Internal Medicine Section

Challenges in Timely Pharmacological Reperfusion Therapy of Acute ST-Elevation Myocardial Infarction Patients: A Cross-sectional Study

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ABSTRACT

Introduction: Acute ST-Elevation Myocardial Infarction (STEMI) is the most severe presentation of an Acute Coronary Syndrome (ACS) resulting from sudden occlusion of one of the major epicardial coronary arteries resulting in myocardial injury and necrosis within minutes to few hours. Despite Primary Percutaneous Coronary Intervention (PPCI) being the gold standard, thrombolytic therapy is still the most common form of reperfusion therapy in eligible patients of acute STEMI even in large metropolitan cities in India.

Aim: To find the proportion of STEMI patients receiving thrombolytic therapy within four hours of the onset of symptoms and within 30 minutes of reaching the hospital and to explore factors related to Pain-To-Door (P2D) delay.

Materials and Methods: This was a single-centre cross-sectional observational study of 147 STEMI patients conducted at a tertiary care hospital in the National Capital Territory (India). from February to May 2017. Ethical clearance was obtained from the Institute's Ethics Committee. All patients were interviewed and their medical records reviewed. Factors related to delay in reaching hospital and association of patient characteristics with those receiving thrombolytic therapy were explored using univariable and multivariable logistic regression.

Results: Mean age of the study population was 52.1±13.1 years and 121 (82.3%) were men. Median P2D time was 4.7 hours (IQR-2.2-17.0). Overall, 64 (43.5%) of 147 patients reached the hospital within four hours of chest pain. Only 5 (3.4%) patients availed ambulance to reach the hospital. Distance from the hospital, seeking care elsewhere and delay in reaction to symptom were reasons for the delay (>4 hours). Median Door-To-Needle (D2N) time was 45.9 minutes (IQR- 30.6-61.2). Patients who reached the hospital at night were more likely to be thrombolysed after adjusting for time to reach the hospital.

Conclusion: Significant P2D and Door-To-Balloon (D2B) delays still exist in large metro cities in India. Action is needed both at the population level as well as system level to reduce these delays.

INTRODUCTION

The STEMI is the most severe presentation of an ACS in which rupture, ulceration, erosion of coronary artery plaque or dissection along with accompanying thrombus results in total occlusion of one of the major epicardial coronary arteries, leading to myocardial injury and necrosis within a period of minutes to few hours [1]. Therapeutic priorities and consequences of delay in treatment in STEMI patients differ from those with other forms of an ACS (NSTE-ACS/unstable angina) in which reperfusion of the blocked coronary artery is the major therapeutic goal in STEMI. In STEMI, the time from coronary occlusion to its recanalisation is significantly correlated to myocardial salvage and viability, ventricular volumes and functions, and long-term development of heart failure and survival [2,3]. India has the highest burden of ACS in the world, with more patients having STEMI (60.6%) than Non-ST elevation-Acute Coronary Syndrome (NSTE-ACS) or unstable angina [4]. It is estimated that more than 3 million STEMIs occur every year in India [5]. In-hospital mortality in STEMI was higher than NSTEMI (10.8% vs.5.0%, p<0.001) in HP-ACS registry and (8.2% vs. 1.8%, p<0.001%) in Kerala-ACS registry reflecting the severity and need for timely reperfusion of STEMI [6,7]. The 30 day outcomes for patients with STEMI in CREATE registry were worse than those with NSTE-ACS/unstable angina death (8.6% vs 3.7%), reinfarction (2.3% vs 1.2%), and stroke (0.7% vs 0.3%, p<0.001 for all comparisons) [4].

Approximately, 50% of deaths due to myocardial infarction occur in the first hour before reaching the hospital and every 30 minutes delay increases the risk of one year mortality by 7.5% [8]. Coronary reperfusion with thrombolysis or angioplasty during the first 1-2 hours may reduce the death rate by half, but the benefit rapidly declines with delays in treatment [9]. Reperfusion therapy within 12 hours via thrombolysis or PPCI remains the major therapeutic goal in STEMI patients [8]. Though, PPCI is the gold standard for reperfusion therapy, it is costly and not readily available even in large metro cities in India, so the majority of patients still receive thrombolysis as the initial reperfusion therapy in STEMI. However, delays exist in timely initiation of thrombolytic therapy that could be due to patient-related (P2D time) or system-related factors (D2N time) [10]. To minimise patient delay, it is necessary to increase public awareness about how to recognise common symptoms of Acute Myocardial Infarction (AMI) and to call the emergency services. System delay is more amenable to modification by organisational measures than is patient delay and it is a predictor of outcome [11].

This study was conducted in the context of an urban referral government hospital to explore the challenges in pharmacological reperfusion therapy in STEMI patients in a tertiary care centre and to get insights into newer factors or change in modifiable factors that were found in earlier studies.

MATERIALS AND METHODS

This was a single-centre cross-sectional study conducted in the Department of Cardiology, Vardhman Mahavir Medical College and Safdarjung Hospital, a tertiary care hospital in New Delhi, India, from February to May 2017. The study was approved by the Institute Ethics Committee vide permission letter no. IEC/SJH/VMMC/PROJECT/OCTOBER 2016/640. The study was conducted as per National

Ethical Guidelines of the Indian Council of Medical Research (ICMR) and latest declaration of Helsinki for research on human subjects [12].

Inclusion and Exclusion criteria: A total of 147 consecutive patients, admitted in the in-patient department with a diagnosis of acute STEMI were included. Patients with prior history of myocardial infarction or revascularisation procedures, underwent thrombolysis before reaching the hospital and receiving PPCI were excluded.

Sample size calculation: The sample size was calculated for the primary outcome of the study, i.e., the percentage of STEMI patients being reperfused. Based on the CREATE and the Kerala ACS registry [4,7], a prevalence of 55% was assumed for this outcome. To obtain a prevalence estimate and a 95% confidence interval with 8% absolute precision, 150 patients were required.

Study Procedure

Data were collected by an interviewer-administered pre-tested structured questionnaire [Appendix-1] in the cardiology ward and Coronary Care Unit (CCU) after obtaining informed consent. Information was collected from the patient and the attendant on socio-demography, symptoms and events at the time of symptom onset, intervals between symptom onset to reaching hospital including information on other clinics/hospitals visited before reaching the study hospital. Time of thrombolytic therapy and details of treatment were collected from in-patient medical records. A composite score for Socio-economic Status (SES) was computed using principal component analysis with proxy variables such as literacy, employment status and possession of certain assets such as house ownership and vehicles [13]. Variable P2D time was categorised in two ways: those who presented within four hours and those beyond four hours. This was further re-categorised as those who presented within four hours, 4-12 hours and beyond 12 hours. All patients provided written informed consent before enrolment in the study.

Pain-to-door time: It was defined as the time taken to reach referral hospital from the onset of chest pain. The time interval from onset of the symptom as reported by the patient and time of admission at emergency as per medical records was used to calculate this interval.

Door-to-Needle (D2N) time: It was defined as the time taken between presentation at the Emergency Department to initiation of thrombolytic therapy. It was obtained from in-patient medical records.

STATISTICAL ANALYSIS

Descriptive statistics were used to present data on patient characteristics, symptoms, time to reach hospital and thrombolysis. Continuous variables were expressed as mean and Standard Deviation (SD) or median and Interquartile Range (IQR) and categorical variables were expressed as percentages and frequencies. Reasons for delay in reaching hospital and association of patient characteristics with those receiving thrombolytic therapy were explored using univariable and multivariable logistic regression. An apriori level of significance for all the analysis was two-tailed p-value less than 0.05. All analyses were performed using Stata 14.

RESULTS

Socio-demographic characteristics of all 147 STEMI patients enrolled in the study are presented in [Table/Fig-1]. The mean age of the study population was 52.1±13.1 years with a higher percentage of males (82.3%). The majority (68%) were from Delhi and the median distance of the place of residence was 15 km (IQR- 8.5-20) and the distance for the overall sample ranged between 1-500 km. Approximately, one-fourth of patients were illiterate. The majority (93.2%) had access to information gadgets like cell phone, radio, newspaper and television.

Symptom onset and immediate actions: The most common symptom in the study population was chest pain with/without radiation (93.2%) and time of onset was equally distributed between

Socio-demographic information	n=147
Male, n (%)	**121 (82.3)**
Mean age in years (SD)	52.1 (13.1)
Age >40 years (%)	123 (83.7)
Marital status, n (%)	
Married	139 (94.6)
Unmarried/widowed	8 (5.4)
Place of residence, n (%)	
Delhi	100 (68.0)
Delhi NCR	36 (24.5)
Outside Delhi NCR	11 (7.5)
Literacy, n (%)	
Illiterate	97 (66.0)
Literate	50 (34.0)
Current earning status, n (%)	
Salaried	45 (30.6)
Daily wage	53 (36.1)
Not earning	37 (25.2)
Retired	12 (8.2)
Family type, n (%)	
Nuclear family	128 (87.1)
Extended family	19 (12.9)
Access to information, n (%)	
Use cell phone	126 (85.7)
Watch television	94 (64.0)
Read newspaper	42 (28.3)
Listen to radio	30 (20.4)
Access to an information device	
Yes	137 (93.2)
No	10 (6.8)
Socio-economic status (SES)*, n (%)	
Low	49 (33.3)
Mid	48 (32.7)
High	50 (34.0)
Co-morbid conditions, n (%)	
Hypertensive	22 (15.0)
Mean years since diagnosis (SD)	7.7 (6.9)
Known diabetic	21 (14.3)
Mean years since diagnosis (SD)	6.1 (4.9)
Smoking, n (%)	
Current smoker	82 (55.8)
Ex-smoker	10 (6.8)
Never	55 (37.4)

[Table/Fig-1]: Socio-demographic characteristics.
*SES computed from principal components analysis

day and night. Further details of the situation around the time of onset and immediate actions taken are summarised in [Table/Fig-2]. Only 5 (3.4%) of 147 patients contacted ambulance to reach the medical facility and an overwhelming majority used paid auto/taxi (73.2%). Two-third (n=94) of patients availed care from a clinic/nursing home before presentation to the tertiary care.
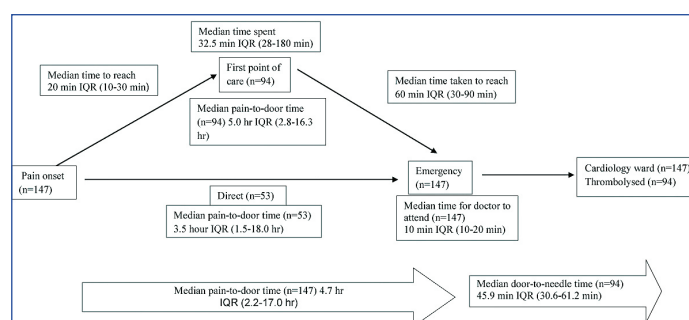
Time intervals between symptom onset, reaching hospital and thrombolytic therapy: The [Table/Fig-3] shows the breakup of time in hours (median and IQR) since symptom onset to reaching emergency room of the study hospital for the overall sample and stratified by those who availed first care at another facility before arriving at the emergency. The median P2D time was 4.7 hours (IQR- 2.2-17.0 hours) range (0.25-274.49 hours). Median P2D time among those who availed first care (n=94) was

Events at the time of symptom onset	n=147
Chief symptoms that prompted to seek care, n (%)	
Chest pain/radiating chest pain	136 (92.5)
Pain in hand/body/abdomen	6 (4.1)
Suffocation/Breathlessness/Restlessness	4 (2.7)
Abnormal sweating	1 (0.7)
Day of symptom onset, n (%)	
Weekday	102 (69.4)
Weekend (Saturday/Sunday)	45 (30.6)
Symptom onset time, n (%)	
Day (6 am-6 pm)	81 (55.1)
Night (6 pm-6 am)	66 (44.9)
Symptom onset situation, n (%)	
At rest/sleep	110 (74.8)
During normal/strenuous physical activity	37 (25.2)
Symptom onset location, n (%)	
Home	119 (80.9)
Work/travel	28 (19.1)
First response towards key symptom, n (%)	
Sought help to reach care (clinic/hospital)	79 (53.7)
Other remedies	68 (46.3)
Reason for not seeking care, (n=68) n (%)	
Not aware about the symptoms	36 (52.9)
Misinterpretation of the symptoms as gastric pain	23 (33.8)
Ignored/misinterpreted the symptoms	7 (10.2)
Did not want to disturb family members	2 (2.9)
Transport, n (%)	
Contacted ambulance	5 (3.4)
Used other mode of transport	142 (96.6)
Paid (taxi/auto)	104 (70.7)
Relative owned vehicle	18 (12.2)
Self-owned	11 (7.4)
Neighbour	9 (6.1)
Availed care in clinic/nursing before reaching study hospital	94 (64.0)
Time from symptom onset to reach study hospital, n (%)	
Less than 4 hours	64 (43.5)
4-12 hours	38 (25.9)
More than 12 hours	45 (30.6)
Door-to-needle time, n (%)	94 (64)
Less than 30 minutes	17 (18.1)
More than 30 minutes	77 (81.9)
Thrombolysis, n (%)	
Received thrombolysis	94 (63.9)
Not received thrombolysis	53 (36.1)
Reason for not initiating thrombolysis	
Out of window period	51 (96.2)
Spontaneous resolution	2 (3.8)

[Table/Fig-2]: Symptom onset and events at the time and after symptom onset.

[Table/Fig-3]: Time intervals between symptom onset, reaching hospital and thrombolytic therapy.

Overall, 94 (63.9%) (95% CI 57, 72) of patients received thrombolysis. Of those who received thrombolysis, 17 (18.1%) received this within 30 minutes of presentation to emergency and overall D2N time for those who received thrombolytic therapy (n=94) was 45.9 minutes (IQR- 30.6-61.2 minutes). Most common reasons for the delay in D2N time (system delay) were transfer of patients from emergency to cardiology ward, admission procedures and obtaining patient consent for thrombolysis.

Association between socio-demographic characteristics and delayed hospital presentation (beyond four hours) is summarised in [Table/Fig-4]. On multivariable analysis, it was found that farther location of residence, availing the first Point-Of-Care (POC) without reperfusion

Socio-demographic characteristics	Within 4 hr, n (%)	Beyond 4 hr, n (%)	Crude OR 95% CI p-value*	Adjusted OR 95% CI p-value*
Gender				
Male (ref)	53 (43.8)	68 (56.2)		
Female	11 (42.3)	15 (57.7)	1.06 (0.5-2.5)	1.14 (0.4-3.5)
p-value			0.88	0.81
Age				
More than 40 yr (ref)	52 (42.3)	71 (57.7)		
Less than 40 yr	12 (50.0)	12 (50.0)	1.36 (0.6-3.3)	0.86 (0.3-2.5)
p-value			0.48	0.78
Place of living				
Delhi (ref)	52 (52.0)	48 (48.0)		
Delhi NCR/Outside NCR	12 (25.5)	35 (74.5)	3.15 (1.5-6.7)	3.70 (1.3-9.8)
p-value			0.003	0.008
SES status				
Low (ref)	18 (36.7)	31 (63.3)		
Middle	21 (43.8)	27 (56.3)	0.75 (0.3-1.7)	0.95 (0.3-2.5)
High	25 (50.0)	25 (50.0)	0.58 (0.2-1.3)	1.21 (0.4-3.7)
p-value			0.41	0.91
Literacy status				
Illiterate (ref)	36 (37.1)	61 (62.9)		
Literate	28 (56.0)	22 (44.0)	0.46 (0.2-0.9)	0.43 (0.2-1.7)
p-value			0.02	0.10
Type of family				
Nuclear (ref)	51 (39.8)	77 (60.1)		
Extended family	13 (68.4)	6 (31.6)	0.30 (0.1-0.9)	0.29 (0.1-1.1)
p-value			0.02	0.06
First point of care				
Study hospital (ref)	28 (52.8)	25 (47.2)		
Another point of care	36 (38.3)	58 (61.7)	1.80 (0.9-3.6)	3.04 (1.1-8.2)
p-value			0.08	0.02
Time of symptom onset				
Day (ref)	35 (43.2)	46 (56.8)		
Night	29 (43.9)	37 (56.1)	0.97 (0.5-1.9)	0.82 (0.3-1.8)
p-value			0.92	0.63

5.0 hours (IQR- 2.8-16.3 hours) range (0.50-274.49 hours) vs 3.5 hours (IQR- 1.5-18.0 hours) range (0.25-250.93 hours) among those who didn't avail first care (n=53). There was no statistically significant difference between P2D time at weekday vs. weekend (p=0.11) or between night vs day (p=0.48). Only 43.5% (95% CI 35.6, 51.7) of patients reached tertiary hospital within four hours.

Median time taken by the doctor to attend the patient in the emergency was 10 minutes (IQR- 10-20 minutes), range (5-120 minutes). Key reasons for the delay in the emergency department were lack of hospital staff and increased patient load.

Place of symptom onset				
Home (ref)	51 (42.9)	68 (57.1)		
Work/Travel	13 (46.4)	15 (53.6)	0.86 (0.4-1.9)	1.06 (0.4-3.2)
p-value			0.73	0.91
Day of symptom onset				
Weekday (ref)	41 (40.2)	61 (59.8)		
Weekend	23 (51.1)	22 (48.9)	0.64 (0.3-1.3)	0.68 (0.3-1.7)
p-value			0.22	0.40
First response towards pain				
Immediate help sought (ref)	48 (60.8)	31 (39.2)		
Other remedies	16 (23.5)	52 (76.5)	5.03 (2.4-10.3)	8.7 (3.4-22.2)
p-value			<0.001	<0.001

[Table/Fig-4]: Univariable and multivariable analysis of patient characteristics and reaching hospital late (beyond 4 hours) (n=147).
*ORs from simple and multivariable logistic regression. OR >1 signifies factor associated with delay and <1 indicated the factor is associated with reaching early

facilities and delayed response towards pain were independently associated with P2D time more than four hours.

Association between patients receiving thrombolytic therapy (n=94) and socio-demographic characteristics is summarised in [Table/Fig-5]. On multivariable analysis, it was found that symptom onset

Socio-demographic characteristics	Received thrombolysis n (%)	Did not receive thrombolysis n (%)	Unadjusted OR, 95% CI p-value	Adjusted OR, 95% CI p-value
Age				
More than 40 yr (ref)	76 (61.8)	47 (38.2)		
Less than 40 yr	18 (75)	6 (25.0)	0.53 (0.2-1.5)	1.27 (0.2-5.9)
p-value			0.20	0.75
Gender				
Male (ref)	77 (63.6)	44 (36.4)		
Female	17 (65.4)	9 (34.6)	1.07 (0.4-2.6)	1.83 (0.3-9.9)
p-value			0.86	0.48
Literacy status				
Illiterate (ref)	61 (62.9)	36 (37.1)		
Literate	33 (66.0)	17 (34.0)	1.14 (0.6-2.3)	-
p-value			0.70	
Place of living				
Delhi (ref)	66 (66.0)	34 (34.0)		
Delhi NCR/Outside Delhi NCR	28 (59.6)	19 (40.4)	0.75 (0.4-1.5)	0.92 (0.3-3.3)
p-value			0.45	0.91
SES status				
Low (ref)	25 (51.0)	24 (49.0)		
Mid	33 (68.7)	15 (31.3)	2.11 (0.9-4.8)	2.2 (0.5-8.8)
High	36 (72.0)	14 (28.0)	2.46 (1.0-5.6)	1.6 (0.4-6.4)
p-value			0.07	0.49
Day of symptom onset				
Weekday (ref)	61 (59.8)	41 (40.2)		
Weekend	33 (73.3)	12 (26.7)	1.84 (0.8-3.9)	0.87 (0.2-3.0)
p-value			0.11	0.83
Time of symptom onset				
Day (ref)	45 (55.6)	36 (44.4)		
Night	49 (74.2)	17 (25.8)	2.30 (1.1-4.6)	4.19 (1.2-14.7)
p-value			0.02	0.02
Place of symptom onset				
Home (ref)	74 (62.2)	45 (37.8)		
Work/Travel	20 (71.4)	8 (28.6)	1.52 (0.6-3.7)	1.24 (0.3-5.0)
p-value			0.35	0.76
First response towards pain				
Sought help to reach care (ref)	63 (79.8)	16 (20.2)		
Other remedies	31 (45.6)	37 (54.4)	0.21 (0.1-0.4)	1.28 (0.3-5.5)
p-value			<0.001	0.73
First point of care				
Another point of care (ref)	60 (63.8)	34 (36.2)		
Safdarjung	34 (64.2)	19 (35.8)	0.98 (0.5-1.9)	0.73 (0.2-2.7)
p-value			0.96	0.64
Pain to door				
Less than 4 hours (ref)	59 (92.2)	5 (7.8)		
4-12 hours	31 (81.6)	7 (18.4)	0.37 (0.1-1.2)	0.32 (0.1-1.3)
More than 12 hours	4 (8.9)	41 (91.1)	0.01 (0.002-0.03)	0.004 (0.001-0.030)
p-value			<0.001	<0.001

[Table/Fig-5]: Factors associated with receiving thrombolysis (n=94).
*ORs from simple and multivariable logistic regression; OR >1 indicate the factor is associated with receiving thrombolytic therapy. For variable literacy got omitted in the multivariable analysis and so no estimates are reported

at night was associated with receiving thrombolytic therapy after adjusting for the P2D time less than four hours and other factors.

DISCUSSION

This single-centre cross-sectional study conducted at a tertiary care hospital situated in the national capital highlights the persisting problem of delay in reaching the hospital and delay in initiating thrombolysis at the hospital. This study finding is relevant in the current context even in the presence of previous studies viz., CREATE, HP ACS and Kerala ACS registry that were conducted a nearly a decade ago [4,6,7].

In this study, the median P2D time was 282 minutes (IQR- 132-1020). Compared to contemporary Indian studies, this interval was similar to CREATE registry median P2D time of 300 minutes (IQR- 137-985) but significantly higher than TN-STEMI program (postintervention phase) median time of 174.5 minutes (IQR- 90-310) [4,14]. However, we are far behind the West. In a Finnish study, conducted more than two decades ago (1995), this time was 100 minutes (IQR- 15-661) [15]. Key factors associated with the pre-hospital delay we report are consistent with findings of Mussi FC et al., CREATE registry, Jaipur study and qualitative analysis of ACS conducted in Kerala, which found that lack of knowledge about serious nature of chest pain was associated with pre-hospital delay [4,16-18]. Large scale community based mass media campaigns on radio, TV, and print media can help create awareness among the general public about how to recognise and respond in case of suspected ACS.

Further, P2D delay is also due to delay in diagnosis and referral by the first POC physicians. Individuals who seek advice from their General Physician (GP) when they experience chest pain take longer to reach the hospital with the presentation to the hospital delayed by nearly an hour [19]. In present study, 94 (64%) of patients went to the first POC where there was no reperfusion facility. A list of hospitals in each locality that have 24x7 thrombolysis or revascularisation facilities should be available along with helplines. Further, the diagnostic facilities for ACS should be available at all licensed hospitals which run 24x7 emergency services.

Another reason for the pre-hospital delay due to the use of public transport and traffic congestion. Similar to CREATE registry where only 5% availed ambulance services, only 3.4% of this study population availed ambulance care. This is extremely low in comparison to other countries [20-23]. Despite good ambulance services {Centralised Accident and Trauma Services (CATS)} [24], the proportion of patients

availing ambulance services was not greater than CREATE registry. This could be due to the supply demand deficit or lack of awareness among the general population about this facility. If a patient cannot reach the hospital within 90 minutes of symptoms, out-of-hospital thrombolysis should be considered [25]. Use of pre-hospital thrombolytic therapy has been suggested not only in rural communities but also in urban areas where traffic congestion may contribute to the delay [25]. Pre-hospital thrombolysis with well equipped ambulance along with trained paramedical staff which need a policy level decision of various departments involved in emergency care can be initiated to reduce P2D time. The ICMR 'Mission DELHI' (Delhi Emergency Life Heart-Attack Initiative), a pilot project launched on 25th April 2019 at the All India Institute of Medical Sciences (AIIMS), New Delhi to provide care to STEMI patients in surrounding areas of AIIMS is a step in this direction [26]. On receiving a call at Mission DELHI's Toll-Free Emergency Helpline numbers (1800111044 and 14430), a pair of mobile motorbike borne medical nurse team is dispatched immediately for examining the patient, providing necessary medication/CPR, transmitting ECG to a consultant at AIIMS and providing doorstep thrombolysis before transporting to the hospital. In other areas, GPs, who are most often the first POC can be a vital tool in this regard because they can interpret the ECG and with the help from ambulance technicians and telemedicine, this is feasible. In the present study, 94 (64%) patients had presented to GPs before reaching hospital and this could have been potential candidates for pre-hospital thrombolysis.

While delay to reach the hospital is a broader issue and requires a change in urban infrastructure and increase in awareness among the general population, the system delay is something that can be and should be addressed at the hospital level. Median D2N time in this study was 45.9 minutes (IQR- 30.6-61.2) and only 18.1% of thrombolysis eligible patients (n=94) received reperfusion therapy within 30 minutes of presentation. The D2N time was higher than Jaipur study but lower than CREATE registry [4,16]. The median D2N time of studies reported from the Western countries range from 32-43 minutes [27-29]. Factors associated with receiving reperfusion therapy were P2D time less than four hours and symptom onset at night. This was consistent with findings from Zed PJ et al., where they reported patients arriving during the night are more likely to receive reperfusion therapy [29]. Similarly, a study conducted by Muller LA et al., found that D2N time was shorter among patients seen in the night shift [21]. A key recommendation to reduce D2N time is to initiate thrombolysis at the emergency department itself or directly referring all cardiac emergencies to 24x7 Heart Command Centre instead of first presenting to general emergency and then referral to Cardiology Department to shorten system delay.

Limitation(s)
It is an urban tertiary care single-centre study at a busy government hospital, so the study results may not be generalisable to whole of India, where wide disparity exists between urban vs rural areas and government vs private hospitals. The sample size was small representing a small geographical area of the country. We didn't capture data on PPCI which is the gold standard revascularisation strategy in this clinical setting. Nonetheless, our study results are similar to the contemporary and past Indian studies on this important life-threatening clinical condition and emphasise the need for improvement in the revascularisation of STEMI even in large metropolitan cities in India.

CONCLUSION(S)
Significant P2D and D2N time delays still exist even in large metro cities in India. Action is needed both at the population level in creating awareness and at the healthcare system level in shortening intra-hospital delays. System delays are more readily amenable and could be reduced by the initiation of thrombolysis in the emergency

department or the creation of a centralised heart command for cardiac emergencies.

REFERENCES
[1] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-35.
[2] McNamara RL, Wang Y, Herrin J, Curtis JP, Bradley EH, Magid DJ, et al. NRMI Investigators. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2006;47(11):2180-86.
[3] Gruppo Italiano per lo Studio Della Streptochinasi nell'Infarto Miocardio (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet. 1986;1(8478):397-402.
[4] Xavier D, Pais P, Devereaux PJ, Xie C, Prabhakaran D, Reddy KS, et al. Treatment and outcomes of acute coronary syndromes in India (CREATE): A prospective analysis of registry data. Lancet. 2008;371(9622):1435-42.
[5] Indian Council of Medical Research. Report of Dissemination Workshop on STEMI TN Project Held on 18 January 2017 at National Institute of Pathology, Safdarjung Hospital Campus, Ansari Nagar, New Delhi, 2017.
[6] Negi PC, Merwaha R, Panday D, Chauhan V, Guleri R. Multicenter HP ACS Registry. Indian Heart J. 2016;68(2):118-27.
[7] Mohanan PP, Mathew R, Harikrishnan S, Krishnan MN, Zachariah G, Joseph J, et al. Presentation, management, and outcomes of 25748 acute coronary syndrome admissions in Kerala, India: Results from the Kerala ACS Registry. Eur Heart J. 2013;34(2):121-29.
[8] De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: Every minute of delay counts. Circulation. 2004;109(10):1223-25.
[9] Gersh BJ, Stone GW, White HD, Holmes DR. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: Is the slope of the curve the shape of the future? JAMA. 2005;293(8):979-86.
[10] Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33(20):2569-619.
[11] Terkelsen CJ, Sorensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA. 2010;304(7):763-71.
[12] Mathur R, Swaminathan S. National ethical guidelines for biomedical & health research involving human participants, 2017: A commentary. Indian J Med Res. 2018;148(3):279-83.
[13] Vyas S, Kumaranayake L. Constructing socio-economic status indices: How to use principal components analysis. Health Policy and Planning. 2006;21(6):459-68.
[14] Alexander T, Mullasari AS, Joseph S, Kannan K, Veerasekar G, Victor SM, et al. A system of care for patients with ST-segment elevation myocardial infarction in India- The Tamil Nadu-ST-Segment Elevation Myocardial Infarction Program. JAMA Cardiol. 2017;2(5):498-505.
[15] Hirvonen TP, Halinen MO, Kala RA, Olkinuora JT. Delays in thrombolytic therapy for acute myocardial infarction in Finland. Results of a national thrombolytic therapy delay study. Finnish Hospitals' Thrombolysis Survey Group. Eur Heart J. 1998;19(6):885-92.
[16] Choudhary R, Sharma SM, Kumar V, Gautam DK. An observational study of prehospital and hospital delay in reperfusion for acute myocardial infarction at a University hospital in India. J Pract Cardiovasc Sci. 2016;2:163-68.
[17] Mussi FC, Mendes AS, de Queiroz DL, Costa ALS, Pereira Á, Caramelli B, et al. Pre-hospital delay in acute myocardial infarction: Judgement of symptoms and resistance to pain. Res Assoc Med Bras. 2014;60(1):63-69.
[18] Patel A, Mohanan PP, Prabhakaran D, Huffman MD. Pre-hospital acute coronary syndrome care in Kerala, India: A qualitative analysis. Indian Heart J. 2017;69(1):93-100.
[19] Finn JC, Bett JHN, Shilton TR, Cunningham C, Thompson PL. On behalf of the National Heart Foundation of Australia Chest Pain Every Minute Counts Working Group. Patient delay in responding to symptoms of a possible heart attack: Can we reduce time to care? Med J Aust. 2007;187(5):293-98.
[20] Novak K, Aljinovic J, Kostic S, Capkun V, Novak Ribicic K, Batinic T, et al. Pain to hospital times after myocardial infarction in patients from Dalmatian mainland and islands, southern Croatia. Croat Med J. 2010;51(4):423-31.
[21] Muller LA, Rabelo ER, Moraes MA, Azzolin K. Delay factors on the administration of thrombolytic therapy in patients diagnosed with acute myocardial infarction in a general hospital. Rev Lat Am Enfermagem. 2008;16(1):52-56.
[22] Park YH, Kang GH, Song BG, Chun WJ, Lee JH, Hwang SY, et al. Factors related to prehospital time delay in acute ST-segment elevation myocardial infarction. J Korean Med Sci. 2012;27(8):864-69.
[23] Peng YG, Feng JJ, Guo LF, Li N, Liu WH, Li GJ, et al. Factors associated with prehospital delay in patients with ST-segment elevation acute myocardial infarction in China. Am J Emerg Med. 2014;32(4):349-55.
[24] Available from: http://web.delhi.gov.in/wps/wcm/connect/DOIT_CATS/cats/home.

[25] Chittari MS, Ahmad I, Chambers B, Knight F, Scriven A, Pitcher D. Retrospective observational case-control study comparing prehospital thrombolytic therapy for ST-elevation myocardial infarction with in-hospital thrombolytic therapy for patients from same area. Emerg Med J. 2005;22(8):582-85.

[26] ICMR launches Mission DELHI, a Delhi Emergency Life Heart-Attack Initiative. Available from: https://www.emedinexus.com/post/11610.

[27] Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomised trials. Lancet. 2003;361(9351):13-20.

[28] Wah W, Pek PP, Ho AF, Fook-Chong S, Zheng H, Loy EY, et al. Symptom-to-door delay among patients with ST-segment elevation myocardial infarction in Singapore. Emerg Med Australas. 2017;29(1):24-32.

[29] Zed PJ, Abu-Laban RB, Cadieu TM, Purssell RA, Filiatrault L. Fibrinolytic administration for acute myocardial infarction in a tertiary ED: Factors associated with an increased door-to-needle time. Am J Emerg Med. 2004;22(3):192-96.

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APPENDIX 1: DATA COLLECTION TOOLS

Practical challenges in reperfusion therapy of STEMI: A single centre cross-sectional study.

A: Has the patient given informed consent (Yes/No). If "Yes" proceed.

Q. No.	Questions	Responses
	Patient ID: Patient initials (F/M/L): Date of interview (DD/MM/YYYY): Date of admission (DD/MM/YYYY):	
1.	**Socio-demographic form**	
	Age in completed years	Years
	Gender	Male/Female
	Marital status	Married/Unmarried/Widowed/Divorced
	Place of residence	Delhi/Delhi NCR/Outside Delhi NCR
	Approximate distance from hospital (in km)	
	Literacy status	Illiterate/Primary education/Secondary education/Graduation and above
	Current earning status	Salaried/Daily wage/Not earning/Retired
	Family type	Nuclear Family/Extended Family/Old age home
	Listen to radio	(Yes/No)
	Use cell phone	(Yes/No)
	Watch television	(Yes/No)
	Read newspaper	(Yes/No)
	Own accommodation	(Yes/No)
	Kitchen separate	(Yes/No)
	Number of rooms	
	Car	(Yes/No)
	Bike	(Yes/No)
	Cycle	(Yes/No)
	Auto	(Yes/No)
2.	**Past medical history**	
	History of diabetes	(Yes/No)
	If yes, then specify the years	Years
	History of hypertension	(Yes/No)
	If yes, then specify the years	Years
	History of kidney disease	(Yes/No)
	History of stroke	(Yes/No)
	Smoking/smokeless tobacco	Current smoker/Never/Ex-smoker
3.	**Pre-hospital events**	
	What was the chief symptom that prompted you to seek care?	

	What were the other symptoms?	
	Date of onset of symptom (DD/MM/YYYY)	
	What was the day of symptom onset? (current attack)	Weekday/Weekend (Saturday/Sunday)
	What was the time of symptom onset?	Day (6 am-6 pm)/Night (6 pm-6 am)/Could not tell
	Time of onset of symptom (24 hr clock)	
	What were you doing at the time of onset of symptom?	At sleep/At rest/During normal activity/During strenuous physical activity
	Where were you at the time of onset of symptom?	Home/Work/Travel
	What was your first response towards pain/key symptom?	Sought help to reach care/Home remedy/Did nothing and tolerated pain/Took medicine OTC
	What was the reason for not seeking care? (if patients say Home remedy/they did nothing/took medicine OTC)	
	Did you try to contact for ambulance?	Yes/No
	If yes, what type of ambulance	Private ambulance/Public ambulance/Both
	How much time did it take ambulance to reach from time of call? (in minutes)	(9999, for never came)
	If No to 3.9, What was the mode of transport to reach hospital?	Self owned/Neighbour/Relative owned vehicle/Paid (Taxi/Auto)
	Did you avail any care clinic/nursing before reaching this hospital?	Yes/No
	If yes, What was the time taken to reach any first point of health? (in minutes)	
	Date when reached the first point of care (DD/MM/YYYY)	
	Time when reached the first point of care (24 hr clock)	
	How much time did you spend in that clinic/nursing home/dispensary? (in minutes)	
	If no to 3.10 then what was the time taken to reach this hospital? (in minutes)	
	Date of reaching this hospital (DD/MM/YYYY)	
	Time of reaching this hospital (24 hr clock)	
	What was the time taken to be attended in emergency by the doctor? in minutes)	(9999 if do not know)
4.	**Clinical presentation (Medical records)**	
	Diagnosis	
	Did the patient receive any reperfusion therapy	Thrombolysis/PTCA/None
	If thrombolysis was given, name the agent	Streptokinase/tPA/TNK
	Was it started in	Ward/Emergency/Prehospital
	Date of start for reperfusion (DD/MM/YYYY)	
	At what time the thrombolysis was started (24 hr clock)	
	If none to 4.2, reason for not receiving thrombolysis? Reason for not thrombolysis (as per record)	
	ST elevation (mV) magnitude (as per ECG records taken before initiation of treatment) Lead 1 Lead 2 Lead 3 Lead 4 Lead 5 Lead 6 Lead 7 Lead 8 Lead 9 Lead 10 Lead 11 Lead 12	