The Influence of Sex on Navigating Acute Coronary Syndrome: A Hospital-Based Cohort Study in South Asia

Udaya Ralapanawa
Faculty of Medicine, University of Peradeniya
Parackrama Karunathilake (paracktramawk@gmail.com)
Faculty of Medicine, University of Peradeniya
Charith Bandara
Faculty of Medicine, University of Peradeniya
Prabhashini Kumarihamy
Teaching Hospital Peradeniya
Sujeewa Gunaratne
Teaching Hospital Peradeniya
Dhammika Ranasinghe
Teaching Hospital Peradeniya
Ruwanthi Jayasinghe
Teaching Hospital Peradeniya
Vishvara Kularathna
Teaching Hospital Peradeniya

Research Article

Keywords: Acute coronary syndrome, Sex, Body Mass Index, Waist-hip ratio, Obesity, Overweight, Symptoms, Smoking, Delay in presentation

Posted Date: July 14th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-654482/v1

Abstract

Background

The cardiovascular risk profile and adverse events following acute coronary syndrome (ACS) differ between the Sex, indicating the importance of studying the sex differences in factors associated with ACS.

Methods

A cross-sectional descriptive study was performed among ACS patients presented to Teaching Hospital Peradeniya. An interviewer-administered prevalidated questionnaire was used to collect data, and analysis was done.

Results

A total of 789 patients were included, consisting of 40.4% females. The mean age of females (62.17±11.06) was higher than males (59.80±11.24) (p=0.004), and in females, the mean age for unstable angina (60.5±10.5) was lower than NSTEMI (63.8±12.5) (p=0.022) and STEMI (64.0±9.2) (p=0.026). The male-female composition for unstable angina (46.3% vs 53.7%) and STEMI (75.8% vs 24.2%) showed varied proportions. The mean BMI (24.95±4.40 kg m^{-3} vs 23.77±3.88 kg m^{-3}) (p=0.008) and obesity (21.6% vs 13.8%) (p=0.048) was higher in females. Overweight (9.4% vs 8.8%) (p=0.048) and the waist-hip ratio (0.98±0.07 vs 0.94±0.10) (p=0.006) was higher in males. Family history of hypertension was higher in females (24.1% vs 17.0%) (p=0.014). Most of the females were co-morbid with diabetes (37.9%) (p=0.008), hypertension (59.8%) (p<0.001) and dyslipidaemia (40.3%) (p<0.001) than males. The prevalence of smoking and alcohol intake was significantly higher in males (p<0.001). The predominant symptom was chest pain (93.4%), regardless of Sex. Right chest pain was primarily present in females (8.0% vs 3.6%) (p=048), and radiation of pain to the right arm mainly occurred in males (18.2% vs 7.5%) (p=0.007). Vomiting and dyspnoea was higher in females (47.7% vs 38.4%, p=0.049 and 53.1% vs 43.2%, p=0.039). The delay in presentation to the hospital was more in females (6:04±6:02) than males (3:55±4:22) with STEMI. The commonest reason for the delay was not suspecting an ACS, and a three-wheeler was the primary mode of transport in both sexes without any sex difference. Only 7.0% was delayed due to the unavailability of a transport facility.

Conclusion

Female and male patients with ACS show differences in the age of onset, the spectrum of ACS, comorbidities, anthropometric measurements, risk factors like smoking and alcohol intake, clinical presentation aspects and delay in presentation to the hospital.

Background

Cardiovascular diseases (CVD) are the leading cause of death globally. An estimated number of 17.9 million people died from CVD in 2019, representing 32% of all global deaths, and of these deaths, 85% were due to heart attack and stroke[3]. According to the annual health bulletin in Sri Lanka 2018, ischaemic heart diseases (IHD) remain the leading cause of hospital deaths, showing a considerably higher incidence in men than in women. At the same time, there is an increasing trend in hospitalisations following ischemic heart disease

(455.4 in 2011and 630.8 in 2018 per 100,000population) [4]. The most significant burden of CVD is in low and middle-income countries (LMICs), with approximately 80% of cardiovascular deaths occurring in LMICs.The patterns of CVDin LMICs are distinct from higher-income countries (HICs), where the majority of CVD deaths are reported in ages more than 60 years, and mortality due to ischaemic heart diseases(IHD) is decreasing. The burden of CVD in LMICs is only expected to rise as these countries progress through the epidemiological transition[5, 6].

CVD includes coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism[3]. Acute coronary syndrome (ACS) is included under coronary heart diseases, which consists of three subtypes; unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction. First, non-ST-elevation ACS (NSTE-ACS) is diagnosed when a patient presents with characteristic symptoms suggestive of myocardial ischaemia in the absence of persistent ST-elevation. Then, if cardiac biomarkers are elevated in those patients, they are considered to have NSTEMI; otherwise, the patient is deemed to haveUA[7]. Second, STEMI is diagnosed when the patient presented with characteristic symptoms of myocardial ischemia associated with persistent electrocardiographic (ECG) ST elevation and subsequent elevation of biomarkers of myocardial necrosis[8].

Although CVD has been seen as a men's disease for decades, it is more common in women. For example, in the European population, 38% of deaths in women before the age of 75 years are due to CVD, and in men, this figure is 37%; a figure that is partly explained by a higher risk of competing events, i.e. the risk of dying from other causes[9]. In addition, in a study done among patients with type 2 diabetes mellitus, there is a male predominance of ACS occurrence but similar ACS-related mortality between men and women[10]. Claassen et al. reported that coronary vascular disease in women develops 7 to 10 years later than in men, potentially because of estrogen's protective effect [11]. Most of the burden of CVD is through the traditional risk factors. While the effects of raised blood pressure, overweight and obesity, and raised cholesterol on cardiovascular outcomes are primarily similar between women and men, prolonged smoking and diabetes are significantly more hazardous for women than men[1]. A study was done in Kerala, India confirmed a higher CVD risk profile, delayed presentation and suboptimal medical care in women presenting with ACS and women were also found to have higher in-hospital and 30-day major adverse cardiac events, even after adjustment for potential confounders[2]. Therefore it is crucial to study the differences in sociodemographic factors, personal characteristics and clinical presentation between men and women.

Methods

Study type

A cross-sectional descriptive study was performed among the patients diagnosed with ACS presenting to the Teaching Hospital Peradeniya.

Sample population, inclusion and exclusion criteria

This study sample consists of 789 patients presented to the Teaching Hospital Peradeniya medical ward with ACS over five years, from February 2015 till February 2020, which includes patients between 20 and 85 years of age, including both males and females. According to the American College of Cardiology/ American Heart Association (ACC/AHA) definitions, they were diagnosed as NSTE-ACS, including UA and NSTEMI or STEMI and were treated as per ACC/AHA recommendations [7, 8]. First, NSTE-ACS was diagnosed when a patient presented with characteristic symptoms suggestive of myocardial ischaemia in the absence of persistent ST-elevation (except in patients with true posterior myocardial infarction). Then, if cardiac biomarkers (troponin) are elevated in those patients, and the clinical context is appropriate, they were considered to have NSTEMI; otherwise, the patient was deemed to have UA. ST depressions, transient ST-elevation, or prominent T-wave inversions were not considered essential for the diagnosis of NSTEMI. STEMI was diagnosed when the patient presented with characteristic symptoms of myocardial ischemia associated with persistent electrocardiographic (ECG) ST elevation and subsequent elevation of biomarkers of myocardial necrosis (troponin). Diagnostic ST elevation in the absence of left ventricular hypertrophy or left bundle-branch block (LBBB) was done when there was new ST elevation at the J point in at least two contiguous leads of ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women in leads V2–V3 and of ≥ 1 mm (0.1 mV) in other contiguous chest leads or the limb leads. New or presumably new LBBB was considered a STEMI equivalent. True-posterior STEMI was diagnosed when ST depression in ≥ 2 precordial leads (V1–V4) or multi-lead ST depression with coexistent ST elevation in lead aVR. Thosewitheithermyocarditis, pericarditis or endocarditis, patients with pre-existing structural heart disease, connective tissue disorders and pregnant patients were excluded from this study.

Data collection

Sociodemographic factors and personal characteristics

Patient age, religion, ethnicity, level of education, occupation, income, and loans were determined by self-report. The interviewer measured the body weight and height to calculate body mass index (BMI, with undernutrition defined as < 18.5, the normal defined as 18.5 to 22.9, overweight defined as 23 to 24.9 and obesity defined as ≥ 25 [calculated as weight in kilograms divided by height in meters squared]). Hip circumference and waist circumference to calculate the waist-hip ratio were measured by the interviewer. The family history of illnesses, ischemic heart disease, diabetes mellitus, hypertension, stroke, dyslipidemia and depression, smoking and alcohol taking behaviour were based on self-report. The comorbidities were obtained from the medical records.

Clinical presentation, reaching the health care system and gynaecological factors

Symptom presentation for the acute phase of ACS was determined in all participants during hospitalisation of ACS using an interviewer-administered prevalidated questionnaire. The questionnaire assessed the presence of chest pain, including its time of onset, site and radiation, and the associated symptoms; faintishness, palpitations, vomiting, sweating and dyspnoea, and the symptoms relevant to the Killip class. The delay in presentation to the health care system, reasons for it, transport mode, age of menopause and the use of contraceptives; oral contraceptive pills (OCP), progesterone implants, depot medroxyprogesterone acetate (DMPA), and intrauterine contraceptive devices (IUCD) were also assessed in the questionnaire. Validationstudiesforthe questionnaire has been conducted in patients with ACS and has demonstrated good test-retest validity($r = 0.82$). In addition, the admission variables, heart rate, systolic blood pressure, respiratory rate, and peripheral oxygen saturation (SpO_2), were collected from medical records.

Statistical analysis

Sociodemographic factors, personal characteristics, clinical presentation, and reaching the health care system were compared between males and females using χ^2 and t-tests for categorical and continuous variables. Gynaecological factors were further stratified by ACS type (i.e., STEMI, NSTEMI, unstable angina) and compared using χ^2 and t-tests. Patients with missing data were either mentioned as no response or excluded from the analyses. Analyses were performed using IBM SPSS Statistics 26.0.

Results

Sociodemographic Factors

Of 789 total patients with ACS included in the study, 319 (40.4%) were females. Table 1 demonstrates the sociodemographic factors and personal characteristics of the population. The mean age of onset of the ACS was higher in females (62.17 ± 11.06 years) than in males (59.80 ± 11.24 years) ($p = 0.004$). Among the whole population, 300 (38.0%) had unstable angina, 253 (32.1%) NSTEMI and 236 (29.9%) STEMI. Most of the females had unstable angina (50.5%); however, most of the males had STEMI (38.1%) ($p < 0.001$). The male-female composition for unstable angina was 46.3% and 53.7%, respectively, and for STEMI, it was 75.8% and 24.2% (Fig. 1).

Table 1
Sociodemographic factors and personal characteristics of the study population stratified by Sex

	Total (n = 789)	**Male (n = 319)**	**Female (n = 470)**	**P value**
Age (years), mean (SD)	60.76 (11.22)	59.80 (11.24)	62.17 (11.06)	0.004
Religion				
Buddhism (%)	641 (81.2)	368 (78.3)	273 (85.6)	
Hindu (%)	37 (4.7)	26 (5.5)	11 (3.4)	
Christian (%)	18 (2.3)	12 (2.6)	6 (1.9)	
Islam (%)	93 (11.8)	64 (13.6)	29 (9.1)	0.082
Ethnicity				
Sinhalese (%)	645 (81.7)	369 (78.5)	276 (86.5)	
Tamil (%)	50 (6.3)	37 (7.9)	13 (4.1)	
Moor (%)	93 (11.8)	64 (13.6)	29 (9.1)	
Other (%)	1 (0.1)	0 (0)	1 (0.3)	0.008
Education				
None (%)	6 (0.8)	3 (0.6)	3 (0.9)	
< O/L (%)	199 (25.2)	113 (24.0)	86 (27.0)	
O/L (%)	95 (12.0)	58 (12.3)	37 (11.6)	
A/L (%)	55 (7.0)	38 (8.1)	17 (5.3)	
Degree (%)	13 (1.6)	6 (1.3)	7 (2.2)	
Postgraduate (%)	2 (0.3)	2 (0.4)	0 (0)	0.398
No response (%)	419 (53.1)	250 (46.8)	169 (53.0)	
Employment				
Unemployed (%)	158 (20.0)	6 (1.3)	152 (47.6)	
Unskilled (%)	90 (11.4)	75 (16.0)	15 (4.7)	
Skilled (%)	98 (12.4)	81 (17.2)	17 (5.3)	
Business (%)	54 (6.8)	48 (10.2)	6 (1.9)	
Professionals (%)	35 (4.4)	26 (5.5)	9 (2.8)	
Retired (%)	59 (7.5)	47 (10.0)	12 (3.8)	0.000
No response (%)	295 (37.4)	187 (39.8)	108 (33.9)	

	Total (n = 789)	Male (n = 319)	Female (n = 470)	P value
Income				
No income (%)	14 (1.8)	1 (0.2)	13 (4.1)	
<Rs.10000 (%)	28 (3.5)	18 (3.8)	10 (3.1)	
Rs.10000–30000 (%)	154 (19.5)	105 (22.3)	49 (15.4)	
Rs.30000–50000 (%)	63 (8.0)	43 (9.1)	20 (6.3)	
Rs.50000–100000 (%)	17 (2.2)	14 (3.0)	3 (0.9)	
>Rs.100000 (%)	2 (0.3)	1 (0.2)	1 (0.3)	0.000
No response (%)	511 (64.8)	288 (61.3)	223 (69.9)	
Loans				
Not taken (%)	273 (34.6)	164 (34.9)	109 (34.2)	
Taken (%)	79 (10.0)	51 (10.9)	28 (8.8)	0.472
No response (%)	437 (55.4)	255 (54.3)	182 (57.1)	
Anthropometry				
Weight (kg), mean (SD)	60.05 (11.38)	62.48 (11.21)	56.87 (10.84)	0.000
Height (m), mean (SD)	1.56 (0.15)	1.61 (0.13)	1.49 (0.15)	0.000
BMI (kg m^{-2}), mean (SD)	24.28 (4.14)	23.77 (3.88)	24.95 (4.40)	0.008
Underweight (%)	20 (2.5)	10 (2.1)	10 (3.1)	
Normal (%)	135 (17.1)	87 (18.5)	48 (15.0)	
Overweight (%)	72 (9.1)	44 (9.4)	28 (8.8)	
Obese (%)	134 (17.0)	65 (13.8)	69 (21.6)	0.048
Not measured	428 (54.2)	264 (56.2)	164 (51.4)	
Hip circumference (cm), mean (SD)	92.4 (12.7)	89.3 (12.7)	95.6 (11.9)	0.000
Waist circumference (cm), mean (SD)	87.7 (13.3)	86.9 (12.8)	88.6 (13.9)	0.325
Waist/Hip ratio, mean (SD)	0.96 (0.09)	0.98 (0.07)	0.94 (0.10)	0.006
Family History				
Ischemic Heart Disease (%)	134 (17.0)	70 (14.9)	64 (20.1)	0.058
Diabetes Mellitus (%)	124 (15.7)	59 (18.5)	65 (13.8)	0.077
Hypertension (%)	157 (19.9)	80 (17.0)	77 (24.1)	0.014

	Total (n = 789)	Male (n = 319)	Female (n = 470)	P value
Stroke (%)	46 (5.8)	23 (4.9)	23 (7.2)	0.173
Dyslipidemia (%)	53 (6.7)	26 (5.5)	27 (8.5)	0.106
Depression (%)	7 (0.9)	5 (1.1)	2 (0.6)	0.707
Comorbidities				
Diabetes Mellitus (%)	123 (30.4)	62 (25.5)	61 (37.9)	0.008
Hypertension (%)	195 (47.6)	97 (39.4)	98 (59.8)	0.000
Dyslipidaemia (%)	108 (26.9)	44 (18.1)	64 (40.3)	0.000
Asthma/COPD (%)	49 (12.2)	33 (13.5)	16 (10.2)	0.320
PVD (%)	8 (2.0)	4 (1.6)	4 (2.5)	0.718
CKD (%)	4 (1.0)	3 (1.2)	1 (0.6)	0.656
Stroke (%)	15 (3.8)	6 (2.5)	9 (5.7)	0.095
Anaemia (%)	11 (2.8)	4 (1.7)	7 (4.5)	0.094
Smoking				
Current	70 (17.7)	70 (29.0)	0 (0)	
Ex-smoker	102 (25.8)	102 (42.3)	0 (0)	
Never	224 (56.6)	69 (28.6)	155 (100.0)	0.000
Pack Years, mean (SD)	8.00 (9.36)	8.66 (9.44)	0 (0)	0.002
Alcohol				
Current	115 (29.1)	114 (47.5)	1 (0.6)	
Ex-smoker	53 (13.5)	53 (22.1)	0 (0)	
Never	227 (57.5)	73 (30.4)	154 (99.4)	0.000
ACS Type				
Unstable angina	300 (38.0)	139 (29.6)	161 (50.5)	
NSTEMI	253 (32.1)	152 (32.3)	101 (31.7)	
STEMI	236 (29.9)	179 (38.1)	57 (17.9)	0.000

The majority of the patients were Sinhalese (81.7%), and the proportion of Sinhalese patients were higher in females (86.5%) than in males (78.5%). On the other hand, the proportion of Tamils and Moors were higher in males (7.9% and 13.6%) than in females (4.1% and 9.1%) (p = 0.008). The occurrence of ACS concerning sex difference was not associated with religion or the education level. Most males with ACS were engaging in skilled occupations (17.2%), but most females were unemployed (47.6%) ($p < 0.001$). The income of the majority of both males and females were between Rs.10000 to Rs.30000 (22.3% and 15.4%) ($p < 0.001$).

Personal Characteristics

Males showed a higher mean weight and height (62.48 ± 11.21 kg and 1.61 ± 0.13 m) compared to females (56.87 ± 10.84 kg and 1.49 ± 0.15 m) ($p < 0.001$); however, the mean BMI was higher in females (24.95 ± 4.40 kg m^{-3}) than in males (23.77 ± 3.88 kg m^{-3}) ($p = 0.008$). The prevalence of obesity was higher in females than in males (21.6% vs 13.8%); nevertheless, the prevalence of overweight was higher in males than in females (9.4% vs 8.8%) ($p = 0.048$). The mean hip circumference was higher in females (95.6 ± 11.9 cm) than in males (89.3 ± 12.7 cm) ($p < 0.001$), though there was no significant difference between the waist circumference. Thus the mean waist-hip ratio was higher in males (0.98 ± 0.07) than in females (0.94 ± 0.10) ($p = 0.006$).

Female patients showed a higher percentage of family history of hypertension than in males (24.1% vs 17.0%) ($p = 0.014$). However, there was no significant difference in family histories of ischaemic heart diseases (IHD), diabetes mellitus, stroke or dyslipidaemia ($p > 0.050$). At the same time, most of the females were co-morbid with diabetes (37.9%) ($p = 0.008$), hypertension (59.8%) ($p < 0.001$) and dyslipidaemia (40.3%) ($p < 0.001$) than males (25.5%, 39.4%, and 18.1%, respectively).

Many males were ex-smokers (42.3%) or currently smoking (29.0%); however, non of the females were ex-smokers or current smokers ($p < 0.001$). The same results were obtained for alcohol intake, where 47.5% of males were currently taking alcohol, and 22.1% had taken alcohol in the past; however, only one female (0.6%) were currently taking alcohol, and none was ex-alcoholics ($p < 0.001$).

Clinical Presentation

The predominant symptom was chest pain which presented in 93.4% of the population, regardless of Sex (Table 2). Right chest pain was primarily present in females (8.0%) than in males (3.6%) ($p = 048$). Other sites of chest pain were not associated with Sex (Fig. 2). Radiation of chest pain to the right arm mainly occurred in males (18.2%) than in females (7.5%). Radiation of chest pain to the other sites were not associated with Sex (Fig. 3). The associated symptoms of vomiting and dyspnoea occurred mainly in females (47.7% and 53.1%) than in males (38.4% and 43.2%) ($p = 0.049$ and $p = 0.039$, respectively). The other associated symptoms, such as faintishness, palpitations and sweating, showed no difference with the Sex. The admission variables such as heart rate, respiratory rate, systolic blood pressure, and peripheral oxygen saturation do not significantly differ between the sex and Killip classes.

Table 2
Clinical features stratified by Sex.

	Total	Male	Female	P value
Chest Pain	484 (93.4)	280 (94.6)	204 (91.9)	0.219
Site of Chest Pain				
Left chest	131 (27.8)	77 (28.0)	54 (27.4)	0.888
Right chest	29 (6.1)	7 (3.6)	22 (8.0)	0.048
Central chest	250 (49.4)	115 (54.0)	135 (46.1)	0.064
Diffuse chest	63 (13.3)	39 (14.2)	24 (12.2)	0.529
Upper abdomen	19 (4.0)	13 (4.7)	6 (3.0)	0.359
Radiation of Chest Pain				
Left Arm	89 (30.9)	46 (30.1)	43 (31.9)	0.743
Right Arm	38 (13.2)	28 (18.2)	10 (7.5)	0.007
Neck	44 (15.3)	19 (12.3)	25 (18.8)	0.130
Jaw	17 (6.0)	9 (6.0)	8 (6.0)	0.997
Associated Symptoms				
Faintishness	181 (37.7)	99 (37.4)	82 (38.1)	0.861
Palpitations	94 (21.5)	48 (20.0)	46 (23.4)	0.396
Vomiting	188 (42.6)	93 (38.4)	95 (47.7)	0.049
Sweating	294 (66.4)	156 (64.2)	138 (69.0)	0.287
Dyspnoea	208 (47.6)	104 (43.2)	104 (53.1)	0.039
Admission Variables				
Heart rate, mean (SD), bpm	77 (13)	76 (15)	78 (12)	0.323
Systolic blood pressure, mean (SD), mmHg	137 (27)	136 (26)	138 (28)	0.436
Respiratory Rate	21 (7)	21 (6)	21 (7)	0.475
SpO_2	96 (11)	97 (8)	94 (14)	0.196
Killip class				
Class 1	369 (91.3)	224 (92.9)	145 (89.0)	
Class 2	29 (7.2)	14 (5.8)	15 (9.2)	
Class 3	6 (1.5)	3 (1.2)	3 (1.8)	
Class 4	0 (0)	0 (0)	0 (0)	0.375

	Total	Male	Female	P value
Not assessed	385 (48.8)	229 (48.7)	156 (48.9)	

Reaching to Health Care System

The average delay from the onset of chest pain till the presentation was 5:52 ± 5:55, 5:51 ± 5:36 and 4:26 ± 4:53 for unstable angina, NTEMI and STEMI, respectively (Table 3). In those who had STEMI, the delay in the presentation was more in females (6:04 ± 6:02) than males (3:55 ± 4:22). The reason for the delay was not suspecting an IHD in most patients regardless of Sex. Three-wheeler was the primary mode of transport (59.0%) to the hospital, and only 7.0% was delayed due to the unavailability of a transport facility.

Table 3
Reaching the health care system stratified by Sex

Delay in presentation to the hospital				
Unstable angina	5:52 (5:55)	5:51 (5:43)	5:52 (6:07)	0.989
NSTEMI	5:51 (5:36)	5:42 (5:38)	6:06 (5:35)	0.721
STEMI	4:26 (4:53)	3:55 (4:22)	6:04 (6:02)	0.033
Reasons for Delay				
No transport (%)	7 (7.0)	3 (6.4)	4 (7.4)	0.840
None to accompany (%)	4 (4.0)	0 (0)	4 (7.5)	0.121
Did not suspect IHD (%)	66 (60.6)	29 (58.0)	37 (62.7)	0.616
Other reason	29 (29.3)	15 (31.9)	14 (26.9)	0.586
Mode of transport				
Car	25 (6.5)	17 (7.4)	8 (5.2)	
Van	47 (12.2)	32 (13.9)	15 (9.7)	
Three-wheeler	227 (59.0)	139 (60.2)	88 (57.1)	
Other	85 (22.1)	42 (18.2)	43 (27.9)	0.109
No response	405 (51.5)	240 (51.3)	165 (51.7)	

Gynaecological factors in Female Patients

The mean age of onset of chest pain (62.2 ± 11.1) was significantly higher than the mean age of menopause (42.3 ± 12.2) in females ($p < 0.001$), and the mean age of onset for unstable angina (60.5 ± 10.5) was significantly lower than the mean age of onset for NTEMI (63.8 ± 12.5) ($p = 0.022$) and STEMI (64.0 ± 9.2) ($p = 0.026$) (Tabel 4). The mean age of menopause does not show any statistically significant difference within the spectrum of ACS. Only 130 (16.5%) had responded regarding the usage of contraceptives, and among them, there was no significant difference within the spectrum of ACS.

Table 4
Gynecological factors in female patients

	Total	Unstable angina [a]	NSTEMI [b]	STEMI [c]	P-value
Age of ACS onset, mean (SD)	62.2 (11.1)	60.5 (10.5)	63.8 (12.5)	64.0 (9.2)	(a,b) 0.022 (a,c) 0.026 (b,c) 0.913
Age of menopause, mean (SD)	42.3 (12.2)	40.6 (17.8)	44.2 (15.1)	44.9 (11.2)	(a,b) 0.257 (a,c) 0.297 (b,c) 0.861
Contraceptive use					
Yes (%)	22 (2.8)	11 (6.8)	7 (6.9)	4 (7.0)	
No (%)	108 (13.7)	56 (34.8)	34 (33.7)	15 (26.3)	0.894
No response (%)	659 (83.5)	94 (58.4)	60 (59.4)	38 (66.7)	
OCP (%)	8 (1.0)	4 (2.5)	3 (3.0)	1 (1.8)	1.000
DMPA (%)	11 (1.4)	7 (4.3)	3 (3.0)	1 (1.8)	0.460
Progesterone implant (%)	1 (0.1)	1 (0.6)	0 (0)	0 (0)	1.000
IUCD (%)	14 (1.8)	6 (3.7)	5 (5.0)	3 (5.3)	0.318

Discussion

Epidemiological studies, including the Framingham study, has shown that coronary heart diseases present at an earlier age in men than in women [12]. Claassen et al. also has reported that coronary vascular disease in women develops 7 to 10 years later than in men, potentially because of a protective effect of estrogens [11]. Our study could confirm these findings where the mean age of onset of ACS was higher in females than in males showing a gap of about 2 to 3 years in our population.

Men are known to have a higher risk of ACS than women. However, data on potential gender differences regarding the occurrence of ACS have been scarce. A French registry of UA admissions reported71.2% of patients to be men, while in an Australian study, the proportion was 60.2%. In smaller studies, male predominance in patients with UA has ranged from 83.9–56.6%. Another study in Finland found 61.9% of patients to be men, with men having a 2.4-fold overall risk for UA admission in the general adult population compared towomen[13]. The incidence rate of STEMI was also higher in men than in women, which was evident by several previous studies [13–16]. However, 53.7% of UA patients were females in our study population, and only 46.3% of UA patients were males.

In contrast, 75.8% of STEMI patients were males, and 24.2% of STEMI patients were females. Furthermore, concerning male and female populations separately, most of the females had unstable angina (50.5%) and, most of the males had STEMI (38.1%). However, the findings for STEMI go according to the previous studies; for unstable angina, the findings contrast.

The sex difference in occupations was marked with most males with ACS were engaging in skilled occupations, but most females being unemployed. However, this can be attributed to the sex-specific population prevalence of economically active proportion in Sri Lanka, where male shows 65.7%, and females show only 34.3% [17].

In 2008, nearly 1.5 billion individuals were overweight; of these, more than 300 million women and nearly 200 million men were obese, and the world's average BMI had increased with 0.5 kg/m^2 per decade in women and 0.4 kg/m^2 in men to an average level of BMI of 24.1 kg/m^2 for women and 23.8 kg/m^2 for men in 2008[18]. The prevalence of overweight in men and women differs according to the country's level of development; BMI levels are typically higher in men than women in most high-income countries, whereas the reverse is more common in lower and middle-income countries[18]. The association between BMI and coronary heart disease is broadly identical between men and women, whereas the risk for stroke associated with increments in BMI may be higher in men than in women[1]. Analyses from the Asian-Pacific Cohort Studies Collaboration (APCSC) also demonstrated the approximately equal strength of the association between overweight or obesity and the risk of CHD between men and women in both Asian and Australian populations[19]. In our population, the mean BMI was higher in females (24.95 ± 4.40 kg m^{-3}) than in males (23.77 ± 3.88 kg m^{-3}). The prevalence of obesity was higher in females than in males; however, the prevalence of overweight was higher in males than in females.

Our study populations showed a higher mean hip circumference in females (95.6 ± 11.9 cm) than in males (89.3 ± 12.7 cm), though there was no significant difference between the waist circumference. Thus the mean waist-hip ratio was higher in males (0.98 ± 0.07) than in females (0.94 ± 0.10). Despite the widely recognised sex dimorphism in the body fat distribution, there is no evidence that measures of abdominal adiposities, such as waist circumference or waist-hip-ratio have a different relationship with risk for ACS than BMI as a measure of general adiposity, nor that the associations between ACS risk induced by measures of abdominal adiposity are differential between men and women[1]. However, the INTERHEART study has identified waist-hip ratio as a separate risk factor for ACS [11], and also evidence suggests that central adiposity measures, waist circumference, might best predict disease risk at the individual level[18]. In LMICs, studies on women show waist circumference have increased and may contribute to CVD increase[5]. South Asians show a higher rate of ACS at a younger age than those in other countries, very likely due to South Asians having more risk factors at ages < 60years when stratified by age, including higher apolipoprotein B100 /apolipoprotein A-I ratio and higher waist to hip ratio[20].

Diabetes, hypercholesterolaemia, hypertension, smoking and alcohol are well-established risk factors for developing coronary artery disease, presenting differently in men and women[9, 10]. Khan et al. have found a higher proportion of family history of premature coronary artery diseases among females than males in a study done on young patients [21]. However, a study done in Netherland has revealed a low prevalence of family history of coronary artery disease in females (40.2%) than the male (42.1%) with ACS [22]. There was no significant difference in family histories of IHD, diabetes mellitus, stroke or dyslipidaemia in our population. However, female patients showed a higher percentage of family history of hypertension than in males (24.1% vs 17.0%).

The eleven-year Spanish National Health Service trend revealed that among the patients with STEMI and NSTEMI, comorbidities including congestive heart failure, cardio-respiratory failure, valvular or rheumatic heart disease, hypertension, stroke, renal failure, and diabetes Mellitus were more frequent in women[16]. Furthermore, many ACS studies have shown women to have higher incidences of comorbidities at presentation[2, 23, 24], which are consistent with the findings in our study where most of the females were co-morbid with diabetes (37.9%), hypertension (59.8%) and dyslipidaemia (40.3%) than males (25.5%, 39.4%, and 18.1%, respectively).

By 2030, it is estimated that each year approximately 10 million deaths will be due to tobacco use, and the Global Adult Tobacco Survey has shown that in 14 LMICs, 48.6% of men and 11.3% of women were tobaccousers[5]. Smoking remains a significant public health issue in Europe. Although smoking has declined in many European countries, the rate of decline is now slow, and rates remain stable or are increasing in some countries, particularly among women. Women are now smoking nearly as much as men in many European countries, and girls often smoke more than boys[9]. However, while some studies were done among ACS patients state the prevalence of smoking in males is higher than females, other studies state that there is no statistically significant difference, or females having a higher prevalence of smoke than males depending on the sociodemographic conditions [9, 11, 20–23, 25]. According to our study, males showed a significantly higher prevalence of smoking than females, where 42.3% were ex-smokers, and 29.0% were currently smoking while non-the females were ex-smokers or current smokers. The same results were obtained for alcohol intake, where 47.5% of males were currently taking alcohol, and 22.1% had taken alcohol in the past; however, only one female (0.6%) were currently taking alcohol, and none was ex-alcoholics. While moderate alcohol consumption (one or two drinks a day) reduces CVD risk, at high levels of intake, mainly when consumed in episodes of hefty consumption, the risk of CVD is increased[9]. However, alcohol consumption in South Asians is low compared to the other countries, and there is no difference in the prevalence of alcohol consumption between the ACS patients and the general public [20]. However, among Indians, it has been shown a significant association between alcohol consumption and ACS [20]. Alcohol abuse is a risk factor for the occurrence of early ACS, and patients with a combination of alcohol abuse and smoking had an even higher risk of developing very early ACS than those with the two individual risk factors alone[26]. The percentage of alcohol-attributable deaths among men amount to 7.7 % of all global deaths compared to 2.6 % of all deaths among women. Total alcohol per capita consumption in 2010 among male and female drinkers worldwide was 19.4 litres for males and 7.0 litres of pure alcohol for females[27]. The prevalence of alcohol consumption in Sri Lanka is significantly higher in males than in females [4]. Therefore the findings on alcohol consumption from this study can be attributed to the population prevalence of alcohol consumption in Sri Lanka.

Many studies have found that chest pain is the main presenting symptom in ACS, with the prevalence ranging from 88–94% [21, 24, 28]. In addition, chest pain is the most common symptom for men and women regardless of ACS type; however, women are more likely to present without chest pain than men[21]. Another study revealed that men and women presented equally with chest pain; however, jaw pain and nausea were more frequent among women[24]. Younger women are even less likely to present with chest pain [22]. Our study confirmed that chest pain is the predominant symptom presented in 93.4% of the population; nevertheless, there was no statistically significant difference between the Sex. However, right chest pain was primarily present in females than in males and radiation of chest pain to the right arm mainly occurred in males than in females. In addition, the associated symptoms of vomiting and dyspnoea occurred mainly in females (47.7% and 53.1%) than in males (38.4% and 43.2%) but, the other symptoms, such as faintishness, palpitations and sweating, showed no difference with the Sex. Previous studies also have found more symptoms in women with ACS than in men [21, 24].

According to clinical guidelines published by the American College of Cardiology/ American Heart Association, invasive therapy is favourable when the patient presents within 24 hours from the onset of chest pain for NSTE-ACS and within 12 hours from the onset of chest pain for STEMI [7, 8]. Primary percutaneous coronary intervention is recommended to perform if the patient presents within 2 hours of the onset of symptoms [8]. The average delay in presentation to the health care facility from the onset of symptoms in ACS patients has been between 1.5 to 2.5 hours, as revealed by several studies [8, 28, 29]. Thus, patients with STEMI do not seek medical care for approximately 1.5 to 2 hours after symptom onset, and little change in this interval has occurred over the past ten years[8]. However, our study revealed that the average delay was 5:52, 5:51 and 4:26 for unstable angina, NTEMI and STEMI, respectively, showing considerably higher values than the previous studies. The main reason for this delay was not suspecting an IHD present in 60% of patients regardless of Sex. Three-wheeler was the primary mode of transport (59.0%) to the hospital, and only 7.0% was delayed due to the unavailability of a transport facility. Although the three-wheeler has not been a safe option to transport an emergency patient[30], it has been the widely available transport facility in Sri Lanka, as evident by this study. In those who had STEMI, the delay in the presentation was more in females (6:04) than males (3:55), confirming the findings from the previous studies that women show a more significant delay in presentation than men [2, 8, 14, 22, 29]. One reason for this may be that women show more atypical symptoms of ACS than men [24, 29].

Menopause signals the transition from reproductive to non-reproductive life and is associated with several biological changes to the endocrine system relevant to cardiovascular health. Age at menopause logically translates to the interval of estrogen and androgen exposure and is associated with a modest risk difference in CVD[1]. However, Atsma et al.'s meta-analysis has found no convincing relationship between postmenopausal status and cardiovascular disease, though there is a modest effect of early menopause on cardiovascular disease[31]. Nevertheless, the mean age of onset of ACS in females is 4 to 8 years later than males, which may be attributed to the protective effect of oestrogen in younger females [2, 22, 25, 26]. Our findings tally with the previous studies where the mean age of onset of chest pain (62.2 years) was significantly higher than the males (59.8 years). At the same time, in females, the mean age of onset for unstable angina (60.5 years) was significantly lower than the mean age of onset for NTEMI (63.8 years) and STEMI (64.0 years), indicating that the severity of ACS increases with age. The mean age of menopause does not show any statistically significant difference within the spectrum of ACS. Since only 130 (16.5%) female patients had responded regarding the usage of contraceptives, the effect of contraceptives on the occurrence of ACS was inconclusive.

Conclusion

Females tend to have ACS later in life than males, potentially because estrogen's protective effect and ACS severity in females increases with age. Males present with more incidence of NSTEMI and STEMI than females, and in contrast, females show more incidence of unstable angina than males. While higher BMI, overweight and obesity being risk factors for CVD, females show a higher mean value of BMI than males, and also the prevalence of obesity was higher in females. However, the prevalence of overweight and the waist-hip ratio, a measurement of central obesity, is higher in males than females, and the mean value of the waist-hip ratio was well above the cut-off for South Asians in both sexes. While several previous studies have shown variable results concerning sex differences in family history, there is no significant difference in IHD, diabetes mellitus, stroke or dyslipidaemia except hypertension, where females showed a higher prevalence. However, female patients with ACS tend to be co-morbid with diabetes, hypertension and dyslipidaemia more than male patients at presentation. Smoking and alcohol intake is significantly higher in males than females, where non of the females were smokers in our study population, indicating a different risk factor profile between the Sex. Chest pain is the predominant symptom in ACS without any significant difference between the Sex, though subtle differences in the site and radiation of chest pain. The associated symptoms such as vomiting and dyspnoea occur mainly in females. There is a delay of presentation ranging 4 to 6 hours to the hospital from the onset of symptoms, mainly due to not suspecting an IHD. The delay is more in females than in males, and it increases in the sequence of STEMI, NSTEMI and UA, where the maximum delay is there for UA. Although a three-wheeler has not been a safe option, it has been shown a valuable method of transport patients to the hospital in an emergency in Sri Lanka.

Abbreviations

ACC: Americal College of Cardiology; ACS: Acute Coronary Syndrome; AHA: Americal Heart Association; APCSC: Asian Pacific Cohort Studies Collaboration; BMI: Body Mass Index; CVD: Cardiovascular Diseases; DMPA: Depot Medroxyprogesterone Acetate; ECG: Electrocardiogram; IHD: Ischaemic Heart Disease; IUCD: Intrauterine Contraceptive Device; LBBB: Left Bundle Branch Block; NSTE-ACS: Non-ST-Elevation Acute Coronary Syndrome; NSTEMI: Non-ST-Elevation Myocardial Infarction; OCP: Oral Contraceptive Pills; SD: Standard Deviation; STEMI: ST-Elevation Myocardial Infarction; UA: Unstable Angina

Declarations

Ethics approval and consent to participate

Ethics approval was granted from the Institutional Ethical Review Committee (IERC) of the Faculty of Medicine, University of Peradeniya. Informed signed consent was obtained from all participants before the collection of data.

Consent for publication

All participants gave written consent for publication before data collection.

Availability of data and materials

All the data are stored in a password-protected computer, and hard copies are also under the corresponding author's custody. Data can be seen by request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

The study was self-funded by the authors of the study.

Authors' contributions

UR conceived the research idea and guided it. Data collection, analysis and interpretation of data and literature review were made by UR, PWK, PK, SG, DR, CB, RJ, and VK. UR guided the other authors in data analysis, interpretation and corrected the final manuscript. All authors were involved in the study and read and approved the final manuscript.

Acknowledgements

We want to express our gratitude to all participants who consented to take part in this study.

References

1. Appelman Y, van Rijn BB, ten Haaf ME, et al. Sex differences in cardiovascular risk factors and disease prevention. Atherosclerosis [Internet]. 2014;241:211–218. Available from: http://dx.doi.org/10.1016/j.atherosclerosis.2015.01.027.
2. Khraishah H, Alahmad B, Alfaddagh A, et al. Sex disparities in the presentation, management and outcomes of patients with acute coronary syndrome: insights from the ACS QUIK trial. Open Hear. 2021;8:1–8.
3. Liu MB. Cardiovascular diseases [Internet]. Chin. Med. J. (Engl). 2014 [cited 2021 Jun 19]. p. 6–7. Available from: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
4. Medical Statistics Unit Ministry of Health Sri Lanka. Annual Health Bulletin 2018. Annu Heal Bull 2018 [Internet]. 2018;33:1–276. Available from: http://www.health.gov.lk/moh_final/english/public/elfinder/files/publications/AHB/2020/AHB_2018.pdf.
5. Bowry ADK, Lewey J, Dugani SB, et al. The Burden of Cardiovascular Disease in Low- and Middle-Income Countries: Epidemiology and Management. Can J Cardiol [Internet]. 2015;31:1151–1159. Available from: http://dx.doi.org/10.1016/j.cjca.2015.06.028.
6. Prabhakaran D, Singh K, Roth GA, et al. Cardiovascular Diseases in India Compared With the United States. J Am Coll Cardiol. 2018;72:79–95.

7. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/acc guideline for the management of patients with Non-ST-Elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64:e139–e228.
8. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of st-elevation myocardial infarction: A report of the American college of cardiology foundation/american heart association task force on practice guidelines. J Am Coll Cardiol. 2013;61:78–140.
9. Nichols M, Townsend N, Rayner M. European cardiovascular disease statistics. Eur. Hear. Netw. Eur. Soc. Cardiol. 2012.
10. Duan JG, Chen XY, Wang L, et al. Sex differences in epidemiology and risk factors of acute coronary syndrome in Chinese patients with type 2 diabetes: A long-term prospective cohort study. PLoS One. 2015;10:1–11.
11. Claassen M. Gender gap in acute coronary heart disease: Myth or reality? World J Cardiol. 2012;4:36.
12. Sytkowski PA, D'Agostino RB, Belanger A, et al. Sex and time trends in cardiovascular disease incidence and mortality: The Framingham Heart Study, 1950-1989. Am J Epidemiol. 1996;143:338–350.
13. Kytö V, Sipilä J, Rautava P. Gender-specific and age-specific differences in unstable angina pectoris admissions: A population-based registry study in Finland. BMJ Open. 2015;5:1–6.
14. de Miguel-Yanes JM, Jiménez-García R, Hernandez-Barrera V, et al. Sex Differences in the Incidence and Outcomes of Acute Myocardial Infarction in Spain, 2016–2018: A Matched-Pair Analysis. J Clin Med. 2021;10:1795.
15. Alkhouli M, Alqahtani F, Jneid H, et al. Age-Stratified Sex-Related Differences in the Incidence, Management, and Outcomes of Acute Myocardial Infarction. Mayo Clin Proc [Internet]. 2021 [cited 2021 Jun 20];96:332–341. Available from: https://mayoclinic.pure.elsevier.com/en/publications/age-stratified-sex-related-differences-in-the-incidence-managemen.
16. Rodríguez-Padial L, Fernández-Pérez C, Bernal JL, et al. Differences in in-hospital mortality after STEMI versus NSTEMI by sex. Eleven-year trend in the Spanish National Health Service. Rev Española Cardiol (English Ed. 2021;74:510–517.
17. Department of Census and Statistics SL. Sri Lanka Labour Force Survey 1st Quarter - 2020. Sri Lanka Labour Force Surv 1st Quart - 2020. 2020;1–4.
18. Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: Systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. Lancet [Internet]. 2011;377:557–567. Available from: http://dx.doi.org/10.1016/S0140-6736(10)62037-5.
19. Ni Mhurchu C, Rodgers A, Pan WH, et al. Body mass index and cardiovascular disease in the Asia-Pacific Region: An overview of 33 cohorts involving 310 000 participants. Int J Epidemiol. 2004;33:751–758.
20. Rashid S, Khandaker N. Risk factors for early myocardial infarction in South Asians [7]. J Am Med Assoc. 2007;297:1880–1881.
21. Khan NA, Daskalopoulou SS, Karp I, et al. Sex differences in acute coronary syndrome symptom presentation in young patients. JAMA Intern Med. 2013;173:1863–1871.

22. ten Haaf ME, Bax M, ten Berg JM, et al. Sex differences in characteristics and outcome in acute coronary syndrome patients in the Netherlands. Netherlands Hear J. 2019;27:263–271.
23. Poon S, Goodman SG, Yan RT, et al. Bridging the gender gap: Insights from a contemporary analysis of sex-related differences in the treatment and outcomes of patients with acute coronary syndromes. Am Heart J [Internet]. 2012;163:66–73. Available from: http://dx.doi.org/10.1016/j.ahj.2011.09.025.
24. Dey S, Flather MD, Devlin G, et al. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: The Global Registry of Acute Coronary Events. Heart. 2009;95:20–26.
25. Kuehnemund L, Koeppe J, Feld J, et al. Gender differences in acute myocardial infarction—A nationwide German real-life analysis from 2014 to 2017. Clin Cardiol. 2021;
26. Ralapanawa U, Kumarasiri PVR, Jayawickreme KP, et al. Epidemiology and risk factors of patients with types of acute coronary syndrome presenting to a tertiary care hospital in Sri Lanka. BMC Cardiovasc Disord. 2019;19:1–9.
27. NIAA. Alcohol facts and statistics. Natl Inst Alcohol Abus Alcohol [Internet]. 2020;7. Available from: https://www.niaaa.nih.gov/sites/default/files/publications/NIAAA_Alcohol_FactsandStats_102020_0.pdf.
28. Andersson PO, Lawesson SS, Karlsson JE, et al. Characteristics of patients with acute myocardial infarction contacting primary healthcare before hospitalisation: A cross-sectional study. BMC Fam Pract. 2018;19:1–8.
29. King-Shier K, Quan H, Kapral MK, et al. Acute coronary syndromes presentations and care outcomes in white, South Asian and Chinese patients: A cohort study. BMJ Open. 2019;9:6–9.
30. WHO. Powered two-and three- wheeler safety. 2017;108.
31. Atsma F, Bartelink MLEL, Grobbee DE, et al. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: A meta-analysis. Menopause. 2006;13:265–279.

Figures

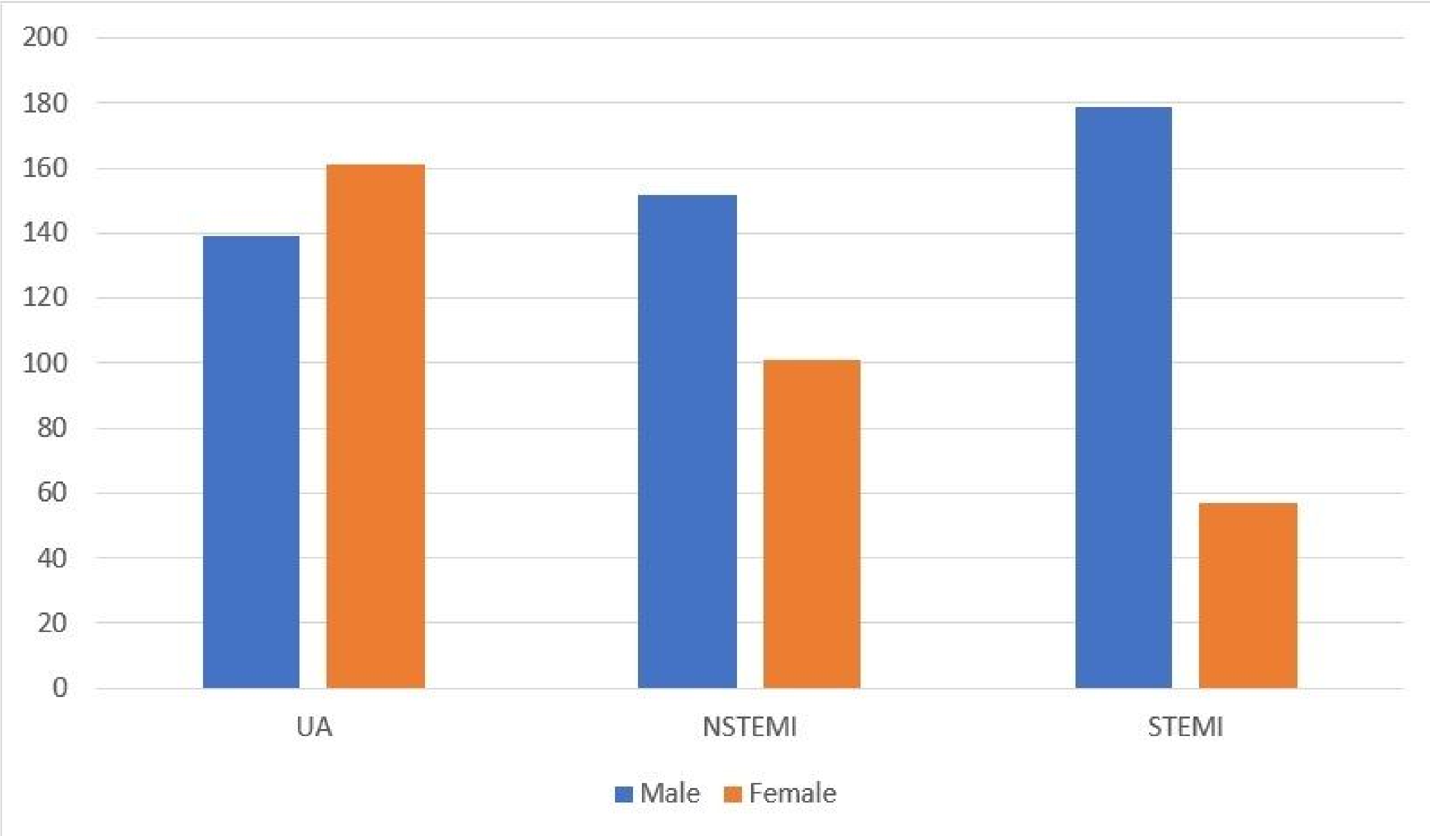

Figure 1

The spectrum of ACS Stratified by Sex

Figure 2

Site of Chest Pain Stratified by Sex

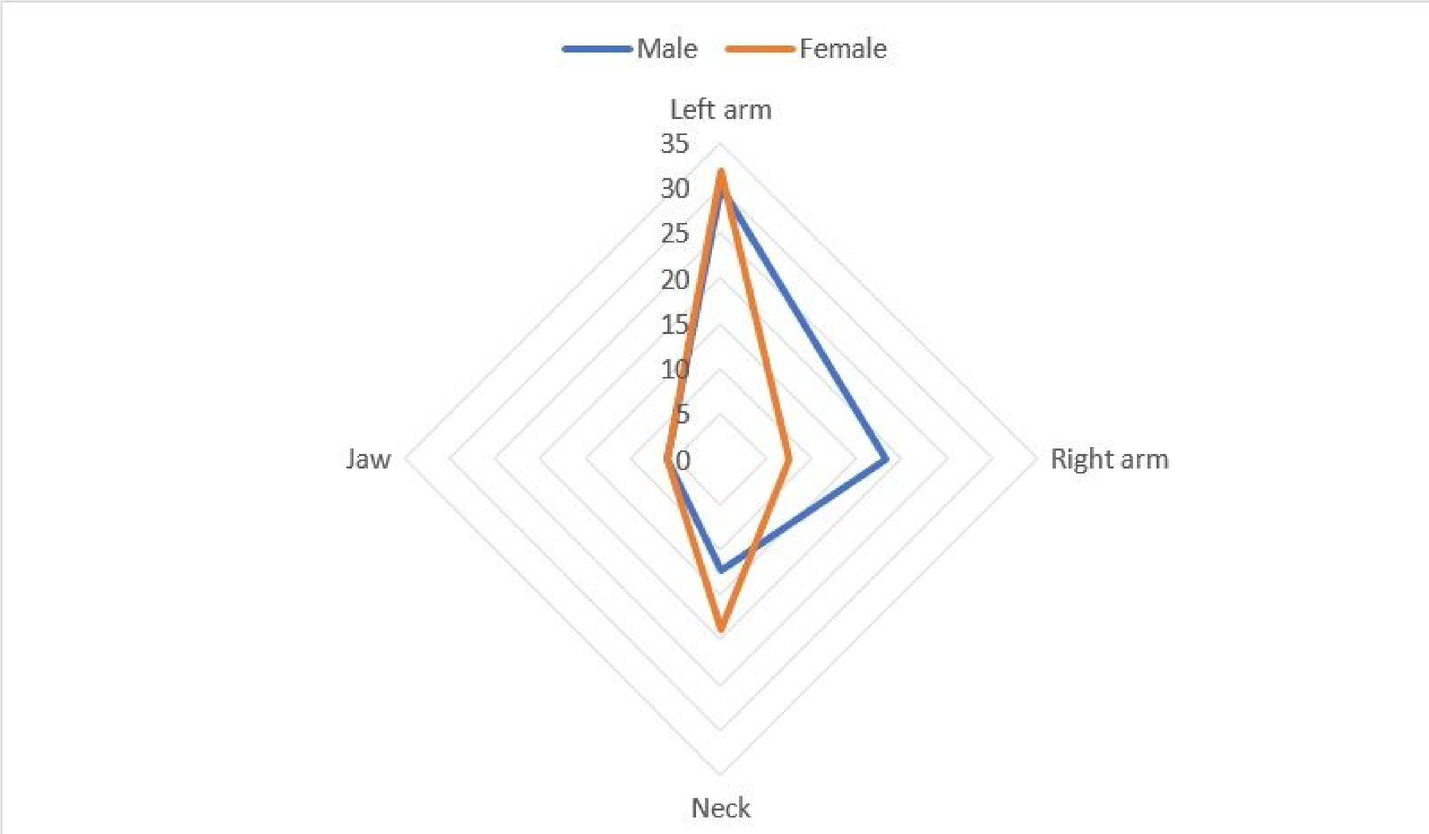

Figure 3

Radiation of Chest Pain Stratified by Sex