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ORIGINAL ARTICLE

Acute ST-Elevation Myocardial Infarction in the Young Compared With Older Patients in the Tamil Nadu STEMI Program

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Objective To compare the clinical presentation, risk factors and outcomes of young patients (≤45 years) presenting with ST segment-elevation myocardial infarction (STEMI) with older STEMI patients in the Tamil Nadu STEMI program (TN-STEMI).

Methods A total of 2,420 patients were enrolled in the TN-STEMI program, which is a pre-implementation and post-implementation quality of care study. The cohort of patients was divided into young STEMI patients (≤45 years) and compared with those aged >45 years.

Results A total of 591(24.4%) patients in this cohort were aged ≤45 years; 92.5% of the young STEMI were males. Smoking was the most common risk factor and its use was significantly more in younger myocardial infarction (MI) patients than in older patients (57% vs 31%; p<0.001). Compared with their older counterparts, younger patients had a lower prevalence of hypertension (14.2% vs 28.3%; p<0.001) and diabetes mellitus (13.2% vs 29.7%; p<0.001). Total ischaemic time was shorter for younger patients (235 vs 255 mins; p=0.03). Young STEMI patients more frequently presented with single vessel disease and the left anterior descending coronary artery was the most common infarct-related artery; they also had a higher thrombus load. Young MI patients had reduced mortality, both in-hospital (3.4% vs 6.4%; p=0.005) and at one year (7.6% vs 17.6%; p<0.001). Younger male STEMI patients also showed lower mortality than younger female patients.

Conclusions Young STEMI patients compared with older STEMI patients had lower prevalence of traditional risk factors, shorter ischaemic time and reduced mortality. Young female STEMI patients had higher mortality than young male STEMI patients.

Introduction

Coronary artery disease (CAD) has assumed epidemic proportions in India and is the largest contributor towards premature mortality and loss of disability-adjusted life years (DALYs) [1]. The INTERHEART study, a large international case-control study across 52 countries, reported that the median age of myocardial infarction (MI) in South Asians

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was 52 years compared with 62 years in the European origin cohort [2]. Similar information has been noted in many other reports from India [3]. The clinical presentation of CAD in younger patients is different from that in older patients: younger patients do not tend to experience angina, an unstable coronary syndrome progresses rapidly to MI and it is the first manifestation of CAD in most cases [4,5]. This early age of presentation coupled with the higher incidence of ST-segment elevation myocardial infarction (STEMI) in the Indian population results in an extremely high economic, social and societal cost [6].

Young patients presenting with STEMI are an important and challenging subset. The age cut-off has traditionally been defined as MI occurring in patients aged ≤45 years, although different age definitions have been used by other studies [4,7,8]. In addition, in-hospital care delivery has been found to be worse for young women compared with men [8]. The current study assessed the prevalence of young patients in a well phenotyped and characterised STEMI population in India (Tamil Nadu, ST-segment elevation myocardial infarction [TN-STEMI] Program). It sought to discuss their risk profile and outcomes [9] and possible reasons for their premature presentations.

Methods

Study Cohort

Details of the TN-STEMI Program have previously been elaborated [9]. Briefly, this was a multicentre program that was run in the state of Tamil Nadu in South India to improve the reperfusion rates in STEMI patients and increase patient access to the superior reperfusion modalities of primary percutaneous coronary intervention (PCI) and pharmacoinvasive treatment (PIT). Four (4) clusters were constructed, each with a hub hospital that was PCI capable and linked to multiple spoke hospitals. Patients presenting to the hub hospitals underwent primary PCI. The spoke hospitals thrombolysed patients and were then encouraged to transfer patients in a timely fashion to the hub hospital for PIT. There were four hub hospitals connected to 35 spoke hospitals.

There were 2,420 patients enrolled between 2012 and 2014 in this pre-implementation and post-implementation quality of care study in the TN-STEMI Program. There were 898 patients in the pre-implementation phase and 1,522 patients in the post-implementation phase. A total of 1,028 patients received fibrinolytic therapy alone, 424 received PIT, 815 underwent direct primary PCI, and 153 patients received no reperfusion. The data from all four clusters, pre-implementation and post-implementation, were combined for this analysis.

Core Laboratory Evaluation

All angiographic analyses were performed in a core laboratory, which was blinded to the clinical presentation and age of the patients. Within the total cohort, 1,062 patients underwent coronary angiograms; this included 385 patients who had PIT and 677 patients who underwent primary PCI. The culprit vessel involvement and number of vessels with significant stenosis was assessed on the total group who underwent angiography. Thrombus grade assessment was performed on the pre-angioplasty angiogram of the patients who underwent primary PCI only. Epicardial coronary flow was assessed using the thrombolysis in myocardial infarction (TIMI) flow grade and the thrombus grading was performed using the TIMI thrombus grading scale [10]. The clinical events reported in this study included all-cause mortality, re-infarction, ischaemic stroke, haemorrhagic stroke, major bleed, minor bleed, angina, or any cardiac symptoms requiring hospitalisation and repeat revascularisations. The major cardio and cerebra-vascular event (MACCE) rate has been reported as a composite of death, re-infarction and stroke. The reported follow-up of the patients was at three stages: in-hospital, 30 days and 1 year. The definitions of the above-mentioned outcomes are provided in Supplementary Appendix A and B [11–14].

Statistical Analysis

Data from all four clusters were combined for analysis. Continuous variables were summarised using mean and standard deviation (SD). Timing intervals were described in median and interquartile ranges (IQR). Categorical variables were expressed in numbers and percentages. Comparisons between two means were tested using two-tailed, unpaired *t*-tests. Timing intervals were compared with Mann-Whitney test and categorical variables were compared using the Chi-squared test. Statistical significance was set at a two-tailed $p<0.05$. All statistical analyses were performed using SPSS statistical software version 25 (IBM Corp., Armonk, NY, USA).

Results

Overall, 591(24.4%) patients in this cohort were aged ≤45 years. Baseline characteristics of the study population are reported in Tables 1 and 2. Men were more likely to be younger than 45 years at the time of presentation than women. Smoking was the most common risk factor and its use was significantly more in younger MI patients than in older patients (57% vs 31%; $p<0.001$). Compared with their older counterparts, younger patients tended to have a lower prevalence of hypertension (14.2% vs 28.3%; $p<0.001$) and diabetes mellitus (13.2% vs 29.7%; $p<0.001$). There were also sex-based differences in the younger patients: young females were more often diabetic (12.1% vs 27.3%; $p<0.009$) and hypertensive (13.1% vs 27.3%; $p=0.02$) compared with their male counterparts. In contrast, smoking was more commonly seen in young males.

Key process measures are shown in Tables 3 and 4. Total ischaemic time was shorter for younger patients (235 vs 255 mins; $p=0.03$). The symptom to first medical contact was also numerically lower (165 vs 176 mins; $p=0.1$), although not statistically significant. Other metrics such as door-to-balloon

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Table 1 Baseline characteristics of the 2,420 patients in the study.

	Total Patients n=2,420	≤45 yr n=591	>45 yr n=1,829	P-value
Age, mean (SD), yr	54.7 (12.1)	39.2 (5.2)	59.7 (9.1)	<0.001
Female (%)	386 (16.0)	44 (7.5)	342 (18.7)	<0.001
Diabetes (%)	621 (25.6)	78 (13.2)	543 (29.7)	<0.001
Hypertension (%)	601 (24.8)	84 (14.2)	517 (28.3)	<0.001
Dyslipidaemia (%)	59 (2.4)	15 (2.5)	44 (2.4)	0.9
Current smoker (%)	972 (40.2)	336 (57.0)	636 (35.0)	<0.001
Prior PCI (%)	23 (1.0)	7 (1.2)	16 (0.9)	0.5
Prior CABG (%)	6 (0.2)	0 (0.0)	6 (0.3)	0.4

Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Table 2 Baseline characteristics of young male vs female patients in the study.

Young MI	Male n=547	Female n=44	P-value
Age, mean (SD), yr	39.1 (5.3)	40.7 (4.0)	0.06
Diabetes (%)	66 (12.1)	12 (27.3)	0.009
Hypertension (%)	72 (13.1)	12 (27.3)	0.02
Dyslipidaemia (%)	14 (2.6)	1 (2.3)	1.00
Current smoker (%)	336 (61.4)	0	<0.001
Prior PCI (%)	7 (1.3)	0	1.00

Abbreviations: PCI, percutaneous coronary intervention; MI, myocardial infarction.

Table 3 Process measure differences between STEMI patients aged ≤45 years and >45 years.

Metric	≤45 yr n=591	>45 yr n=1,829	P-value
Time from symptom onset to first medical contact, median (IQR), min[a]	165 (214)	176 (220)	0.1
Door-to-balloon time for Primary PCI, median (IQR), min[b]	107.5 (89)	109.5 (68)	0.5
Total ischaemic time, median (IQR), min[c]	235 (265)	255 (255)	**0.03**
Time from fibrinolysis to PCI, median (IQR), min[d]	943 (1,190)	1,115 (1,400)	0.4

Bold values are statistically significant.

Abbreviations: STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; IQR, interquartile range.

[a]There were 536 patients in the ≤45 years and 1,703 in the >45 years.

[b]There were 172 patients in the ≤45 years and 666 in the >45 years.

[c]There were 505 patients in the ≤45 years and 1,539 in the >45 years.

[d]There were 51 patients in the ≤45 years and 164 in the >45 years.

Table 4 Measure differences between ST-elevation myocardial infarction (STEMI) patients aged ≤45 yr – male vs females.

Young MI	Male n=547	Female n=44	P-value
Door-to-balloon time for primary PCI, median (IQR), min[a]	106 (90)	116 (89)	0.7
Time from symptom onset to first medical contact, median (IQR), min[b]	155 (201)	228 (349)	0.09
Total ischaemic time, median (IQR), min[c]	230 (260)	285 (320)	0.4
Time from fibrinolysis to PCI, median (IQR) min[d]	923 (1,194)	1,557	0.2

[a]There were 167 patients in the male and four in the female.

[b]There were 494 patients in the male and 42 in the female.

[c]There were 466 patients in the male and 39 in the female.

[d]There were 49 patients in the male and two in the female.

time (D2B) and fibrinolytic use to PCI (for patients receiving PIT) were similar between the two groups. Symptom to first medical contact was longer for young female STEMI patients compared with young male STEMI patients, although it did not reach statistical significance (228 vs 155 mins; p=0.09). All other key process measures were numerically longer for females compared with males.

Core lab analysis of the angiograms of patients who had coronary angiography (1,062 of 2,420 patients) is shown in Table 5. Young STEMI patients more frequently presented with single vessel disease compared with older STEMI patients (88.3% vs 70%; p<0.001) and the left anterior descending artery was the most common infarct-related artery (66.2% vs 54.8%; p<0.001). TIMI thrombus grade was evaluated for the 677 patients who presented to the hub hospitals for primary PCI. Moderate and large thrombus burden (indicated by TIMI thrombus Grade 3-5) were not

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Table 5 Angiographic data of STEMI patients aged ≤45 years and >45 years.

	≤45 yr n=249	>45 yr n=813	P-value
SVD (%)	220 (88.3)	599 (70.0)	**<0.001**
DVD (%)	16 (6.4)	98 (12.1)	**0.01**
TVD (%)	13 (5.2)	113 (13.9)	**<0.001**
LM (%)	0	3 (0.3)	0.6
Culprit vessel			
RCA (%)	68 (27.3)	263 (32.3)	0.1
LAD (%)	165 (66.2)	446 (54.8)	**<0.001**
LCX/RI (%)	16 (6.4)	101 (12.4)	**0.008**
LM (%)	0	3 (0.3)	0.6
Primary n=677	**≤45 yr n=137**	**>45 yr n=540**	**P-value**
Thrombus Grade 0–2 (%)	18 (13.1)	99 (18.3)	0.2
Thrombus Grade 3–5 (%)	119 (86.8)	441 (81.7)	
Post fibrinolysis n=385	**≤45 yr n=112**	**>45 yr n=273**	**P-value**
TIMI 0–2 (%)	60 (53.5)	189 (69.2)	**<0.001**
TIMI 3 (%)	52 (46.4)	84 (30.8)	
Post PCI n=869	**≤45 yr n=183**	**>45 yr n=686**	**P-value**
POST TIMI 0–2 (%)	13 (7)	82 (12)	0.06
POST TIMI 3 (%)	170 (93)	604 (88)	

Bold values are statistically significant.

Abbreviations: STEMI, ST-elevation myocardial infarction; SVD, single vessel disease; DVD, double vessel disease; TVD, triple vessel disease; LM, left main; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; RI, ramus intermedius; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

Table 6 Clinical outcomes between patients aged ≤45 years and >45 years.

Outcome	≤45 yr n=591	>45 yr n=1,829	P-value
Mortality			
In-hospital (%)	20 (3.4)	117 (6.4)	0.005
1 mo (%)	26 (4.3)	165 (9.0)	0.01
1 yr (%)	45 (7.6)	322 (17.6)	<0.001
In-hospital MACE			
Stroke (%)	2 (0.3)	5 (0.3)	0.7
Haemorrhage (%)	0	2 (0.1)	1
Minor and major bleeding (%)	1 (0.2)	16 (0.9)	0.07
Shock (%)	12 (2)	72 (3.9)	**0.02**
Ischaemia (%)	7 (1.2)	25 (1.3)	0.8
Others (%)	11 (1.8)	77 (4.2)	**0.007**
1-yr MACE			
Re-infarction (%)	7 (1.2)	22 (1.2)	1
Readmission (%)	75 (12.6)	218 (12.0)	0.7
Symptomatic ischaemia (%)	43 (7.3)	102 (5.6)	0.08
Stroke (%)	0	5 (0.3)	0.3
Cardiac failure (%)	5 (0.8)	6 (0.3)	0.2
Repeat Revascularisation (%)	12 (2.0)	36 (2.0)	1

Bold values are statistically significant.

Abbreviations: MACE, major adverse cardiac events.

different between the younger and older groups (86.8% vs 81.7%; p=0.2), although this did not reach statistically significant levels. Data from the thrombolytic group who were transferred for catheterisation also showed better post-fibrinolytic TIMI III flow in young patients (46.4% vs 30.8%; p<0.005).

The outcome data are shown in Tables 6 and 7. Young MI patients had reduced mortality, both in-hospital (3.4% vs 6.4%; p=0.005) and at one year (7.6% vs 17.6%; p<0.001). Younger male STEMI patients also showed lower mortality than younger female patients (in-hospital 3% vs 9.1%; p=0.05 and 1-year mortality 6.7% vs 18.2%; p=0.006). Table 8 provides a summary of published data of young MI patients.

Discussion

Several reports in the young STEMI patient population have been published in both Western [26–28] and Indian populations [18,21,29], with the latter suggesting a higher proportion of young patients compared with the former. In the current study, which included a contemporary population presenting STEMI in India, nearly a quarter of patients were aged ≤45 years. This is much higher than that published in earlier, mostly Western reports, of 4–10%. Like other reports, this appears to disproportionately affect men more than women. In the current study, young men had a higher prevalence of smoking but a significantly lower prevalence of diabetes and hypertension when compared with younger women. In addition, younger patients usually presented with single vessel disease, with the left anterior descending being the most common infarct-related artery. This is similar to previously published studies from India [18,21,29]. Results from this core laboratory analysis showed a higher thrombus load in younger patients, with better TIMI flow after fibrinolytic therapy. These are interesting findings and need to be validated; they could have implications for more aggressive management of thrombus in young MI patients and the utility of thrombolytics in young STEMI patients.

Both in-hospital and 1-year outcomes were significantly better for young STEMI patients compared with older STEMI patients. The prevalence of cardiogenic shock at presentation was also significantly lower in this group. The lower prevalence of diabetes, hypertension and multi-vessel disease in this group could partly explain the better prognosis. In

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Table 7 Clinical outcomes between patients aged ≤45 years – male and female.

Outcome	≤45 yr n=547	>45 yr n=44	P-value
Mortality			
In-hospital (%)	16 (3.0)	4 (9.1)	0.05
1 mo (%)	21 (4.0)	5 (11.4)	0.01
1 yr (%)	37 (6.7)	8 **(18.2)**	0.006
In-hospital MACE			
Stroke (%)	2 (0.4)	0	1
Haemorrhage (%)	0	0	-
Minor and major bleeding (%)	0	1 (2.3)	0.07
Shock (%)	12 (2.2)	0	1
Ischaemia (%)	6 (1.1)	1 (2.3)	0.4
Others (%)	9 (1.6)	0	0.2
1-yr MACE			
Re-infarction (%)	7 (1.3)	0	1
Readmission (%)	70 (12.8)	5 (11.4)	1
Symptomatic ischaemia (%)	40 (7.3)	3 (6.8)	1
Stroke (%)	0	0	-
Cardiac failure (%)	4 (0.7)	1 (2.3)	0.3
Repeat revascularisation (%)	12 (2.2)	0	1

Bold values are statistically significant.
Abbreviations: MACE, major adverse cardiac events.

addition, the total ischaemic time was lower in younger MI patients in this cohort. Delayed presentation to a reperfusion centre is very common in India and other low-middle income countries [30,31]; the reasons for this are many and include patient delays, delays in transportation and delays within hospitals. Younger patients, who do not expect to have cardiac illness or classical risk factors, tend to delay presenting to a hospital.

The increased percentage of young patients with STEMI in this population, coupled with the lack of traditional risk factors like diabetes and hypertension, is an area that requires detailed investigation. Multiple studies from India have shown that–unlike Western data, where about 60–70% of ACS patients present as NSTEMI [32,33]–about 60% of ACS in India present as STEMI [30]. This could reflect the disproportionately higher contribution of young MIs to the total STEMI cases. It may be interesting to study whether these two are in some way linked; there are two strands of evidence that could probably offer an explanation. First, it is well known that post-mortem studies in the Western population show that most STEMI patients show plaque rupture as the underlying cause for a thrombotic occlusion. In <25% of the cases it could be precipitated by plaque erosions and rarely by calcific nodules [34]. It has also been shown that in most NSTEMI patients, the underlying pathology is plaque erosion. Optical coherence tomography studies performed in

Table 8 Literature review of young MI cohorts.

Study	Number of Patients with young MI	Male (%)	DM (%)	HTN (%)	Smoking (%)	Dyslipidaemia (%)	SVD (%)	DVD (%)	TVD (%)	LM (%)	LAD (%)	LCX (%)	RCA (%)	In-Hospital Mortality (%)
Pandya et al. [15]	300	93.3	21.3	16.0	64.3	28.7	46.0	15.0	1.0	3.0	45.3	15.3	26.7	0.3
Sinha et al. [16]	1,116	95.1	17.2	20.5	78.5	21.2	71.5	16.1	6.6	3.2	-	-	-	2.0
Swain et al. [17]	150	85.3	15.3	26.7	65.3	9.3	68.6	22.6	8.6	0.2	-	-	-	-
Bhardwaj et al. [18]	124	99.2	8.1	44.3	58.8	33.1	51.3	27.3	6.3	0.9	62.4	17.6	20.0	1.6
Rajan et al. [19]	180	97.2	22.7	24.4	93.3	85.0	79.3	8.0	3.3	2.0	61.3	18.7	9.3	2.2
Shukla et al. [20]	787	93.5	9.5	12.1	39.1	25.1	44.7	9.7	4.4	-	-	-	-	0.4
Kumbhalkar et al. [21]	70	84.3	11.5	22.8	17.1		57.1	11.5	7.1	-	82.5	5.0	12.5	-
Kanitz et al. [22]	209	83.0	3.3	25.8	72.0	19.6	62.2	14.2	2.4	-	-	-	-	1.9
Jamil et al. [23]	148	92.6	20.9	29.7	67.6	22.3	81.7	14.9	3.4	-	48.0	17.6	18.2	-
Hoit et al. [4]	203	92.0	4.0	29.0	80.0	13.0	63.0	20.0	18.0	-	-	-	-	2.5
Agarwal et al. [24]	50	60.0	25.0	10.0	70.0	27.0	62.0	12.0	8.0	-	-	-	-	-
Sricharan et al. [25]	49	90.0	25.0	5.0	34.0	18.0	28.0	8.0	2.0	-	63.3	16.6	20.0	-
Current study	591	92.5	13.2	14.2	57.0	2.5	88.3	6.4	5.2	-	66.2	6.4	27.3	3.4

Abbreviations: MI, myocardial infarction; DM, diabetes mellitus; LM, left main; HTN, systemic hypertension; LAD, left anterior descending artery; SVD, single vessel disease; RCA, right coronary artery; DVD, double vessel disease; LCX, left circumflex; TVD, triple vessel disease.

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young MI patients, particularly smokers, have on the other hand shown plaque erosion in many of them [35]. Second, studies from India in young MI patients have also shown an increase in circulating pro-thrombotic factors, more so in heavy smokers [36]: lipoprotein a, fibrinogen, anti-thrombin III, plasminogen activator inhibitor I, tissue plasminogen activator, von Willebrand factor, and homocysteine.

It is possible that young STEMI patients in India, particularly heavy smokers, with plaque erosions, which in the Western population would typically present with sub-total occlusion and NSTEMI, would in the setting of a pro-thrombotic milieu present with thrombotic occlusion and STEMI. This hypothesis would require testing and optical coherence tomography studies together with measuring prothrombotic factors could help clarify this further. If this were the case, it could have a profound impact on the management of young STEMI patients–including the use of thrombolytics, stents and aggressive thrombus management during the acute event and in the long term–to prevent future thrombotic occlusion.

Another important observation in this study is the gender-based differences in process metrics and outcomes. There was a significantly higher prevalence of risk factors such as diabetes mellitus and hypertension in young females. Females sought medical attention after the onset of chest pain much later than males, as evidenced by longer total ischaemic times (285 vs 230 mins, respectively). As previously shown, females most often have atypical symptoms and are less likely to seek medical attention than males. These factors might have contributed to the inferior outcomes in females [37].

Conclusions

This sub-group analysis of the TN-STEMI Program found that young STEMI patients constituted one fourth of the STEMI population and approximately 90% were males. The main risk factor was smoking and the prevalence of diabetes mellitus and hypertension was significantly less than in older populations. Young females had higher traditional risk factors and inferior outcomes than young males. These patients have a better prognosis, and lifestyle changes may play a critical role in preventing future events. The role of plaque erosion in the setting of a pro-thrombotic milieu as a primary cause of STEMI in many of these young patients needs to be further explored.

Conflicts of Interest

There are no conflicts of interest to disclose.

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Appendices. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2021.04.013.

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