Atherosclerosis Plus 50 (2022) 25–31

Contents lists available at ScienceDirect

Atherosclerosis Plus

journal homepage: www.elsevier.com/locate/atherosclerosis

Clinical characteristics and cardiovascular outcomes among young patients with acute myocardial infarction in Kerala, India: A secondary analysis of ACS QUIK trial☆

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ARTICLE INFO

Article history:
Received 29 April 2022
Received in revised form
12 August 2022
Accepted 22 August 2022
Available online 26 August 2022

Keywords:
Premature coronary artery disease
Young adults
India
Low- and middle-income countries (LMICs)
Sex differences
Gender disparities

ABSTRACT

Background: Limited data exist on the risk profile and outcomes among young patients with acute myocardial infarction(AMI) in low-and middle-income countries(LMICs). This study explored differences in the clinical characteristics, medical care, and outcomes of AMI in young adults in India with a sub-analysis focusing on sex disparities amongst the young.
Methods: Using the Acute Coronary Syndrome Quality Improvement in Kerala trial database, we compared baseline characteristics, management, and outcomes amongst the young patients(≤50 years) and their older counterparts. The primary outcomes were the rates of in-hospital and 30-day composite of in-hospital major adverse cardiovascular events(MACE).
Results: Of the 21,374 adults enrolled, 4762(22%) were young, of which 614 (12.9%) were females. Young patients with AMI were more likely to be smokers(41.9% vs. 27.8%;$P < 0.001$) and undergo coronary angiography (66.3%vs.57.3%;$P < 0.001$) and percutaneous coronary intervention (PCI)(57.5% vs. 47.0%;$P < 0.001$), compared to older patients. After adjustment for potential confounders, younger patients had a lower likelihood of in-hospital (RR = 0.49; 95%CI 0.40–0.61;$P < 0.001$) and 30-day MACE (RR = 0.54; 95%CI 0.46–0.64;$P < 0.001$). Subgroup analysis comparing young males and females revealed worse cardiovascular risk profile among young women except for smoking. In-hospital MACE(RR = 1.60; 95%CI, 1.0–2.45;$P = 0.048$) were higher for young women compared to men.
Conclusion: Young AMI patients had higher prevalence of modifiable risk factors, were more likely to receive reperfusion therapy, and had better short and intermediate outcomes, compared to older patients. Compared to young men with AMI, young women had worse cardiovascular risk profile, were less likely to be treated with diagnostic angiography or PCI and experienced higher in-hospital death and MACE.

1. Introduction

Despite the considerable progress in the prevention and treatment of cardiovascular disease (CVD) in the past five decades, CVD continues to be the leading cause of death globally [1]. Compared to

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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https://doi.org/10.1016/j.athplu.2022.08.003

high-income countries, the toll of CVD disproportionately impacts South Asian countries where patients are typically younger with higher CVD morbidity and mortality [2,3]. Data on the risk factors and outcomes of young individuals experiencing acute myocardial infarction (AMI) in low- and middle-income countries (LMICs) are largely lacking [3]. Prior studies from India have focused on extremes of young age (<30 years) or have been limited by modest sample size [4,5]. Furthermore, those studies often observed a predominance of men and an inconsistent burden of conventional atherosclerotic CVD risk factors [5]. Moreover, studies investigating sex disparities in AMI among young women are sparse in LMICs. Using data from the Acute Coronary Syndrome Quality Improvement in Kerala, India (ACS QUIK) randomized clinical trial, our aim was to investigate the clinical presentation, management, and outcomes of AMI among young patients and to examine differences in these characteristics between young men and women.

2. Methods

2.1. Data acquisition

Data were acquired from the previously published ACS QUIK trial; a large pragmatic, cluster-randomized, stepped-wedge clinical trial evaluating the effect of a quality improvement tool kit intervention on major adverse cardiovascular events (MACE) in patients with AMI. The study design and primary results of the trial were published elsewhere [6,7] As a summary, a total of 21,374 AMI patients from 63 hospitals in Kerala, India participated in the trial between November 10, 2014, and November 9, 2016, to evaluate the impact of a locally adapted quality improvement toolkit to improve AMI outcomes (including ST-elevation MI (STEMI) and non-ST elevation MI (NSTEMI) [8]. Criteria for AMI were met if participants had two out of the three of the following characteristics which included chest pain, ST segment elevation on electrocardiography, and cardiac biomarker elevation greater than 3 times the upper limit of normal). Patients with unstable angina were excluded [9].

2.2. Ethical approval

The trial received institutional review board (IRB) approval from the ethics committees of the participating centers and was approved by the Indian Health Ministry Screening Committee [6]. The current retrospective analysis was approved by Mass General Brigham Healthcare Institutional Review Board (Boston, MA) and Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC; National Heart, Lung and Blood Institute, Bethesda, Maryland) and informed consent was waived.

2.3. Study population

We examined the differences between young (≤50 years) and older (>50 years) AMI patients, in terms of baseline characteristics, management, and outcomes [9]. In a sub-analysis, we explored the sex differences in presentation, management patterns, and outcomes amongst young AMI patients. Lastly, we looked at sex differences in amongst young patients.

2.4. Outcomes

The primary outcomes of the current study were the rates of in-hospital and 30-day mortality and a composite of MACE (death, reinfarction, stroke, and major bleeding). Thirty-day outcomes were collected through in-person visits or by telephone and were reported centrally. A patient would be considered lost to follow-up if they were unreachable after three attempts [7]. Major bleeding was defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [GUSTO] criteria [11]. Additional outcomes included in-hospital heart failure and cardiac arrest.

2.5. Statistical analysis

We summarized normally distributed continuous variables by mean and standard deviation. Non-normally distributed continuous variables were summarized by median and interquartile range (IQR) whereas categorical and binary variables by number and percentage. We applied student t-test, Mann-Whitney U, Chi-square and Fisher's exact tests accordingly.

To calculate the relative risks (RR), we fitted multivariable log Poisson regression models that can model probabilities of the in-hospital and 30-day outcomes. First, we ran unadjusted models to understand the crude relationship followed by separate models for each outcome after adjusting for selected a priori confounders: age (linear), diabetes (yes/no), hypertension (yes/no), current tobacco smoking (yes/no), type of MI (STEMI/NSTEMI), and receiving percutaneous coronary intervention (PCI) (yes/no) [12]. In these models we accounted for clustering of observations by fitting a generalized linear mixed effects model with random intercepts for each hospital. The estimates were derived from non-parametric penalized quasi-likelihood. The interpretation of the fixed coefficient of interest can be described as the overall relative risk of any given outcome comparing young to old and then comparing young females to young males. To understand the effect of unmeasured confounding by hospitals, we also conducted a sensitivity analysis with dummy variables for each hospital.

Effect measure modification by diabetes, hypertension, current tobacco smoking, type of MI, and PCI were examined by stratification and interaction terms with age and sex. The stratified coefficients of interest can be interpreted as the relative risk of in-hospital MACE comparing young vs old, and young females vs young males within that stratum. Wald test p-values from the interaction term in the full sample size were reported. For all data analyses, alpha was set at the 0.05 level. Analyses were conducted using R v.3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata/IC v.15.0 (StataCorp LLC). Mixed effects models were fitted using the 'nlme' R package and 'glmmpql' function.

3. Results

3.1. Baseline characteristics

Table 1 demonstrates the baseline characteristics of the study population stratified by age. Out of 21,374 AMI patients in the ACS QUIK trial, 4762 (22.2%) were young (≤50 years old) with a male predominance of 87%. Young patients were less likely to have hypertension (33.8% vs 50.8%; $p < 0.001$) and diabetes mellitus (35.7% vs 46.9%; $p < 0.001$) but more likely to be tobacco smokers (41.9% vs 27.8%; $p < 0.001$) and have higher low-density lipoprotein cholesterol (LCL-C) levels (130 ± 41 vs 120 ± 41 mg/dL; $p = 0.001$) compared to older patients. They were also more likely to present with STEMI (73.0% vs 61.5%; $p < 0.001$) but had shorter symptom-to-door time (median [IQR], 220 [110–738] vs 255 [120–855] min; $p < 0.001$).

3.2. Young vs. old patients with AMI

3.2.1. In-hospital and on-discharge management

Table 2 demonstrates a comparison of in-hospital medical and reperfusion therapy along with discharge medications in ACS QUIK

Table 1
Baseline characteristics of ACS QUIK patients stratified by age.

	Total	Young (Age ≤50)	Older (Age >50)	P-value
	(n = 21, 374)	(n = 4762)	(n = 16, 612)	
Baseline Characteristics				
Age, mean (SD)	60 (12)	44 (5)	65 (9)	<0.001
Male, No (%)	16,183 (75.7%)	4148 (87.1%)	12,035 (72.4%)	<0.001
Transferred from another facility, No. (%)	8401 (39.3%)	2022 (42.5%)	6379 (38.4%)	<0.001
No insurance, No. (%)	15,542 (72.7%)	3363 (70.6%)	12,179 (73.3%)	<0.001
ST-elevation myocardial infarction, No. (%)	13,689 (64.0%)	3478 (73.0%)	10,211 (61.5%)	<0.001
Symptom-to-door time, median [IQR], min	246 [118–830.5] (n = 20,560)	220 [110–738] (n = 4590)	255 [120–855] (n = 15,970)	<0.001
Body weight, mean (SD), kg	63.0 (10.0)	66 (10)	63 (10)	<0.001
Systolic blood pressure, mean (SD), mm Hg	139 (29)	135 (26)	139 (30)	<0.001
Heart rate, mean (SD),/min	80 (19)	80 (17)	80 (19)	0.14
Initial troponin, median [IQR], ng/mL	1.32 [0.29–5.82] (n = 9049)	1.66 [0.321–7.69] (n = 1819)	1.25 [0.28–5.48] (n = 7230)	<0.001
Low-density lipoprotein cholesterol, mean (SD), mg/dL	123 (41) (n = 14,830)	130 (41) (n = 3312)	120 (41) (n = 11,518)	<0.001
Triglycerides, median [IQR], mg/dL	121 [90–165] (n = 14,860)	137 [99–191] (n = 3327)	117 [87–158] (n = 11,533)	<0.001
Serum creatinine, median [IQR], mg/dL	1.0 [0.9–1.2] (n = 13,835)	1.0 [0.8–1.11] (n = 3061)	1.04 [0.9–1.3] (n = 10,774)	<0.001
Fasting glucose, median [IQR], mg/dL	127 [102–176] (n = 13,398)	122 [99–171] (n = 2922)	129 [103–177] (n = 10,476)	<0.001
Hemoglobin, mean (SD), mg/dL	13 (2) (n = 20,842)	14 (2) (n = 4642)	13 (2) (n = 16,200)	<0.001
Killip class I	18,459 (86.4%)	4320 (90.7%)	14,139 (85.1%)	<0.001
Risk factors, n (%)				
Hypertension	10,042 (47.0%)	1609 (33.8%)	8433 (50.8%)	<0.001
Diabetes mellitus	9484 (44.4%)	1701 (35.7%)	7783 (46.9%)	<0.001
History of tobacco use, No. (%)	6614 (30.9%)	1995 (41.9%)	4619 (27.8%)	<0.001
PAD	211 (1.0%)	22 (0.5%)	189 (1.1%)	<0.001
History of stroke	470 (2.2%)	45 (0.9%)	425 (2.6%)	<0.001
Hospital type				
Government (n = 9)	7133 (33.4%)	1758 (36.9%)	5375 (32.4%)	<0.001
Non-profit/Charity (n = 12)	5749 (26.9%)	1168 (24.5%)	4581 (27.6%)	
Private (n = 42)	8492 (39.7%)	1836 (38.6%)	6656 (40.1%)	
Hospital size				
Extra large (>1000) (n = 5)	3560 (16.7%)	826 (17.3%)	2734 (16.5%)	<0.001
Large (501–1000) (n = 15)	8523 (39.9%)	1897 (39.8%)	6626 (39.9%)	
Medium (201–500) (n = 24)	7415 (34.7%)	1702 (35.7%)	5713 (34.4%)	
Small (≤200) (n = 19)	1876 (8.8%)	337 (7.1%)	1539 (9.3%)	
Presence of onsite Cath lab				
Installed During Study (n = 3)	496 (2.3%)	145 (3.0%)	351 (2.1%)	<0.001
No (n = 17)	3552 (16.6%)	754 (15.8%)	2798 (16.8%)	
Yes (n = 43)	17,326 (81.1%)	3863 (81.1%)	13,463 (81.0%)	

patients stratified by age. There were no significant differences in the rates of in-hospital medication use between younger and older patients. Younger patients, however, were more likely to be discharged on beta-blockers (70.5% vs 64.8%; p < 0.001). Compared to older patients with AMI, young patients were more likely to undergo diagnostic coronary angiography (66.3% vs 57.3%; p < 0.001) and PCI during hospitalization (57.5% vs 47.0%; p < 0.001); however, no difference was noted amongst STEMI patients. Younger patients with STEMI had shorter median door-to-balloon time (median [IQR], 80 [55–165] vs 85 [59–205] min; p < 0.001) when compared to their older counterparts.

3.2.2. Outcomes

Table 3 presents in-hospital and 30-day outcomes in ACS-QUIK patients stratified by age. The adjusted relative risk (RR) of in-hospital and 30-day MACE outcomes were lower for younger patients compared to older at 0.49 (95% CI: 0.40–0.61, p < 0.001) and 0.54 (95% CI 0.46–0.64, p < 0.001), respectively. Younger patients were 54% less likely to experience in-hospital death (adjusted RR 0.46, 95% CI, 0.46–0.59, p < 0.001), 50% less likely to receive blood transfusions (adjusted RR 0.50, 95% CI, 0.33–0.76, p < 0.001), and 29% less likely to develop in-hospital heart failure (adjusted RR 0.71, 95% CI, 0.62–0.80, p < 0.001) compared to older patients. Except for reinfarction and major bleeding, the general trends for in-hospital and 30-day outcomes for younger patients were better than their older counterparts. Subgroup analyses consistently showed worse MACE in older compared to younger patients within the strata of diabetes, hypertension and smoking. Among patients with NSTEMI, older patients had also worse outcomes compared to younger patients (76% lower MACE amongst young patients; 95% CI, 88%–53%, p for interaction = 0.039).

3.3. Young females vs. young males

Out of 4762 young ACS QUIK patients (≤50 years old), 614 (12.9%) were women. Mean age was approximately 45 years and similar between the two groups (Supplemental Table 1). Young women were more likely to have hypertension (47.7% vs 31.7%; p < 0.001) and diabetes mellitus (51.3% vs 33.4%; p < 0.001) but less likely to be tobacco smokers (3.9% vs 47.5%; p < 0.001) compared to young men (Table 4). Additionally, young women were less likely to present with STEMI (64.3% vs 74.3%; p < 0.001) and had longer door-to-balloon time (median [IQR]: 90 [60–245] vs 76 [55–158] min; p = 0.002). Compared to their male counterparts, young

Table 2
In-hospital and on-discharge treatment patterns ACS QUIK patients stratified by age.

	No./Total No. (%)			P-value
	Total	Young (Age ≤50)	Older (Age >50)	
	(n = 21, 374)	(n = 4762)	(n = 16, 612)	
Medications				
Prehospital aspirin	3796/21,352 (17.8%)	800/4758 (16.8%)	2996/16,594 (18.1%)	0.050
In-hospital aspirin	20,885/21,328 (97.9%)	16,194/4759 (97.7%)	16,194/16,569 (97.7%)	<0.001
In-hospital second antiplatelet	20,973/21,347 (98.2%)	16,288/4760 (98.2%)	16,288/16,587 (98.2%)	0.32
In-hospital β-blocker	8314/20,759 (40.1%)	6363/4688 (39.6%)	6363/16,071 (39.6%)	0.013
In-hospital anticoagulant	18,256/21,332 (85.6%)	14,202/4758 (85.7%)	14,202/16,574 (85.7%)	0.40
Studies and procedures				
Echocardiography	19,725 (92.3%)	4392/4762 (92.2%)	15,333/16,612 (92.3%)	0.88
Diagnostic angiography	12,681 (59.3%)	3156/4762 (66.3%)	9525/16,612 (57.3%)	<0.001
PCI	10,553 (49.4%)	2738/4762 (57.5%)	7815/16,612 (47.0%)	<0.001
Primary PCI (STEMI)	6710/13,689 (49.0%)	1753/3478 (50.4%)	4957/10,211 (48.5%)	0.059
Door-to-balloon time (STEMI), median [IQR], min	83 [57–190] (n = 9462)	80 (55–165) (n = 2448)	85 (59–205) (n = 7014)	<0.001
Thrombolysis (STEMI)	3167/13,689 (23.1%)	845/3478 (24.3%)	2322/10,211 (22.7%)	0.063
Door-to-needle time (STEMI), median [IQR], min	44 [30–70] (n = 2888)	43 (29–69) (n = 773)	45 (30–70) (n = 2115)	0.31
Any reperfusion (STEMI)	9872/13,689 (72.1%)	2598/3478 (74.7%)	7274/10,211 (71.2%)	<0.001
Rescue PCI	1675/13,659 (12.3%)	456/3474 (13.1%)	1219/10,185 (12.0%)	0.077
Discharge treatment and counseling				
Discharge aspirin	19,137/19,557 (97.9%)	4373/4432 (98.7%)	14,764/15,125 (97.6%)	<0.001
Discharge Second anti-platelet agent	19,201/19,591 (98.0%)	4339/4434 (97.9%)	14,862/15,157 (98.1%)	0.43
Discharge β-blocker	12,607/19,072 (66.1%)	3090/4383 (70.5%)	9517/14,689 (64.8%)	<0.001
Discharge statin	18,989/19,585 (97.0%)	4287/4434 (96.7%)	14,702/15,151 (97.0%)	0.23
Discharge ACE inhibitor or ARB	9232/19,193 (48.1%)	2202/4384 (50.2%)	7030/14,809 (47.5%)	0.001
Cardiac rehabilitation referral	5684/20,019 (28.4%)	1273/4553 (28.0%)	4411/15,466 (28.5%)	0.47

Table 3
Risk of adverse clinical outcomes among very young ACS patients stratified by age.

	No./Total No. (%)		Unadjusted RR (95% CI)	P-value	Adjusted* RR (95% CI)	P-value
	Young (Age ≤50) (n = 4762)	Older (Age >50) (n = 16, 612)				
In-hospital Outcomes						
MACE	91 (1.9%)	744 (4.5%)	0.43 (0.34–0.53)	<0.001	0.49 (0.40–0.61)	<0.001
Death	66 (1.4%)	586 (3.5%)	0.39 (0.30–0.51)	<0.001	0.46 (0.36–0.59)	<0.001
Reinfarction	27 (0.6%)	140 (0.8%)	0.67 (0.45–1.02)	0.059	0.71 (0.51–1.00)	0.05
Blood transfusion	21 (0.4%)	214 (1.3%)	0.34 (0.22–0.54)	<0.001	0.50 (0.33–0.76)	<0.001
Stroke	9 (0.2%)	84 (0.5%)	0.37 (0.19–0.74)	0.005	0.45 (0.25–0.84)	0.01
Heart failure	216 (4.5%)	1249 (7.5%)	0.60 (0.52–0.70)	<0.001	0.71 (0.62–0.80)	<0.001
Cardiac arrest	78 (1.6%)	579 (3.5%)	0.47 (0.37–0.60)	<0.001	0.53 (0.42–0.66)	<0.001
Major bleeding	3 (0.1%)	24 (0.1%)	0.44 (0.13–1.45)	0.175	0.48 (0.14–1.65)	0.24
30-day Outcomes						
MACE	147 (3.1%)	1100 (6.7%)	0.47 (0.39–0.55)	<0.001	0.54 (0.46–0.64)	<0.001
Death	96 (2.0%)	858 (5.2%)	0.39 (0.32–0.48)	<0.001	0.46 (0.38–0.56)	<0.001
CVD death	94 (2.0%)	834 (5.1%)	0.39 (0.32–0.49)	<0.001	0.46 (0.38–0.57)	<0.001
Reinfarction	44 (0.9%)	212 (1.3%)	0.72 (0.52–1.00)	0.051	0.78 (0.58–1.04)	0.095

RR = Relative risk from multivariate regression, multi-level analysis for women compared to men.
MACE included a composite of death, reinfarction, major bleeding and stroke.
Models adjusted for sex, smoking, diabetes, hypertension, cardiac status (STEMI vs. NSTEMI), and PCI with random intercepts for centers.
Abbreviation: MACE, major adverse cardiac endpoint; CVD, cardiovascular disease.

women were less likely to undergo diagnostic coronary angiography (60.9% vs 67.1% of men, p = 0.003) and PCI during hospitalization (49.8% vs 58.6%, p < 0.001). There were no significant differences in the rates of in-hospital and discharge medications between young men and women. The use of in-hospital and discharge aspirin, adjuvant antiplatelet therapy and discharge statin prescriptions were >95% (Supplemental Table 2).

The adjusted RR of in-hospital and 30-day MACE outcomes were higher for young women compared to men at 1.60 (95% CI 1.0–2.45, p = 0.048) and 1.16 (95% CI 0.77–1.76, p = 0.473), respectively (Table 4). Young women were more likely to experience in-hospital death (adjusted RR 1.90, 95% CI, 1.15–3.10, p = 0.012) and develop incident heart failure (adjusted RR 1.21, 95% CI, 1.04–1.41, p = 0.016). Except for reinfarction and stroke, the general trends for in-hospital and 30-day outcomes for young women were worse than men, although not all these effects were statistically significant (Supplemental Table 3). There was no significant interaction of sex and in-hospital MACE for risk factors such as diabetes, hypertension, smoking, or presentation with STEMI or receipt of PCI during hospitalization (Supplemental Fig. 1).

4. Discussion

In this secondary analysis of the ACS QUIK randomized clinical trial, younger patients (≤50 years of age) presenting with AMI were more likely to receive guideline-directed therapies and to undergo

Table 4
Baseline characteristics, management modalities, and clinical outcomes of ACS QUIK young patients (Age ≤50) stratified by sex.

	Total (n = 4762)	Females (n = 614)	Males (n = 4148)	P-value
Baseline Characteristics				
STEMI, No. (%)	3478 (73.0%)	395 (64.3%)	3083 (74.3%)	<0.001
Symptom-to-door time, median [IQR], min	220 (110–738) (n = 4590)	250 [115–840] (n = 593)	214 [110–720] (n = 3997)	0.100
Initial troponin, median [IQR], ng/mL	1.66 (0.321–7.69) (n = 1819)	1.01 [0.195–4.155] (n = 252)	1.79 (0.37–8.24) (n = 1567)	<0.001
Fasting glucose, median [IQR], mg/dL	122 (99–171) (n = 2922)	140 (104–199) (n = 369)	120 (98–168) (n = 2553)	<0.001
Hypertension	1609 (33.8%)	293 (47.7%)	1316 (31.7%)	<0.001
Diabetes mellitus	1701 (35.7%)	315 (51.3%)	1386 (33.4%)	<0.001
History of tobacco use, No. (%)	1995 (41.9%)	24 (3.9%)	1971 (47.5%)	<0.001
Studies and procedures				
Diagnostic angiography	3156/4762 (66.3%)	374 (60.9%)	2782 (67.1%)	0.003
PCI	2738/4762 (57.5%)	306 (49.8%)	2432 (58.6%)	<0.001
Primary PCI (STEMI)	1753/3478 (50.4%)	192/395 (48.6%)	1561/3083 (50.6%)	0.45
Door-to-balloon time (STEMI), median [IQR], min	80 (55–165) (n = 2448)	90 (60–245) (n = 275)	76 (55–158) (n = 2173)	0.002
Thrombolysis (STEMI)	845/3478 (24.3%)	86/395 (21.8%)	759/3083 (24.6%)	0.24
Door-to-needle time (STEMI), median [IQR], min	43 (29–69) (n = 773)	50 (30–75) (n = 85)	41 (29–66) (n = 688)	0.11
Any reperfusion (STEMI)	2598/3478 (74.7%)	278/395 (70.4%)	2320/3083 (75.3%)	0.042
Rescue PCI	456/3474 (13.1%)	37/395 (9.4%)	419/3079 (13.6%)	0.018
Outcomes	No. (%) Females (n = 614)	Males (n = 4148)	Adjusted* RR (95% CI)	P-value
In-hospital MACE	19 (3.1%)	72 (1.7%)	1.60 (1.00–2.54)	0.048
In-hospital death	16 (2.6%)	50 (1.2%)	1.90 (1.15–3.10)	0.012
In-hospital heart failure	42 (6.8%)	174 (4.2%)	1.21 (1.04–1.41)	0.016
30-day MACE	25 (4.1%)	122 (2.9%)	1.16 (0.77–1.76)	0.473
30-day CVD death	18 (2.9%)	76 (1.8%)	1.34 (0.84–2.16)	0.223

RR = Relative risk from multivariate regression, multi-level analysis for women compared to men.
MACE included a composite of death, reinfarction, major bleeding and stroke.
Models adjusted for smoking, diabetes, hypertension, cardiac status (STEMI vs. NSTEMI), and PCI with random intercepts for centers.
Abbreviation: MACE, major adverse cardiac endpoint; CVD, cardiovascular disease.

diagnostic angiography and PCI compared to older patients. After adjustment for risk factors, younger patients had a lower likelihood of in-hospital and 30-day MACE. Subgroup analysis comparing young males with females revealed a striking higher burden of CVD risk factors among young women except for smoking. Moreover, young women were less likely to undergo diagnostic angiography and PCI compared to young men and had higher rates of in-hospital MACE and death.

4.1. Young vs. old patients with AMI

Despite successful public health efforts in decreasing the incidence of ischemic heart disease (IHD) since the 1960s in high-income countries (HICs), IHD continues to exert a significant toll in LMICs, with over half of all IHD deaths occurring in LMICs [3]. Interestingly, MI rates in the young have not decreased compared to older patients due to underestimation of CVD risk factors like familial hypercholesteremia, the dramatic increase in CVD risk factors such as obesity, and the presence of non-traditional risk factors, including drug use [13]. Collectively, these factors may contribute to an overall delay in the prevention and optimal treatment of CVD among young patients.

Prior studies from India have focused on extremes of young age (<40 years) or have been limited by modest sample size [4,5]. Similar to previous reports from HICs and LMICs, cigarette smoking was the most prevalent risk factor among younger AMI patients [4,14–17]. Prior reports from Indian states of Uttar Pradesh [4] and Bengaluru [17] have reported a prevalence of smoking as high as 78% among younger patients presenting with AMI. However, the prevalence of smoking in our cohort was less than previously reported (30.9% for the entire cohort). The prevalence of hypertension and diabetes amongst younger patients with AMI were similar to the INTERHEART study South Asian cohort (around 35%) [18]. Consistent with previous reports, younger patients were more likely to present with STEMI and less likely to exhibit heart failure symptoms as reflected in lower Killip score on presentation [14]. This could be explained by delayed presentation in older individuals due to altered pain thresholds, more advanced coronary disease, associated comorbidities, and/or limited access to transportation or medical insurance [19]. Additionally, patients with STEMI (younger in our case) are more likely to present with symptoms typical of ischemia compared to NSTEMI, prompting an earlier visit to the hospital [19].

Similar to prior reports, our study demonstrates better short and intermediate outcomes amongst younger patients with AMI compared to older patients, even after adjustment for potential confounders [14,19,20]. The rate of in-hospital and discharge use of aspirin, dual antiplatelet therapy, and a statin was high (≥95%) and similar in both young and older patients. Younger patients, however, were more likely to be discharged on a beta-blocker, likely due to the lower prevalence of acute heart failure signs on presentation compared with older adults [4,21]. Younger patients with AMI were more likely to undergo diagnostic angiography, PCI, and primary PCI (although not statistically significant), compared to older patients. It should also be noted that the rate of utilization of primary PCI amongst STEMI patients was low in both groups (≤50%), which could be explained by the limited number of around the clock PCI-capable hospitals in India [14].

4.2. Young females vs. young males

Most studies investigating ACS in young women have been from HICs with limited studies from LMICs. While there are several studies in India investigating sex disparities in ACS management

and outcomes, to our knowledge, this is the first report to explore disparities affecting young women in India. Similar to our current study, Nazzal et al. [22] demonstrated that young women (≤45 years of age) in Chile were more likely to have CVD risk factors (hypertension and diabetes), and had worse in-hospital mortality, compared to young men. In contrast to our study, young women in Chile were less likely to receive guideline-directed medical therapies (beta-blockers, aspirin, and statins), compared to young men. A study of 31,620 patients (2033 women) with ACS from 7 Arabian Gulf registries found that young women were less likely to undergo revascularization and had a higher risk of in-hospital mortality compared to young men, which is also consistent with our study results [23]. Our previous study on sex disparities using the ACS QUIK database showed significant differences in in-hospital (1.53; 95% CI 1.32–1.77; $p < 0.001$) and 30-day MACE outcomes (1.39; 95% CI 1.23–1.57, $p < 0.001$) between men and women overall [12]. Conversely, the CREATE [24] and DEMAT [25] studies from India showed similar 30-day mortality between men and women with ACS, although the investigators did not stratify outcome by age. Similarly, studies from HICs have demonstrated sex-based disparities in ACS care in younger patients. The VIRGO study, which enrolled 3501 ACS patients from the US and Spain (67% women), showed that young women (≤55 years of age) with ACS had more cardiovascular risk factors and comorbidities, were less likely to receive reperfusion therapy, and were more likely to experience delays to timely reperfusion compared to younger men [26]. Previous US-based studies have demonstrated sex disparities in ACS care, with younger women having worse short and intermediate outcomes compared to their male counterparts [27–29].

The causes of the sex disparities observed in young adults with AMI in this secondary analysis are not clear. Differences in the pathophysiological mechanisms of ACS could potentially contribute to the worse outcomes observed in younger women compared to younger men [25]. The underlying pathophysiologic mechanisms of ACS in younger women with ACS is more likely to be related to microvascular dysfunction, spontaneous coronary artery dissection, vasospasm, stress-related (Takotsubo) cardiomyopathy, and plaque erosion rather than plaque rupture, which is more typically seen in men [25,30,31]. Young women have a more-varied pathophysiology of ACS and a better understanding of these differences could mitigate the greater risks and outcomes observed in young women. Implicit biases may also contribute to disparities seen in the diagnosis, treatment, and outcomes of young women with CVD. A series of studies conducted by Chiaramonte et al. [32] found that when CVD symptoms were presented in the context of a stressful life event, women were more likely to be diagnosed with a psychogenic disorder as compared to men who were more likely to be diagnosed with an organic etiology.

Recent studies also illustrate the role of gender bias in that patients with feminine traits of personality rather than female sex are less likely to receive timely primary cutaneous intervention and invasive procedures than those with masculine traits of personality [33]. In our study, younger women had longer door-to-balloon times and were less likely to undergo diagnostic angiography or PCI compared to younger men but received evidence-based in-hospital and discharge pharmacological treatments at similar rates as young men.

4.3. Limitations

This study has a number of limitations. First, the symptoms of presentation, other modifiable risk factors (such as body mass index, history of hyperlipidemia) and non-modifiable risk factors, such family history of IHD and familial hypercholesteremia were not collected. Additionally, data on preadmission medications and angiographic findings were not available. Secondly, because the dataset was restricted to patients below 50 years of age, controlling for age provided very little that can be added beyond fine differences in years among the young cohort. Furthermore, there were many fewer young women vs young men in this ACS cohort, which reduced statistical power for the interaction analyses. Third, controlling for tobacco smoking was not optimal as we could not obtain long-term use. If smoking in India is highly prevalent among men and smoking is associated with adverse cardiovascular events, then residual confounding by smoking may have attenuated the observed relationship. Other individual information such as educational attainment and socio-economic factors were not collected. However, in a sensitivity analysis with fixed effects for hospitals, we did not find appreciable effects of unmeasured confounders that could be associated with clustering by hospital. Still, this may not account for the protective effect of individual education. Finally, the low event rates of significant in-hospital bleeding may impact the interpretation of results in young female's vs males.

5. Conclusion

To date, this is one of the largest reports investigating the clinical characteristics and cardiovascular outcomes of AMI in a young South Asian population. Young patients with AMI had a higher burden of modifiable risk factors (smoking), more likely to undergo diagnostic angiography, and receive reperfusion therapy, compared to older individuals. After adjustment for potential confounders, younger patients had a lower likelihood of in-hospital and 30-day MACE. Subgroup analysis comparing young males with females revealed a significantly higher burden of CVD risk factors among young women except for smoking. Moreover, young women were less likely to undergo diagnostic angiography and PCI compared with young men and had higher rates of in-hospital MACE and death. These observations suggest the need for implementing aggressive primary and secondary prevention strategies in both young and older patients in LMICs. Future studies evaluating the causes of and strategies to mitigate sex and gender disparities among young women with AMI in LMIC are needed.

Funding disclosure

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.athplu.2022.08.003.

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