vessel disease (3VD). The infarct-related artery was defined as the culprit vessel. Lesion length was classified into Type A (≤ 10 mm), Type B (10–20 mm), and Type C (> 20 mm) based on the ACC/AHA classification. The location of the lesion was defined as proximal, mid, or distal. MACE was reported as all-cause mortality, cerebrovascular accident (CVA), heart failure (HF), arrhythmias, re-infarction, and repeat revascularization in-hospital and at the three-month follow-up post-discharge.

The collected data were analyzed using IBM SPSS (version 21). The study variables were summarized using descriptive statistics, such as mean ± standard deviation, frequency, and percentage. Both primary and secondary endpoints were compared between the male and female groups using the appropriate statistical test. Independent sample t-test or Mann-Whitney U test were applied for the continuous

variables based on the normality of distribution of variable. The Chi-square test was applied for the categorical response variables, in cases with expected cell frequency of ≤5, Fisher's Exact test for 2 response categories or Likelihood ratio test for more than 2 response categories were applied. Relative risk (RR) along with 95% confidence interval (CI) for female gender were computed for in-hospital and 90-day outcomes. A two-sided p-value of ≤ 0.05 was considered as a criterion for significance.

RESULTS

Among the 2,035 ACS patients who underwent coronary angiogram during the study interim, 16.46% (335) were young, falling in the age range of 20–45 years, and they were enrolled according to the study protocol and analyzed. Among them, 80.6% (270) were men, and 19.4% (65) were women.

The mean age of men versus women was 38 ± 6 vs. 40 ± 5, p = 0.014. Considering the clinical profile in the male and female groups, 37.8% vs. 58.5% (p = 0.002) were hypertensive, 17.4% vs. 35.4% (p = 0.001) were diabetic, 50.4% vs. 6.2% (p ≤ 0.001) were active smokers, and 14.1% vs. 4.6% (p = 0.037) used smokeless tobacco, respectively. The average BMI was 27.3 ± 3.4 vs. 27.6 ± 4.9 (p = 0.517), dyslipidemia was 8.9% vs. 10.8% (p = 0.639), CKD was 0.4% vs. 0%, and alcohol use was 1.1% vs. 0% in the male and female groups, respectively (Table 1).

The median time from symptom onset to the first medical contact in men and women was 270 [420–165] min vs. 346 [499.5–240] min (p = 0.047), respectively. With regard to ACS type, 89.6% vs. 78.5% (p = 0.015) of men and women presented with STEMI, 8.5% vs. 18.5% (p = 0.019) with NSTEMI, and 1.9% vs. 3.1% (p = 0.625) with USAP, respectively. SVD was 54.8% vs. 52.3% (p = 0.716), 2VD was 26.3% vs. 24.6% (p = 0.781), 3VD was 10.7% vs. 21.5% (p = 0.019), non-obstructive CAD was 4.4% vs. 0%, and normal coronary was 3.7% vs. 1.5% (p = 0.379) in the male and female subsets, respectively (Figure 1). The management strategy was primary percutaneous coronary intervention (PCI) in 83% vs. 72.3% (p = 0.05), early invasive PCI in 7.8% vs. 16.9% (p = 0.024), medical treatment alone in 8.5% vs. 9.2% (p = 0.855), and CABG in 0.7% vs. 1.5% (p = 0.478) in men and women, respectively (Table 2).

The angiographic findings, including culprit vessel, lesion location, and lesion length, were almost similar in the male and female groups, as shown in Figure 1. However, an LVEF of above 40% after one month was significantly greater in men than in women at 65.6% vs. 50.8% (p = 0.027).

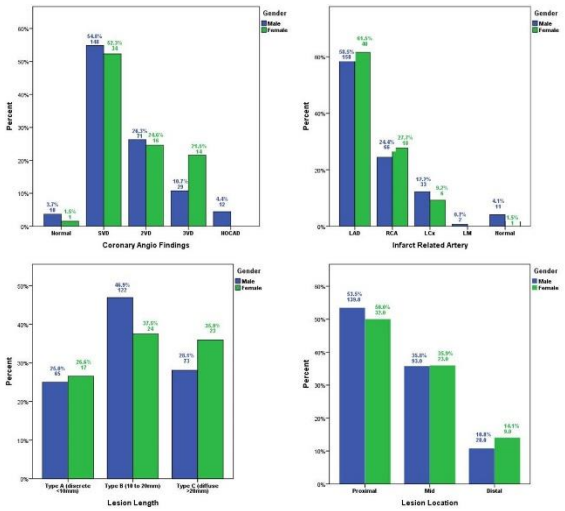

Figure 1: Comparison of angiographic pattern by gender

SVD = single vessel disease, 2VD = two vessel disease, 3VD = three vessel diseases, NOCAD = non-obstructive coronary artery diseases, LAD = left anterior descending artery, RCA = right coronary artery, LCx = left circumflex, LM = left main

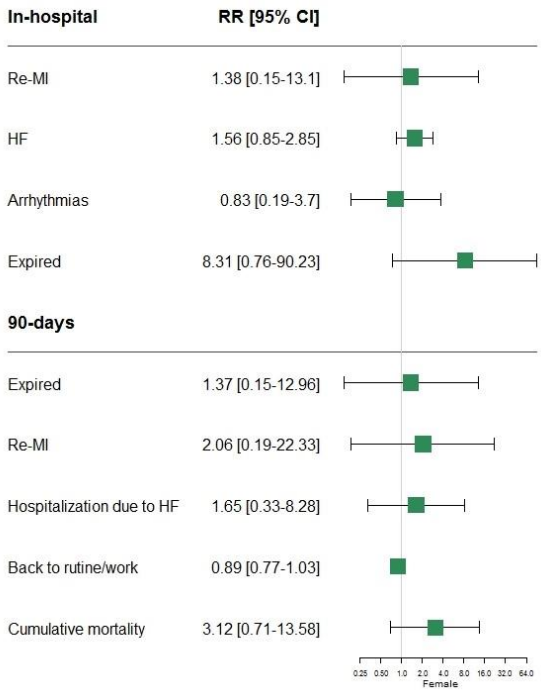

Figure 2: Relative risk of in-hospital and 90-day MACE in women

HF = heart failure, MI = myocardial infarction

The secondary outcomes in the male and female groups were as follows, respectively: in-hospital mortality in 0.4% vs. 3.1% (p = 0.097), RR 8.31 [95% CI: 0.76–90.23], arrhythmia in 3.7% vs. 3.1% (p > 0.999), recurrent MI in 1.1% vs. 1.5% (p = 0.580), repeat revascularization in 1.1% vs. 0%, CVA in 0.4% vs. 0%, and heart failure in 11.9% vs. 18.5% (p =

0.157). At a median follow-up of 95 days, the cumulative all-cause mortality was 1.5% vs. 4.6% (p = 0.136), RR was 3.12 [95% CI: 0.71–13.58], recurrent MI was 0.8% vs. 1.7% (p = 0.480), repeat revascularization was 0.8% vs. 0%, CVA was 1.2% vs. 0%, and hospitalization due to HF was 2.1% vs. 3.4% (p = 0.626) in the male and female subsets, respectively. Medication compliance and resumption of routine activities were 95.5% vs. 100% (p = 0.130) and 87.2% vs. 78% (p = 0.070) in the male and female groups, respectively (Table 2 and Figure 2)

Table 1: Comparison of measured (24 h) and estimated sodium

Characteristics	Total	Gender		P-value
		Male	Female	
Total (N)	335	270 (80.6%)	65 (19.4%)	-
Age (years)	39 ± 6	38 ± 6	40 ± 5	0.014[a]
Body mass index (kg/m^2)	27.4 ± 3.7	27.3 ± 3.4	27.6 ± 4.9	0.517[a]
Under weight	2 (0.6%)	1 (0.4%)	1 (1.5%)	0.321[b]
Normal weight	65 (19.4%)	50 (18.5%)	15 (23.1%)	
Over weight	211 (63%)	176 (65.2%)	35 (53.8%)	
Obese	57 (17%)	43 (15.9%)	14 (21.5%)	
Systolic blood pressure (mmHg)	135.6 ± 23.3	135.1 ± 23.1	137.9 ± 24.2	0.390[a]
Diastolic blood pressure (mmHg)	86.4 ± 15.2	86.7 ± 14.9	85.5 ± 16.3	0.568[a]
Heart Rate (bpm)	86 ± 15	86 ± 16	87 ± 14	0.818[a]
Hypertension	140 (41.8%)	102 (37.8%)	38 (58.5%)	0.002[c]
Diabetes mellitus	70 (20.9%)	47 (17.4%)	23 (35.4%)	0.001[c]
Non-Insulin dependent	62 (88.6%)	42 (89.4%)	20 (87%)	>0.999[d]
Insulin dependent	8 (11.4%)	5 (10.6%)	3 (13%)	
Smoking	140 (41.8%)	136 (50.4%)	4 (6.2%)	<0.001[c]
Current smokers	120 (85.7%)	117 (86%)	3 (75%)	0.464[d]
Ex-smokers	20 (14.3%)	19 (14%)	1 (25%)	
Positive Family History	30 (9%)	27 (10%)	3 (4.6%)	0.172[c]
Dyslipidemia	31 (9.3%)	24 (8.9%)	7 (10.8%)	0.639[c]
Chronic kidney disease	1 (0.3%)	1 (0.4%)	0 (0%)	-
Smokeless tobacco use	41 (12.2%)	38 (14.1%)	3 (4.6%)	0.037[c]
Paan	13 (31.7%)	11 (28.9%)	2 (66.7%)	0.232[d]
Gutka	15 (36.6%)	15 (39.5%)	0 (0%)	-
Naswar	10 (24.4%)	10 (26.3%)	0 (0%)	-
Chewable Tobacco	20 (48.8%)	17 (44.7%)	3 (100%)	0.107[d]
Alcohol consumption	3 (0.9%)	3 (1.1%)	0 (0%)	-
Average time from symptoms onset to first medical contact (min)	300 [476-209.5]	270 [420-165]	346 [499.5-240]	0.047[e]
Type of Acute Coronary Syndrome				
Unstable angina	7 (2.1%)	5 (1.9%)	2 (3.1%)	0.625[d]
NSTEMI	35 (10.4%)	23 (8.5%)	12 (18.5%)	0.019[c]
STEMI	293 (87.5%)	242 (89.6%)	51 (78.5%)	0.015[c]
Anterior wall MI	177 (60.4%)	145 (59.9%)	32 (62.7%)	0.707[c]
Inferior wall MI	116 (39.6%)	97 (40.1%)	19 (37.3%)	

NSTEMI = Non-ST segment elevation myocardial infarction, STEMI = ST segment elevation myocardial infarction, MI = myocardial infarction

[a]Independent sample t-test, [b]Likelihood ratio test, [c]Chi-square test, [d]Fisher's Exact test, [e]Mann-Whitney U test

Table 2: Management strategy and outcomes

Characteristics	Total	Gender		P-value
		Male	Female	
Total (N)	**335**	**270**	**65**	-
LVEF (%) by echo at 30 days				
< 30%	53 (15.8%)	40 (14.8%)	13 (20%)	0.304[c]
30 to 40%	72 (21.5%)	53 (19.6%)	19 (29.2%)	0.091[c]
> 40%	210 (62.7%)	177 (65.6%)	33 (50.8%)	0.027[c]
Management Strategy				
Primary PCI	271 (80.9%)	224 (83%)	47 (72.3%)	0.050[c]
Early invasive PCI	32 (9.6%)	21 (7.8%)	11 (16.9%)	0.024[c]
Medical treatment only	29 (8.7%)	23 (8.5%)	6 (9.2%)	0.855[c]
CABG	3 (0.9%)	2 (0.7%)	1 (1.5%)	0.478[d]
In-hospital outcomes				
Re-infarction	4 (1.2%)	3 (1.1%)	1 (1.5%)	0.580[d]
Repeat revascularization	3 (0.9%)	3 (1.1%)	0 (0%)	-
Cerebrovascular accident	1 (0.3%)	1 (0.4%)	0 (0%)	-
Heart Failure	44 (13.1%)	32 (11.9%)	12 (18.5%)	0.157[d]

Arrhythmias	12 (3.6%)	10 (3.7%)	2 (3.1%)	>0.999[d]
Expired	3 (0.9%)	1 (0.4%)	2 (3.1%)	0.097[d]
^Successful 3-month follow-up	302 (90.7%)	243 (90.7%)	59 (90.8%)	0.852[c]
^Median follow-up time (days)	95 [111-79]	95 [112-78]	95 [111-82]	0.815[e]
Follow-up outcomes				
Expired	4 (1.3%)	3 (1.2%)	1 (1.7%)	0.583[d]
Re-infarction	3 (1%)	2 (0.8%)	1 (1.7%)	0.480[d]
Repeat revascularization	2 (0.7%)	2 (0.8%)	0 (0%)	-
Cerebrovascular accident	3 (1%)	3 (1.2%)	0 (0%)	-
Hospitalization due to HF	7 (2.3%)	5 (2.1%)	2 (3.4%)	0.626[d]
Medication compliance	291 (96.4%)	232 (95.5%)	59 (100%)	0.130[d]
Back to routine/work	258 (85.4%)	212 (87.2%)	46 (78%)	0.070[c]
Cumulative mortality	7 (2.1%)	3 (1.5%)	5 (4.6%)	0.136[d]

LVEF = left ventricular ejection fraction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting
^based on survived patients
[c]Chi-square test, [d]Fisher's Exact test, [e]Mann-Whitney U test

DISCUSSION

Mostly previous studies have looked into gender differences regardless of the age of presentation of ACS. Conversely, the current study is unique, as we focused on young individuals (≤ 45 years) to determine the gender-based variations in the different aspects of ACS. It is important to focus on this subset of the population because, with greater urbanization, traditional risk factors are becoming more prevalent, causing the development of premature CAD.[12]

Thus far, studies conducted to analyze gender-based differences in ACS patients have revealed conflicting results. Our study showed that women were older than men, with a mean age of 40 ± 5 vs. 38 ± 6 (p = 0.014), and that the median time from symptom onset to the first medical contact was significantly greater at 346 [499.5–240] min vs. 270 [420–165] min (p = 0.047). These findings are consistent with those from earlier studies, which showed that women sought medical attention later than men did[13, 14] and tended to have more atypical manifestations of ACS.[15] A higher prevalence of traditional risk factors was also observed in women compared with men, including hypertension, 58.5% vs. 37.8% (p = 0.002), and diabetes 35.4% vs. 17.4% (p = 0.001). This is consistent with earlier studies that showed significantly higher incidences of hypertension and diabetes among women who presented with ACS,[16] which could have contributed to their higher mortality.[17]

No significant difference was found between men and women in BMI, dyslipidemia, and chronic kidney disease, with p-values of 0.517, 0.639, and > 0.999, respectively. Men tended to have higher tobacco use, such as in tobacco smoking, 50.4% vs. 6.2% (p ≤ 0.001), and use of smokeless tobacco, 14.1% vs. 4.6% (p = 0.037). Similar findings were also reported in a Saudi study by Bassiony, who found that 26.5% of males were current smokers compared with only 9% of females.[18]

STEMI was the most common presentation in men, 89.6% vs. 78.5% (p = 0.015), whereas non-STEMI was more common in women, 8.5% vs. 18.5% (p = 0.019). This observation is consistent with earlier studies, which showed that women mostly presented with non-STEMI.[19]

Angiographic analysis showed that women tended to have a more extensive involvement of coronaries, as evidenced by a significantly higher frequency of 3VD, 10.7% vs. 21.5% (p = 0.019), compared with men, and they also had a higher trend in the in-hospital mortality, 0.4% vs. 3.1% (p = 0.097), with a RR of 8.31 [95% CI: 0.76–90.23]. In a large meta-analysis of 11 randomized trials on ACS, the gender-based variation in 30-day mortality in patients with different types of ACS was largely explained by clinical variation at presentation and the criticality of angiographically documented coronary disease.[13] This trend was also seen in another study that showed a higher prevalence of triple-vessel CAD and higher mortality in women.[20] Other angiographic spectra comprising smaller caliber coronaries, lesser collateral supply, and reduced coronary flow reserves could be responsible for the variation in outcomes between men and women.[21] However, the current study did not show any significant gender-based differences in the angiographic pattern of the disease itself, including the lesion length or location and the culprit vessel, as shown in Figure 1.

In the context of STEMI, both men and women showed comparable benefits from the primary PCI of the culprit vessel, and it was the most common mode of management in both genders compared with the other strategies. Moreover, as the majority of the women also presented with STEMI regardless of their higher frequency of 3VD, they also underwent primary PCI of the culprit vessel to keep the revascularization time as short as possible and were planned for subsequent revascularization for other vessels as staged. Conversely, the men tended to have significantly more primary PCI, 83% vs. 72.3% (p =

0.05), and less early invasive PCI, 7.8% vs. 16.9% (p = 0.024), proving the fact that women have more atypical presentation and are late to seek medical attention. With USAP or NSTEMI, trials such as FRISC II and RITA 3 favor the early invasive strategy for men with a decrease in mortality but not in women.[22] In a meta-analysis of several NSTEMI trials, an initial conservative approach in low-risk females was superior to an early invasive strategy translated by the current practice guidelines.[23]

At a median follow-up of 95 days, cumulative all-cause mortality trended to be higher in women than in men, 4.6% vs. 1.5% (p = 0.136), with a RR of 3.12 (95% CI: 0.71–13.58) showed a similar tendency as observed in the in-hospital outcome. LVEF of above 40% was significantly greater in men than in women, 65.6% vs. 50.8% (p = 0.027), again indicating that women were more prone to developing the worse consequences of ACS than men. However, this finding is in contrast to that of Cader et al. who showed that women tended to have a better ejection fraction and less severe coronary involvement.[24]

This study highlights data from our part of world, as data on gender differences in young adults who presented with ACS are sparse. Our results were similar to those of earlier studies (but they were from an older age population) and our study emphasized that young women were relatively older in age, sought medical attention later, and had poor overall outcomes than men. Despite that, the frequency of ACS in young women was five times lower than in young men, consistent with previous studies, and this was likely due to the protective effect of estrogen in the premenopausal stage.[25] However, premenopausal women with CAD are expected to have more comorbidities, as observed in our study, which can be attributed to the increased risk of adverse outcomes compared with men.

This study has some limitations, including being single-centered and the participants' refusal to take part in the study, which could have induced some biases. Due to the lower incidence of ACS among young (≤ 45 years) patients, especially females, the sample size of the study was not sufficiently high. Thus, the power of comparison between male and female patients could be low, and the generalizability of the findings could be limited. Larger multi-center studies are needed to further evaluate the gender differences in the young ACS subgroup in different ethnic groups worldwide.

CONCLUSION

Among the young patients who presented with ACS, the women tended to have a lower frequency but a greater age at presentation, more frequent traditional risk factors, frequent late presentation after symptom onset, more presentation with NSTEMI or 3VD, and trended towards higher mortality both in-hospital and in the short-term follow-up. By contrast, the men mostly presented with STEMI and had higher tobacco use. This study also highlighted the importance of increasing awareness among young women regarding the primary prevention of modifiable risk factors, the early recognition of symptoms, and timely medical contact in case of symptoms.

AUTHORS' CONTRIBUTION:

KAK, JAS, TS, and ASA contributed to the concept and design of study, KAK, DK, AHS, DQ, MA, SK, and KB contributed to the collection, analysis and interpretation of data, KAK, DK, AHS, DQ, MA, KB, and SK contributed to the drafting of the manuscript, and JAS, TS, and ASA critically analysed for content. All authors have read and approved the manuscript.

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