Diagnoses and Outcomes of Patients with Suspicion of Acute Coronary Syndrome and Raised High Sensitive Troponin I: A Single Center Study from Pakistan

Fatima Kanani[1] Sidra Maqsood[2] Vandana Wadhwani[3] Maliha Zubairy[1] Imran Iftikhar[3] Adnan Mustafa Zubairi[1]

[1] Section of Chemical Pathology, Indus Hospital & Health Network, Karachi, Pakistan
[2] Indus Hospital Research Centre, Indus Hospital & Health Network, Karachi, Pakistan
[3] Department of Cardiology, Indus Hospital & Health Network, Karachi, Pakistan

Address for correspondence Fatima Kanani, MBBS, FCPS, Section Head and Consultant Chemical Pathologist, Indus Hospital & Health Network, Plot C-76, Sector 31/5, Opposite Darussalam Society Korangi Crossing, Karachi 75190, Pakistan (e-mail: fatimakanani@hotmail.com).

J Lab Physicians 2023;15:409–418.

Abstract

Objectives Troponins are classically raised in acute coronary syndrome (ACS) although other cardiovascular and non-cardiovascular causes are recognized. We aimed to see the association of high sensitivity (Hs) Troponin I values exceeding the sex-specific 99th percentile upper reference limit (URL) with diagnoses, emergency department (ED) outcomes, 30-day outcomes of admitted patients and predictors of ACS in both genders.

Materials and Methods A retrospective study of all patients presenting to the emergency department from January 2019 to April 2021 with suspicion of ACS and Hs-Troponin I values greater than the sex-specific 99th percentile URL.

Statistical Analysis SPSS version 24 was used, Pearson's chi-square tests, Fisher's exact test, Kruskal–Wallis test, Mann–Whitney *U* test, and odds ratios, including the 95% confidence intervals, for each characteristic were used for analysis. A *p*-value of < 0.05 was considered significant.

Results There were a total of 5,982 patients (3,031 males, 2,951 females), out of which 878 patients were admitted under the cardiology specialty. In patients who were admitted to the ward, mortality was higher in females (8.2%) with less than a 10-fold rise in Hs-Troponin I while similar in both genders (7.6%) in patients with Hs-troponin I greater than 10-fold of sex-specific 99th percentile URL. Raised low-density lipoprotein-cholesterol was a significant factor associated with 2.4 times higher odds of ACS.

Conclusion Women with Hs-Troponin values up to 10 times the URL, i.e., 15.6–160 ng/L have higher mortality than their male counterparts. LDL-cholesterol is a significant risk factor for ACS which should be controlled for its prevention.

Keywords
- acute coronary syndrome
- myocardial infarction
- non-ST-elevation myocardial infarction (NSTEMI)
- cardiac troponin
- LDL cholesterol
- emergency department

article published online
April 4, 2023

DOI https://doi.org/10.1055/s-0043-1761940.
ISSN 0974-2727.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Cardiac troponin is one of the most common clinical laboratory tests to be ordered from the emergency department (ED). With the advent of high sensitivity troponin assays, detectable values are now seen in a greater proportion of patients. Troponin values are pivotal for the diagnosis of myocardial infarction, especially for non-ST elevation myocardial infarction (NSTEMI), in which typical electrocardiogram (ECG) findings of myocardial infarction are not apparent. The fourth universal definition of myocardial infarction warrants a rise or fall of troponin with at least one value above the 99th percentile upper reference limit (URL), along with evidence of ischemia.[1] Another hallmark of the high-sensitive troponin assays is the availability of sex-specific upper reference limits. As troponins are directly related to the myocardial mass, the values are generally higher in males. Raised troponin values are also indicators of a poorer outcome.[2]

Troponins are classically raised in acute coronary syndrome (ACS) including both ST-elevation myocardial infarction (STEMI) and NSTEMI. However, as troponins are released from the myocytes in any preceding injury or trauma, they are also frequently raised in conditions other than ACS. Non-ACS causes of raised troponins include both cardiovascular disease (CVD) and non-cardiovascular etiologies, of which myocarditis, heart failure, arrhythmias, anemia, and renal disease are just a few.[3] Serial testing can differentiate acute change versus a chronically elevated value due to a non-ischemic episode.

Here we sought to study the cohort of patients presenting with suspicion of ACS to the ED with Hs-Troponin I levels above the 99th percentile sex-specific URL. We looked at the final diagnoses of these patients admitted to the cardiology unit and aimed to see the association between the Hs-Troponin I levels with the ED, ward, and 30-day outcomes in both genders. We also analyzed the predictors of ACS in our patient cohort.

Materials and Methods

This was a retrospective study with exempt approval granted by the Institutional Board Review. The study was undertaken following the principles of the Declaration of Helsinki. Data of all consecutive patients presenting to the ED between January 2019 and April 2021 with suspected ACS and Hs-Troponin I values above the sex-specific 99th percentile URL were extracted from the electronic medical record (EMR). Patients less than 16 years of age, those with positive COVID-19 PCR and missing data were excluded from the study. The first ED visit was considered as the index visit for the data analysis. A fellow cardiologist reviewed the data of all patients admitted under cardiology specialty for ultimate diagnosis in view of angiography and ECG findings.

Troponin Assay

The assay used for the study was Alinity STAT High Sensitive Troponin I assay (Hs-Troponin I) by Abbott Diagnostics on Alinity i. The limit of blank (LoB), the limit of detection (LoD), and the limit of quantification (LoQ) of the assay were 1.0, 1.6, and 5.1 ng/L, respectively. The 99th percentile upper reference limit for males was 34.2 ng/L while for females it was 15.6 ng/L.

Characteristics of High Sensitivity Troponin Assay

According to the International Federation of Clinical Chemistry (IFCC) working group and American Association of Clinical Chemistry (AACC) guidelines, the high sensitivity troponin assay should have performance specifications ensuring that it is detectable in at least 50% of the population and has a coefficient of variation (CV) of less than 10% at the 99th percentile URL.[4] Recommendations by the IFCC working group and AACC[4] also include reporting the results of high sensitive assays in whole numbers (ng/L) rather than decimals which are used in conventional assays, and running three levels of internal quality controls every day of use, with values of the low-level control at the 99th percentile URL. Alinity i STAT Hs-Troponin I Controls at three levels (20, 200, and 1500 ng/L) were used to monitor the quality of the assay in our laboratory. The analytical coefficient of variation (CV) of the assay at the 99th percentile URL was less than 7% during the study interval. The laboratory is enrolled in proficiency testing survey by College of American Pathologists (CAP) and is ISO 15189 certified.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Studies (SPSS; IBM, version 24.0 Corporate headquarters 1 New Orchard Road Armonk, New York 10504-1722 United States). Median (Interquartile range [IQR]) was computed for age, Hs-Troponin I levels, and days of hospital stay as data were not normally distributed. Frequencies with percentages were computed for sex, diagnoses, ED outcomes, comorbidities, angiography status, ward outcomes, and 30-day outcomes of discharged patients. We analyzed the data with Pearson's chi-square tests, Fisher's exact test, Kruskal–Wallis test, Mann–Whitney *U* test, and odds ratios, including the 95% confidence intervals, for each characteristic. Regression analysis (univariate and multivariate) was performed to assess the predictors associated with the presence of ACS. At this stage, factors exhibiting a *p*-value less than or equal to 0.25 were included in multivariable analyses. Results were reported as odds ratio with a 95% confidence interval and *p*-values < 0.05 were considered statistically significant.

Results

There were a total of 5,982 patients (3,031 males, 2,951 females) who had a Hs-Troponin I above 99th percentile URL at index presentation to the ED. Subjects were divided into four groups according to the quartiles of their in years < 48.00 (first quartile), 48.01–61.00 (second quartile), 62.01–69.00 (third quartile), and >69 (fourth quartile). The characteristics of the study population stratified by gender and age were shown in ►**Table 1**. The median (IQR) age of the patients was 61 (52–70) years. The median (IQR) levels of Hs-Troponin I was

Table 1 Characteristics of the study population stratified by age

Overall study population			**Male** $N = 3031$		**Female** $N = 2951$		***p*-Value**	
Age (y)								
Median (IQR)			61 (52-70)		61 (51-70)		0.004*[a]	
Hs- Troponin I ng/L								
Median (IQR)			166 (64-787)		68 (31-304)		<0.0001*[a]	
Age stratification of ED patients in years								
	<48 ($n = 902$)	***p*-Value**	**48-61 ($n = 1,690$)**	***p*-Value**	**62-69 (n = 1057)**	***p*-Value**	**>69 ($n = 1455$)**	***p*-Value**
Gender *n* (%)								
Male	387(42.9)	<0.0001*[b]	826 (48.9)	0.812[b]	561 (53.1)	0.004*[b]	734 (50.4)	0.239[b]
Female	515(57.1)		864 (51.1)		496 (46.9)		721 (49.6)	
Hs-Troponin I ng/L								
Male Median (IQR)	109 (53-501)	<0.0001*[a]	130.5 (62.7-544.5)	<0.0001*[a]	131 (64-656)	<0.0001*[a]	137 (58.7-549.2)	<0.0001*[a]
Female Median (IQR)	61 (28-176)		60 (29-245)		66 (31-322)		64 (31-230.5)	
Patients admitted under cardiology specialty stratified by age in years								
	<48 ($N = 145$)	***p*-Value**	**48-61 ($N = 365$)**	***p*-Value**	**62-69 ($N = 208$)**	***p*-Value**	**>69 ($N = 160$)**	***p*-Value**
Gender *n* (%)								
Male Female	82 (56.6) 63 (43.4)	0.459[b]	221 (60.5) 144 (39.5)	0.626[b]	132 (63.5) 76 (36.5)	0.197[b]	88 (55) 72 (45)	0.212[b]
Hs-Troponin I ng/L								
Male Median (IQR)	630 (152.2-4764.5)	0.001*[a]	705 (127-3869)	<0.0001*[a]	640 (132.2-3032.7)	0.019*[a]	866 (142.7-4712)	0.003*[a]
Female Median (IQR)	217 (42.30-940)		198 (50.2-1162.2)		365 (45.2-2500.2)		295.5 (57.2-1265.7)	

Note:*= Significant value, a = Mann–Whitney *U*, b = Pearson's chi-square.

Table 2 Demographic and ED outcomes by gender according to the rise of Hs-Troponin I

	Females with Hs-Troponin I values 15.6–160 ng/L *n* = 1955	Females with Hs-Troponin I values >160 ng/L *n* = 996	*p*-Value	Males with Hs-Troponin I values 34.2–340 ng/L *n* = 1,884	Males with Hs-Troponin I values >340 ng/L *n* = 1,147	*p*-Value
Age (y) Median (IQR)	60 (50-70)	61 (51-70)	0.147[a]	62 (52-70)	61 (52-70)	0.685[a]
Hs- Troponin I ng/L Median (IQR)	39 (25–68)	636 (292.2-1982.5)	0.000[a*]	137 (75–230)	5590 (1327–16745)	0.000[a*]
Discharged on request *n* (%)	9 (0.5)	3 (0.3)	0.761[b]	14 (0.7)	1(0.1)	0.013[c*]
No follow-up required *n* (%)	41 (2)	3 (0.3)	0.000[c*]	43(2.3)	4(0.3)	0.000[c*]
Referred for admission *n* (%)	415 (21.2)	330 (33.1)	0.000[c*]	446(23.7)	467(40.7)	0.000[c*]
Referred to Clinic *n* (%)	428 (21.9)	48 (4.9)	0.000[c*]	337(17.9)	33(2.9)	0.000[c*]
Referred to other location *n* (%)	928 (47.5)	521 (52.3)	0.013[c*]	886(47)	509(44.4)	0.156[c]
LAMA *n* (%)	97 (5)	45 (4.5)	0.594[c]	94(5)	63(5.5)	0.544[c]
Expired *n* (%)	37 (1.9)	46 (4.6)	0.000[c*]	64(3.4)	70(6.1)	0.000[c*]

Note: a= Mann–Whitney *U*, b = Fisher's exact test, c= Pearson chi-square * = Significant value.

significantly lower in females at 68 (31–304) ng/L as opposed to 166 (64–787) ng/L in males. The difference remained significant in all age groups. The median Hs-Troponin I values increased with age up to 69 years.

The ED outcome of the patients based on their Hs-Troponin I levels are shown in ►**Table 2**. Patients were categorized into two groups; those with Hs-Troponin I values between 99th percentile sex-specific URL and up to ten times URL increase, and those with an increase of more than 10 times sex-specific URL. In patients with more than a 10-fold increase in Hs-Troponin I values above 99th percentile sex-specific URL, significantly more males (40.7%) were referred for admission as compared to females (33.1%) while significantly more females (52.3%) were referred to an outside facility or referred to the outpatient clinic of the institute (4.9%). The ED mortality was higher in males at 3.4% and 6.1% compared to females i.e., 1.9% and 4.6% with Hs-Troponin I values below and above the ten times sex-specific URL, respectively (►**Table 2**).

The breakdown of the eventual diagnoses of the patients admitted under Cardiology specialty with raised Hs-Troponin I from the ED is given in ►**Table 3**. Out of the total study cohort of 5,982 patients, 878 (14.6%) including 523 males and 355 females, were admitted under the Cardiology specialty. NSTEMI was the most frequent cause of raised Hs-Troponin I in these admitted patients (57.1%), followed by STEMI (16.6%), other non-ACS cardiovascular causes (12.6%), unstable angina (9.1%) and non-cardiovascular conditions (4.6%). Males had a significantly higher proportion of STEMI (68.5%) and NSTEMI (64.5%) compared to females, while females predominantly had a higher frequency of unstable angina (53.8%) and non-ACS cardiovascular conditions (61.3%). STEMI occurred in a relatively younger age group of patients with a median (IQR) of 56 (48–65) years, while NSTEMI and other cardiovascular and non-cardiovascular causes occurred in older age groups with a median of 59, 60, and 63 years, respectively. However, the median Hs-Troponin I was as expected the highest in STEMI (3085 ng/L), followed by NSTEMI (771 ng/L). In the ward, 11.6% of STEMI and 4.4% of NSTEMI patients expired. Further, the 30-day outcome of 818 (93.1%) discharged patients is shown in ►**Table 3**.

A total of 297 (4.96%) patients underwent serial Hs-Troponin I testing within 24 hours. The median(IQR) time between the serial testing was 4.14 (2.5–6.15) hours. The median (IQR) hospital stay was 2 (1–3) days for both STEMI and NSTEMI.

The demographics, diagnoses, and outcomes according to the rise of Hs-Troponin I in patients admitted under the cardiology specialty are shown in ►**Table 4**. In patients with more than a 10-fold increase in Hs-Troponin I values above 99th percentile sex-specific URL, NSTEMI was the most frequent cause of raised Hs-Troponin I, 70.8% in males and 70.1% in females. Comorbidities including diabetes mellitus (DM), hypertension (HTN), ischemic heart disease (IHD), and chronic kidney disease (CKD) were reported as depicted in ►**Table 4**. Angiography was done on a total of 377 males and 198 females. Mortality was higher in admitted females compared to males in the category of patients with Hs-Troponin I rise less than 10-fold (8.2% vs. 3.6%). The 30-day outcome also infers the higher death rates in females (►**Table 4**).

Table 3 Demographics and outcome according to diagnoses of patients admitted under Cardiology Specialty ($n = 878$)

Patients admitted under Cardiology Specialty ($N = 878$)						
Diagnoses	**STEMI ($n = 146$)**	**NSTEMI ($n = 501$)**	**Unstable angina ($n = 80$)**	**Other cardiovascular conditions ($n = 111$)**	**Non-cardiovascular conditions ($n = 40$)**	***p*-Value**
Gender *n* (%)						
Male ($n = 523$)	100 (68.5)	323 (64.5)	37(46.3)	43 (38.7)	20 (50)	<0.0001*[a]
Female ($n = 355$)	46 (31.5)	178 (35.5)	43 (53.8)	68 (61.3)	20 (50)	
Age (y)						
Median (IQR)	56 (48–65)	59 (52–67)	58.5 (52-67)	60 (49–70)	63 (52–71)	0.025*[b]
Hs-Troponin I (ng/L)						
Median (IQR)	3085 (413.2–14259)	771 (257–3170)	45 (36.7–63.5)	63 (35–113)	210 (38.25–1678.1)	<0.0001*[b]
Length of stay						
Median (IQR)	2 (1-3)	2 (1-3)	2(1-2)	3 (1-6)	3 (2-5)	<0.0001*[b]
Females with Hs-Troponin I values below and above 10-fold rise *n* (%)						
15.6-160 ng/L (n = 158)	6 (13)	40(22.5)	43 (100)	55 (80.9)	14 (70)	<0.0001*[a]
>160 ng/L (n = 197)	40 (87)	138(77.5)	–	13 (19.1)	6 (30)	
Males with Hs-Troponin I values below and above 10-fold rise *n* (%)						
34.2-340 ng/L ($n = 194$)	21 (21)	90 (27.9)	37 (100)	38 (88.4)	8 (40)	<0.0001*[a]
>340 ng/L ($n = 329$)	79 (79)	233 (72.1)	–	5 (11.6)	12 (60)	
Angiography *n* (%)						
Yes ($n = 575$)	129 (88.4)	372 (74.3)	62 (77.5)	11 (9.9)	1 (2.5)	<0.0001*[a]
No ($n = 303$)	17 (11.6)	129 (25.7)	18 (22.5)	100 (90.1)	39 (97.5)	
Ward Outcome *n* (%)						
Discharged ($n = 818$)	129 (88.4)	479 (95.6)	78 (97.5)	102 (91.9)	30 (75)	<0.0001*[a]
Expired ($n = 60$)	17(11.6)	22 (4.4)	2 (2.5)	9 (8.1)	10 (25)	
30-Day Outcome of Discharged patients *n* (%)						
Stable ($n = 630$)	99 (76.7)	374 (78.1)	62(79.5)	75 (73.5)	20 (66.7)	0.691[c]
Unstable ($n = 185$)	29 (22.5)	103 (21.5)	16 (20.5)	27 (26.5)	10 (33.3)	
Expired ($n = 3$)	1 (0.8)	2 (0.4)	0	0	0	

Abbreviations: ACS, Acute coronary syndrome; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction.
*= Significant value, a = Pearson's chi-square, b = Kruskal–Wallis, c = Fisher's exact test.

Of the 828 admitted patients, ACS was diagnosed in 727 (83%) cases, while 151 (17%) were diagnosed as non-ACS. Logistic regression analysis was carried out to assess the association of various demographic, clinical, and laboratory predictors with the risk of developing ACS. Univariate analysis showed that ACS was significantly associated with ages <48, 48–61, and >69 years, respectively. ACS was 1.5 and 1.9 folds higher among participants with age < 48 (OR = 1.53 95% CI: 0.9–2.3, $p = 0.053$) and > 69 (OR = 1.98 95% CI: 1.3–2.9, $p = 0.001$) years of age, respectively. Patients with ages 48 to 61 years demonstrated 50% ($p \leq 0.001$) while male patients had 41% ($p \leq 0.0001$) chance of getting ACS. ACS was 0.71 and 0.75 folds higher among patients with comorbidities, i.e., DM ($p = 0.068$) and HTN ($p = 0.116$), respectively. Patients with hypertriglyceridemia and high low density lipoprotein cholesterol (LDL-C) had 53% ($p = 0.146$) and 40% ($p \leq 0.025$) chance of having ACS respectively. It was further observed that smoking was associated with a 55% risk of ACS ($p = 0.086$).

After adjusting for age, sex, comorbidities, smoking, and hypertriglyceridemia, the patients with high LDL-C were

Table 4 Demographics, diagnoses, and outcomes according to the rise of Hs-Troponin I in patients admitted under cardiology specialty

	Females with Hs-Troponin I values 15.6-160 ng/L (*N* = 158)	Females with Hs-Troponin I values >160 ng/L (*N* = 197)	*p*-Value	Males with Hs-Troponin I values 34.2-340 ng/L (*N* = 194)	Males with Hs-Troponin I values >340 ng/L (*N* = 329)	*p*-Value
Diagnosis *n* (%)						
STEMI	6 (3.8)	40 (20.3)	<0.0001*[a]	21 (10.8)	79(24)	<0.0001*[a]
NSTEMI	40 (25.3)	138 (70.1)	<0.0001*[a]	90 (46.4)	233 (70.8)	<0.0001*[a]
Unstable Angina	43 (27.2)	0	<0.0001*[a]	37 (19.1)	0	<0.0001*[a]
Other Cardiovascular Conditions	55 (34.8)	13 (6.6)	<0.0001*[a]	38 (19.6)	5 (1.5)	<0.0001*[a]
Non-cardiac conditions	14 (8.9)	6 (3)	0.018*[a]	8 (4.1)	12 (3.6)	0.784 [a]
Age (y) Median (IQR)	58 (51-67)	60 (50-67)	0.894[b]	59 (52-67)	59 (51-67)	0.863[b]
Hs-Troponin I (ng/L) Median (IQR)	43 (29-74.5)	4260 (990-13837)	<0.0001*[b]	90.5 (56-178.5)	2202 (825-7831.5)	<0.0001*[b]
Length of stay (days) Median (IQR)	2 (1-4)	2 (1-4)	0.898[b]	2(1-3)	2(1-3)	0.929[b]
Co-morbidities *n* (%)						
DM	94 (59.5)	126 (64)	0.441[a]	76 (39.2)	124 (37.7)	0.736 [a]
HTN	113 (71.5)	148 (75.1)	0.444[a]	109 (56.2)	174 (52.9)	0.465 [a]
IHD	53 (33.5)	48 (24.4)	0.057[a]	60 (30.9)	81 (24.6)	0.116 [a]
CKD	16 (10.1)	25 (12.7)	0.453[a]	14 (7.2)	24 (7.3)	0.973[a]
Angiography *n* (%)						
Yes	68 (43)	130 (66)	<0.0001*[a]	122 (62.9)	255 (77.5)	<0.0001*[a]
No	90 (57)	67 (34)		72 (37.1)	74 (22.5)	
Ward Outcome n (%)						
Discharged	145 (91.8)	182 (92.4)	0.831 [a]	187 (96.4)	304 (92.4)	0.066[a]
Expired	13 (8.2)	15 (7.6)		7 (3.6)	25 (7.6)	
30-Day Outcome of Discharged patients *n* (%)						
Stable	119 (82.1)	137 (75.3)	0.232[c]	141 (75.4)	233 (76.6)	0.841[c]
Unstable	25 (17.2)	44 (24.2)		46 (24.6)	70 (23)	
Died	1 (0.7)	1(0.5)		0	1(0.3)	

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease.
*= Significant value, a = Pearson's chi-square, b = Mann–Whitney *U*, c = Fisher's exact test.

found to have 2.4 ($p = 0.040$) times higher odds of having ACS. Also, patients with diabetes mellitus were found to have 2.5 times higher odds of having ACS; however, the results were not statistically significant ($p = 0.056$, ►**Table 5**). Among hazardous predictors, the highest odds were by DM followed by smoking and high LDL-C; however, smoking failed to demonstrate significant association after controlling the effect of other predictors of ACS.

Discussion

Troponin I values above the sex-specific URL along with evidence of ischemia are essential for the diagnosis of myocardial infarction. Our study cohort consisted of all patients presenting in ED with suspected ACS and Hs-Troponin I values above the sex-specific 99th percentile URL. Patients with ST-elevation typically are diagnosed on ECG and their troponins were often not requested. This accounts for the significantly higher NSTEMIs seen in this study.

In our cohort, out of 5,982 patients seen in the ED with raised Hs-Troponin I, 727 were admitted with an ultimate diagnosis of ACS. Out of these, 237 (32.5%) patients had Hs-Troponin I values less than 10 times sex-specific cutoffs on index ED visits. It is thus crucial to have a high index of suspicion and subject patients with suggestive symptoms to serial troponin testing. However, limitations of space and personnel are some of the practical factors involved in on-the-ground management strategies. Fast rule-in/rule-out

Table 5 Univariate and multivariate analyses of demographics, clinical and laboratory risk factors for ACS

Univariate binary logistic regression				Multivariable binary logistic regression		
Variables	**Crude OR**	**95% CI**	***p*-Value**	**Adjusted OR**	**95% CI**	***p*-Value**
Age (y)						
<48 (Yes)	1.536	0.994-2.373	0.053*	0.765	0.225-2.606	0.669
<48 (No)	Ref			ref		
48-61 (Yes)	0.501	0.342-0.734	<0.0001*	1.786	0.604-5.278	0.294
48-61 (No)	ref			ref		
62-69 (Yes)	0.882	0.578-1.344	0.560	–	–	–
62-69 (No)	ref			–	–	–
>69 (Yes)	1.989	1.324-2.987	0.001*	0.357	0.120-1.059	0.063
>69 (No)	ref			ref		
Gender						
Male	0.415	0.290-0.593	<0.0001*	1.821	0.724-4.577	0.202
Female	ref			ref		
DM						
Yes	0.718	0.503-1.024	0.068*	2.537	0.976-6.593	0.056
No	ref			ref		
HTN						
Yes	0.751	0.527-1.073	0.116*	1.07	0.448-2.560	0.877
No	ref			ref		
IHD						
Yes	0.826	0.551-1.238	0.356	–	–	–
No	ref			–	–	–
Smoking						
Yes	0.550	0.279-1.087	0.086*	2.434	0.622-9.522	0.201
No	ref			ref		
Tobacco intake						
Yes	0.590	0.205-1.696	0.328	–	–	–
No	ref			–	–	–
Hypercholesterolemia (cholesterol > 200 mg/dL)						
Yes	0.699	0.202-2.420	0.572	–	–	–
No	ref			–	–	–
Hypertriglyceridemia (triglycerides > 150 mg/dL)						
Yes	0.536	0.231-1.243	0.146*	1.658	0.664-4.138	0.278
No	Ref			ref		
High LDL-C (LDL-C > 100 mg/dL)						
Yes	0.404	0.184-0.891	0.025*	2.415	1.040-5.611	0.040**
No	Ref			–	–	–
Low HDL-C (HDL-C < 40 mg/dL)						
Yes	1.068	0.390-2.927	0.898	–	–	–
No	Ref			–	–	–

Abbreviations: DM, diabetes mellitus; HDL, high density lipoprotein; HTN, hypertension; IHD, ischemic heart disease; LDL, low-density lipoprotein.
Note: *≤0.25 (univariate analysis), **≤ 0.05 (multivariable analysis).

protocols for ACS have been evaluated for quick diagnosis.[5] Our center is a free-of-cost, high-quality, tertiary care setup located near a rural populace. The majority of our patients, therefore, come from the underprivileged sector of society and the ED is a busy place with a per-day flux of 700 to 1000 patients. The ED environment is highly volatile and the physicians are under constant stress for faster turnover of patients. The limitation of in-patient beds is the key factor involved in the huge number of referrals seen in our study.

Although several studies have been done on the white population, literature on South Asians is relatively scarce. As diagnostic cut points are generally made on the 99th percentile URL, and a number of variables affect the biological variation in troponin value; therefore, the cut-off has to have a basis in the community. Studies in the local setting are somewhat preliminary.[6,7] Troponin has also been shown to be an independent predictor of all-cause of hospital mortality but should be measured only in those in whom there is a clinical indication,[8] as there are a number of non-ACS and non-cardiovascular causes of raised troponins. Hs-Troponin I values should be interpreted along with the clinical scenario in outlining management plans to safeguard against unnecessary therapeutic interventions with consequent multifaceted implications for both the patient and institute.

It is typically recommended that blood specimens for the measurement of cardiac troponin should be collected on initial assessment and repeated 3 to 6 hours later (1–3),[9] although as mentioned, there are faster rule-in and rule-out algorithms for high-sensitive troponin assays.[5,10,11] In our study, 297 (4.96%) patients underwent serial monitoring within 24 hours. The time difference median (IQR) was 4.14 (2.5–6.15) hours. Wassie et al[12] claims that there is no difference in 30-day outcome between patients who have been tested once for troponin in the ED with negative results and those who underwent serial testing. Their study was done on a large cohort of nearly 28,000 patients over 15 ED facilities. They concluded that physicians' clinical judgment should be trusted to define the ordering of troponin in individual patients.

There is evidence to show that high-sensitive troponin I levels, even below the 99th percentile, have predictive power for future cardiovascular events and mortality.[13] There is a positive association with age regardless of history of any cardiovascular disease.[13] Our study shows rising Hs-Troponin I value with age up to 69 years. As anticipated, patients with ACS had higher Hs-Troponin I value than patients with other cardiovascular conditions, and more so in STEMI compared to NSTEMI. This has also been shown by other researchers.[9]

We noted increased ED mortality with higher Hs-Troponin I values. A study has shown that a higher troponin result, greater than the 99th percentile URL, resulted in a 3-year higher mortality hazard of 3.2 (95% CI 3.1–3.2). Mortality varied with age, with a hazard ratio of 10.6 (8.5–13.3) in 18- to 29-year-old, and 1.5 (1.4–1.6) in those older than 90 years.[14] The high mortality was predominantly seen in the first few weeks of the sentinel event. We observed a similar trend with the maximum mortality seen in the ED or during the initial admission days although the patients were followed for their 30-day outcome. Lee et al have found elevated troponin levels in patients attending ED to be associated with increasing age, compromised physiological functions, comorbidities, and increased mortality.[15]

Comorbidities including DM, HTN, CKD, dyslipidemias as well as smoking have been associated in the past with cardiovascular events. Vidali et al have reported higher troponin I value in patients with hypertension, diabetes, and CKD.[9] They have demonstrated that age, hypertension, diabetes, kidney disease, absence of chest pain, tachycardia ($>$ 100 bpm), and ECG changes are significantly associated with troponin I positivity in univariate analysis. However, only age, tachycardia, and ECG changes remained independently associated with troponin I positivity at admission in multivariable analysis.[9] Another study has shown age, CKD and smoking to be independent predictors of STEMI.[16] Omidi suggests that age, gender, DM, HTN, family history and dyslipidemia have significant effects on the severity of CAD.[17] We too demonstrated that raised LDL-C had a high likelihood of ACS in multivariable analysis although male gender, age group 49 to 61 years, age greater than 69 years, DM, and HTN were also additionally significant in univariate analysis. South Asians are more prone to the early development of atherosclerotic cardiovascular disease and a reduction in LDL-C improves the outcome of ACS patients. This has also prompted the Lipid Association of India to recommend aggressive lipid-lowering management in these patients after ACS.[18]

We observed approximately equal numbers of male and female patients presenting to ED with Hs-Troponin I levels above the 99th percentile URL. The median (IQR) age of males and females was 61 (51/52–70) years. Higher Hs-Troponin I values were associated with a worse ED outcome in both males and females; however, the overall ED mortality was higher for males. In patients less than 48 years of age, significantly more males than females presented to the ED with raised Hs-Troponin I values, while there were more females than males with raised Hs-Troponin I in the older age group. However, amongst all age quartiles, more males than females were admitted to the Cardiology specialty.

It was noted in our study that a significantly higher percentage of males compared to females with Hs-Troponin I values greater than 10-fold sex-specific URL were processed for admission within the institute, while a greater percentage of females with these values were referred to other institutes for admission or to the out-patient facility. The in-patient mortality rate of females was higher than that of males when the Hs-Troponin I values were less than 10-fold higher than the sex-specific URL and similar when the troponin values were greater than 10-fold. It was also seen that angiography was performed in a lower percentage of women than men in both categories of Hs-Troponin I, which could account for possibly missed diagnoses in some females. This is also alarming considering that a greater majority of female with raised Hs-Troponin I were referred to out-patient clinics or other centers from ED. Shah et al suggest that there is under-diagnosis of AMI in women.[19] They claim that women are less likely to be referred to a

specialist cardiologist or for interventional measures than men. There is the general impression amongst medical and non-medical communities alike that women have a cardiovascular protective element due to the presence of estrogen which partly accounts for more complacent management.[20] However, physical inactivity, increased central obesity and BMI with the ultimate development of metabolic syndrome increases the risk of morbidity and mortality in women, more so in the post-menopausal stage. In our study cohort too, the frequency of diabetes and hypertension was higher in women. Menyar et al,[21] in their review, have also noted that gender difference exists in all stages of coronary artery disease diagnosis and intervention. These could be due in part to the more atypical presentation of ACS in women. The pathophysiology behind the possible unstable atherosclerotic plaques or hypercoagulability in women could be genetic, hormonal, or inflammatory as they have, in general, thinner and less pliable coronary arteries than men. Alabas et al[22] have found higher mortality in women with STEMI and NSTEMI at 1 and 5 years and propose that stricter adherence to myocardial infarction management guidelines in women may alleviate premature cardiovascular-related mortality in them. We concur with their suggestion that following standardized clinical guidelines may help to reduce premature cardiovascular mortality in females.

To the best of our knowledge, there are no large-scale studies available as yet from our part of the world on the use of highly sensitive cardiac troponin I in the diagnoses of ACS. However, our study had certain limitations. Data were extracted from the EMR department and patients with missing or incomplete data were excluded. The study relied on the existing data in the EMR and lost to follow-up patients were not called in person.

Conclusion

Increased Hs-Troponin I values were strongly associated with a worse ED outcome in both genders; however, in-patient mortality was higher in females with values up to 10 times URL. High LDL-cholesterol was associated with significant odds of developing ACS, highlighting the crucial role of lipid and lifestyle management in the prevention of ACS.

Authors' Contributions

F.K. conceived the idea and designed the study. S.M. and V.W. analyzed and interpreted the patient data. F.K., and A.M.Z. did the initial drafting of the manuscript. I.I. and A.M.Z. revised critically afterward for important intellectual content. All authors read and approved the final manuscript.

IRB Consideration

IRB exemption was given before the start of the study (IRB number: IHHN_IRB_2021_12_017).

Funding

None.

Conflict of Interest

None declared.

References

1 Thygesen K, Alpert JS, Jaffe AS, et al; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40(03):237–269
2 Chapman AR, Lee KK, McAllister DA, et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndrome. JAMA 2017;318(19):1913–1924
3 Herman DS, Kavsak PA, Greene DN. Variability and error in cardiac troponin testing: an ACLPS critical review. Am J Clin Pathol 2017; 148(04):281–295
4 Wu AHB, Christenson RH, Greene DN, et al. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem 2018;64(04):645–655
5 Mueller C, Giannitsis E, Christ M, et al; TRAPID-AMI Investigators. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. Ann Emerg Med 2016;68(01):76–87.e4
6 Bahadur K, Ijaz A, Salahuddin M, Alam A. Determination of high sensitive cardiac troponin I 99th percentile upper reference limits in a healthy Pakistani population. Pak J Med Sci 2020;36(06): 1303–1307
7 Kanani F, Zubairi AM, Zubairy M, Maqsood S. High-sensitivity cardiac troponin I levels below 99th percentile upper reference limit in patients presenting with suspicion of acute coronary syndrome (ACS) in emergency department at a tertiary care hospital in Karachi, Pakistan. High Blood Press Cardiovasc Prev 2022;29(05):445–450
8 Docherty AB, Sim M, Oliveira J, et al. Early troponin I in critical illness and its association with hospital mortality: a cohort study. Crit Care 2017;21(01):216
9 Vidali M, Verzotti E, Cabraz N, et al. "Real life use" of troponin in the emergency department: a survey of over 3000 cases. Biochem Med (Zagreb) 2015;25(03):421–429
10 Marcusohn E, Epstein D, Roguin A, Zukermann R. Rapid rule out for suspected myocardial infarction: is the algorithm appropriate for all? Eur Heart J Qual Care Clin Outcomes 2020;6(03): 193–198
11 Neumann JT, Sörensen NA, Ojeda F, et al. Early diagnosis of acute myocardial infarction using high-sensitivity troponin I. PLoS One 2017;12(03):e0174288
12 Wassie M, Lee M-S, Sun BC, et al. Single vs serial measurements of cardiac troponin level in the evaluation of patients in the emergency department with suspected acute myocardial infarction. JAMA Netw Open 2021;4(02):e2037930
13 Thorsteinsdottir I, Aspelund T, Gudmundsson E, et al. High-sensitivity cardiac troponin I is a strong predictor of cardiovascular events and mortality in the AGES-Reykjavik community based cohort of older individuals. Clin Chem 2016;62(04):623–630
14 Kaura A, Panoulas V, Glampson B, et al. Association of troponin level and age with mortality in 250 000 patients: cohort study across five UK acute care centres. BMJ 2019;367:l6055
15 Lee KK, Noaman A, Vaswani A, et al. Prevalence, determinants, and clinical associations of high-sensitivity cardiac troponin in patients attending emergency departments. Am J Med 2019; 132(01):110.e8–110.e21
16 El-Menyar A, Zubaid M, Shehab A, et al. Prevalence and impact of cardiovascular risk factors among patients presenting with acute coronary syndrome in the middle East. Clin Cardiol 2011;34(01): 51–58

17 Omidi N, Sadeghian S, Salarifar M, et al. Relationship between the severity of coronary artery disease and cardiovascular risk factors in acute coronary syndrome: based on Tehran Heart Center's Data Registry. J Tehran Heart Cent 2020;15(04):165–170
18 Puri R, Mehta V, Duell PB, et al. Evidence for intensive LDL-C lowering for acute coronary syndrome: recommendations from the Lipid Association of India. J Clin Lipidol 2022;16(03):261–271
19 Shah ASV, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. BMJ 2015;350(19):g7873
20 Desai S, Munshi A, Munshi D. Gender bias in cardiovascular disease prevention, detection, and management, with specific reference to coronary artery disease. J Midlife Health 2021;12(01):8–15
21 El-Menyar AA, Al Suwaidi J. Impact of gender in patients with acute coronary syndrome. Expert Rev Cardiovasc Ther 2009;7 (04):411–421
22 Alabas OA, Gale CP, Hall M, et al. Sex differences in treatments, relative survival, and excess mortality following acute myocardial infarction: national cohort study using the SWEDEHEART registry. J Am Heart Assoc 2017;6(12):e007123

