Optimization of care for ST-elevation myocardial infarction

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CHAPTER 3

Association between angiographic culprit lesion and out-of-hospital cardiac arrest in ST-elevation myocardial infarction patients

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Abstract

Background: Factors related to the occurrence of out-of-hospital cardiac arrest (OHCA) in ST-elevation myocardial infarction (STEMI) are still poorly understood. The current study sought to compare STEMI patients presenting with and without OHCA to identify angiographic factors related to OHCA.

Methods: This multicenter registry consisted of consecutive STEMI patients, including OHCA patients with return-of-spontaneous circulation. Patients were treated with primary percutaneous coronary intervention (PCI) and therapeutic hypothermia when indicated. Outcome consisted of in-hospital neurological recovery, scored using the Cerebral Performance Categories (CPC) scale, and 1-year survival. Logistic regression was used to identify factors associated with OHCA and survival was displayed with Kaplan Meier curves and compared using log rank tests.

Results: In total, 224 patients presented with OHCA and 3259 without OHCA. Average age was 63.3 years and 75% of patients were male. OHCA occurred prior to ambulance arrival in 68% of patients and 48% required intubation. Culprit lesion was associated with OHCA: risk was highest for proximal left coronary lesions and lowest for right coronary lesions. Also, culprit lesion determined the risk of cardiogenic shock and sub-optimal reperfusion after PCI, which were strongly related to survival after OHCA. Neurological recovery was acceptable (CPC≤2) in 77.1% of OHCA patients and did not differ between culprit lesions.

Conclusions: In the present STEMI population, coronary culprit lesion was associated with the occurrence of OHCA. Moreover, culprit lesion influenced the risk of cardiogenic shock and success of reperfusion, both of which were related to prognosis of OHCA patients.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a common and life threatening condition frequently caused by coronary artery disease.[1] Historically, prognosis of OHCA has been poor.[2] Revascularization techniques in OHCA have been under investigation for some time in an attempt to improve the prognosis of these patients. While thrombolysis during resuscitation failed to proof beneficial, coronary angiography with angioplasty showed promising results.[3,4] Early or primary percutaneous coronary intervention (PPCI) has been shown to improve survival after OHCA due to ST-elevation myocardial infarction (STEMI) and at present, PPCI is readily available in the Netherlands for STEMI patients suffering an OHCA due to extensive nationwide networks of care designed to minimize ischemic times.[5-7]

Although PPCI for OHCA due to STEMI is commonly performed, factors associated with the occurrence of OHCA in setting of STEMI are still poorly understood. The current study sought to compare STEMI patients presenting with and without OHCA to identify angiographic factors related to the occurrence and prognosis of OHCA treated with PPCI and therapeutic hypothermia (TH).

Methods

Design and patients

The current Dutch registry prospectively included STEMI patients treated in 3 high-volume tertiary centers in the Netherlands. The design of this registry has been described previously.[8] In short, all consecutive STEMI patients undergoing PPCI between January 2006 and December 2009 were included. STEMI was defined as symptoms of angina lasting longer than 30 minutes along with typical electrocardiographical changes (ST-segment elevation ≥0.2 mV in ≥2 contiguous leads in V1 through V3 or ≥0.1 mV in other leads or presumed new left bundle branch block) or presumed new regional wall motion abnormalities on echocardiogram when these criteria were unavailable or inconclusive. In case of OHCA, only patients with return-of-spontaneous-circulation (ROSC) on arrival at the catheterization laboratory were included. Patients permanently living outside the Netherlands were excluded to make follow-up through municipality records possible.

Emergency medical services (EMS) were staffed with nurses trained in advanced cardiac life support. Patients were triaged in the field by 12-lead electrocardiogram faxed to the operator on call. In-ambulance medication included aspirin, intravenous heparin bolus and loading dose of clopidogrel. Glycoprotein IIb/IIIa inhibitors were administered up-front in the Leiden University Medical Center and periprocedurally in the other hospitals. Upon arrival at the hospital, unresponsive patients were admitted to the emergency department and following stabilization transferred directly to the catheterization laboratory. Stable patients were transferred directly

to the catheterization laboratory. Procedures were performed according to current clinical guidelines. Patients remaining unresponsive (Glasgow Coma Scale <8) after resuscitation were transferred to the intensive care unit, where TH (32-34°C) was induced for 24 hours using ice packs, cooling blankets and intravenous NaCl 0.9% of 4°C, if necessary. After this period, TH was ceased and as body temperature returned to normal values sedation was weaned. Patients remaining unresponsive (Glasgow Coma Scale motor response <5) 24 hours after reaching normothermia and weaning of sedation underwent sensory evoked potentials testing. Severe and permanent neurologic dysfunction was diagnosed if the N20 response was bilaterally absent. Patients with a positive N20 response remaining comatose after 72 hours underwent neurological clinical examination and electro-encephalography after which further treatment strategy was decided.

Patients treated in the Leiden University Medical Center were treated according to the institutional MISSION! protocol, a standardized pre-hospital, in-hospital and outpatient clinical framework for STEMI care.[9] These patients were intensively monitored at the outpatient clinic for 1 year, after which they were referred to the general practitioner or regional cardiology clinic. In the other centers, local residents were managed at the outpatient clinics and patients referred from regional hospitals were referred back for further management by regional cardiologists.

Data collection

All hospitals prospectively registered patients. Close collaboration with regional EMS supplied pre-hospital times and resuscitation characteristics. Vital status was obtained using municipality records. In-hospital outcome was a composite of all-cause mortality and neurological outcome. Neurological outcome was scored retrospectively using the Cerebral Performance Categories (CPC) scale consisting of 5 categories: 1. Conscious, good cerebral performance, able to work; 2. Conscious, moderate cerebral disability, able to work in a sheltered environment; 3. Conscious, severe cerebral disability, dependent on others; 4. Coma or vegetative state; 5. Brain death.[10] Long term outcome consisted of 1-year all-cause mortality. Deaths were considered cardiac unless a clear non-cardiac cause could be identified.

Statistical analyses

Continuous variables are presented as mean ± standard deviation or median (25th to 75th percentile) and were compared using Student's t-test in case of mean and Mann-Whitney U test in case of median. Categorical variables are expressed as counts and percentages and were compared by means of Pearson's χ^2 test. All statistical tests were 2-tailed and a p-value <0.05 was considered statistically significant. Univariable logistic regression was performed to investigate the association of angiographic factors with OHCA and other prognostic factors. Cumulative incidences of endpoints were displayed visually using Kaplan-Meier plots and compared with log rank tests. Analyses were performed using IBM SPSS Statistics version 20.

Results

Of the 3483 consecutive STEMI patients treated during the inclusion period, 224 (6.4%) presented with OHCA and 3259 (93.6%) without cardiac arrest. Baseline characteristics (Table 1) showed that symptom-to-balloon time was shorter in patients presenting with OHCA. In contrast, door-to-balloon time was longer in OHCA patients compared to non-arrest patients. During angiography, patients presenting with OHCA more frequently showed left coronary artery culprit lesions compared to patients without arrest. Also, OHCA patients were more often in cardiogenic shock and were treated more commonly with intra-aortic balloon pumps. Thrombolysis-in-myocardial infarction flow pre- and post-procedure was comparable between the groups.

Table 1. Baseline and procedural characteristics

	OHCA (N=224)	**No OHCA** (N=3259)	p-Value
Age, years, mean ± standard deviation	62.5 ± 12.1	63.3 ± 12.5	0.365
Male sex	78.6 (176/224)	74.8 (2439/3259)	0.212
Diabetes mellitus	9.1 (20/219)	11.3 (366/3230)	0.318
Previous myocardial infarction	10.9 (24/221)	10.8 (351/3241)	0.989
Previous percutaneous coronary intervention	6.8 (15/221)	8.5 (275/3241)	0.378
Previous coronary artery bypass grafting	3.2 (7/221)	2.4 (78/3246)	0.477
Symptoms-to-balloon time, median minutes	150 (116-192)	181 (131-285)	<0.001
Door-to-balloon time, median minutes	53 (36-79)	46 (33-66)	0.014
Culprit artery			<0.001
Left main	3.1 (7/224)	1.2 (40/3257)	0.017
Left anterior descending	55.8 (125/224)	39.4 (1282/3257)	<0.001
Left circumflex	21.9 (49/224)	15.5 (504/3257)	0.011
Right coronary artery	18.3 (41/224)	42.8 (1393/3257)	<0.001
Bypass graft	0.9 (2/224)	1.2 (38/3257)	0.710
Multivessel disease	50.9 (114/224)	53.1 (1729/3256)	0.522
Stenting	96.9 (217/224)	95.6 (3114/3257)	0.367
Cardiogenic shock during PCI	30.8 (69/224)	4.8 (158/3259)	<0.001
Intra-aortic balloon pump implantation	25.4 (57/224)	2.8 (92/3259)	<0.001
TIMI flow ≤1 pre-procedure	79.9 (179/224)	79.3 (2582/3254)	0.841
TIMI flow 3 post-procedure	91.1 (204/224)	91.5 (2976/3254)	0.842

Values are percentage (n) or median (25^{th} to 75^{th} percentile). TIMI = Thrombolysis in myocardial infarction. *defined as systolic blood pressure lower than 90 mmHg with signs of tissue hypoperfusion requiring treatment in form of inotropic agents or assistant devices.

Table 2 shows the characteristics of the OHCA patients according to moment of arrest. Approximately two thirds of patients suffered a cardiac arrest before arrival of EMS. Most OHCAs were witnessed and delay in basic life support occurred in a quarter of patients with OHCA before EMS arrival. In most cases, the first observed rhythm was ventricular fibrillation or tachycardia. Intubation was performed in 108 patients. Of these patients, 95.4% (103/108) survived PCI and 88.0% (95/108) underwent TH. The rest had no indication for TH due to return of consciousness.

Table 2. Characteristics and treatment of out-of-hospital cardiac arrest

	OHCA witnessed by EMS (N=71)	**OHCA not witnessed by EMS** (N=153)
Delay in basic life support >5 minutes*	0.0 (0/71)	24.2 (37/153)
Bystander witnessed arrest	100 (71/71)	90.8 (139/153)
First observed rhythm		
Ventricular fibrillation / tachycardia	95.8 (68/71)	93.4 (142/152)
Bradycardia	2.8 (2/71)	2.0 (3/152)
Asystole / Pulseless electrical activity	1.4 (1/71)	4.6 (7/152)
Treatment performed		
Automatic external defibrillator	0.0 (0/71)	17.6 (27/153)
Defibrillation	95.7 (3/70)	94.1 (143/152)
Average number of shocks	1 (1-2)	2 (1-4)
Chest compressions	51.4 (36/70)	88.2 (135/153)
Intubation	10.0 (7/70)	66.0 (101/153)
Therapeutic hypothermia†	100 (7/7)	87.1 (88/101)

Values are percentage (n) or median (25^{th} to 75^{th} percentile).
*Based on history from bystanders; † The denominator is intubated patients.

Factors associated with OHCA

Angiographic culprit lesion was associated with risk of OHCA (Figure 1, Table 3). Lesions located in the left coronary artery (with the exception of diagonal branch lesions) were found to result in the highest risk of OHCA. In addition, proximally located left coronary artery lesions displayed a higher risk of OHCA compared to non-proximally located left coronary artery lesions: OR 1.43 (95% CI 1.05-1.95, p=0.025). Separately, proximal vs. non-proximal left anterior descending or left circumflex culprit lesions were not significantly associated with higher risk. Left main and proximal left anterior descending artery lesions were also associated with development of cardiogenic shock (Table 3, Figure 1). Moreover, culprit lesions in the left main and bypass grafts were associated with sub-optimal TIMI flow after PCI (Table 3).

Table 3. Association of angiographic culprit location with OHCA, cardiogenic shock and TIMI flow

Culprit artery	**OHCA**	OR (95% CI)	p-Value	**CarSh**	OR (95% CI)	p-Value	**TIMI <3 after PCI**	OR (95% CI)	p-Value
Right coronary									
Proximal (N=530)	2.4 (12)	Reference	-	5.0 (25)	Reference	-	8.7 (44)	Reference	-
Non-proximal (N=834)	3.1 (29)	1.31 (0.66-2.59)	0.436	4.5 (42)	0.90 (0.54-1.50)	0.685	8.8 (82)	1.00 (0.68-1.47)	0.984
Left main (N=43)	16.3 (7)	7.96 (2.95-21.45)	<0.001	51.2 (22)	20.03 (9.74-41.18)	<0.001	18.6 (8)	5.96 (2.37-14.99)	<0.001
Left anterior descending									
Proximal (N=816)	10.0 (82)	4.57 (2.47-8.47)	<0.001	8.9 (73)	1.88 (1.18-3.00)	0.008	9.2 (75)	1.06 (0.72-1.56)	0.780
Non proximal (N=521)	7.5 (39)	3.31 (1.71-6.40)	<0.001	4.4 (23)	0.88 (0.49-1.58)	0.674	7.9 (41)	0.90 (0.57-1.40)	0.624
Side branch (N=72)	5.6 (4)	2.41 (0.76-7.68)	0.138	2.8 (2)	0.55 (0.13-2.36)	0.418	4.2 (3)	0.45 (0.14-1.50)	0.195
Circumflex									
Proximal (N=220)	10.0 (22)	4.55 (2.21-9.36)	<0.001	8.2 (18)	1.70 (0.91-3.19)	0.096	6.8 (15)	0.76 (0.42-1.40)	0.384
Non-proximal (N=216)	7.9 (17)	3.50 (1.64-7.45)	0.001	5.1 (11)	1.03 (0.50-2.12)	0.945	4.6 (10)	0.51 (0.25-1.03)	0.059
Side branch (N=134)	7.5 (10)	3.30 (1.39-7.81)	0.007	6.0 (8)	1.21 (0.54-2.76)	0.643	9.8 (13)	1.13 (0.59-2.17)	0.712
Bypass graft (N=22)	2 (9.1)	4.09 (0.86-19.52)	0.077	13.6 (3)	3.02 (0.84-10.88)	0.091	8 (36.4)	2.38 (1.04-5.46)	0.040

CarSh = cardiogenic shock; OR = odds ratio; other abbreviations as in table 1.

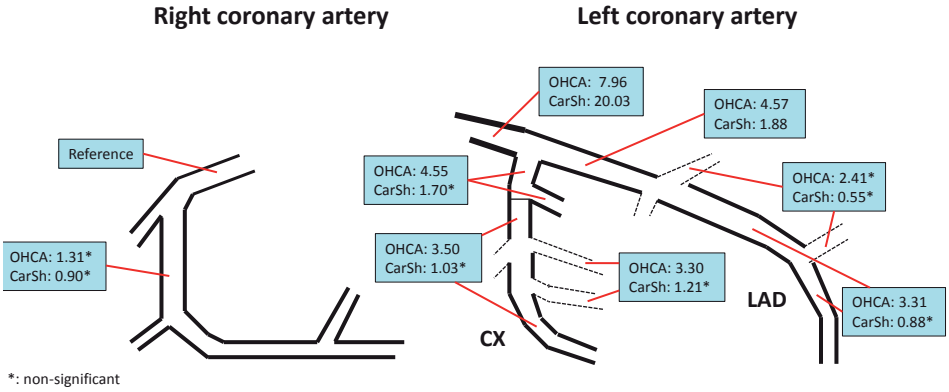

Figure 1. Culprit location and risk of out-of-hospital cardiac arrest and cardiogenic shock. Values are odds ratios. CarSh = cardiogenic shock; CX = circumflex artery; LAD = left anterior descending artery; OHCA = out-of-hospital cardiac arrest.

Neurological recovery and outcome during 1-year follow-up

Discharge CPC was known in 218 OHCA patients (97.3%) (Figure 2). The majority of patients had acceptable CPC scores (CPC≤2 in 77.1%, n=168). Thirty-five patients were in CPC 5/dead, of which 21 patients were brain dead and 14 patients suffered cardiac death. Of the 107 patients with a proximal left coronary culprit lesion, 77 recovered (72.0%). This rate was slightly higher for the patients with a non-proximal left culprit lesion (84.1%, 58/69 patients recovered) and the patients with a right culprit lesion (80%, 32/40 patients recovered). Of the 2 patients with a bypass graft culprit lesion, one died due to neurological causes. The p-value for trend between the culprit groups was 0.212.

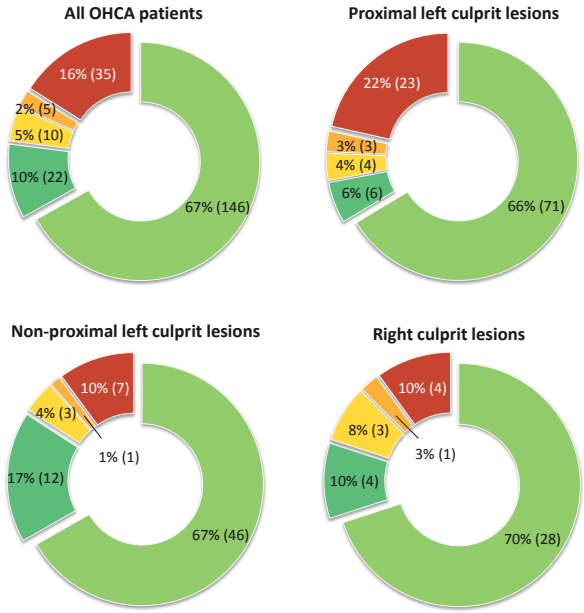

Figure 2. In-hospital Cerebral Performance Categories scale according to culprit lesion. CPC = cerebral performance categories scale. Other abbreviations as in figure 1.

One-year survival status was known in 3479 patients. In-hospital mortality was higher in OHCA patients compared to patients without OHCA (16.5% vs. 3.1%, p<0.001). Also, 1-year mortality (19.2% vs. 6.6%, p<0.001) was higher, which was due to in-hospital mortality as post-discharge survival was similar between patients with and without OHCA (3.2% vs. 3.6%, p=0.774). Figure 3A and 3B show the association between culprit location and mortality during follow-up in patients with and without OHCA. Figure 3C and 3D shows the association of cardiogenic shock and success of reperfusion with survival. OHCA patients with optimal TIMI flow after PCI had a better prognosis than OHCA patients with a sub-optimal TIMI flow after procedure, regardless of cardiogenic shock during PCI. In contrast, presence of cardiogenic shock was more important than success of reperfusion in patients without OHCA.

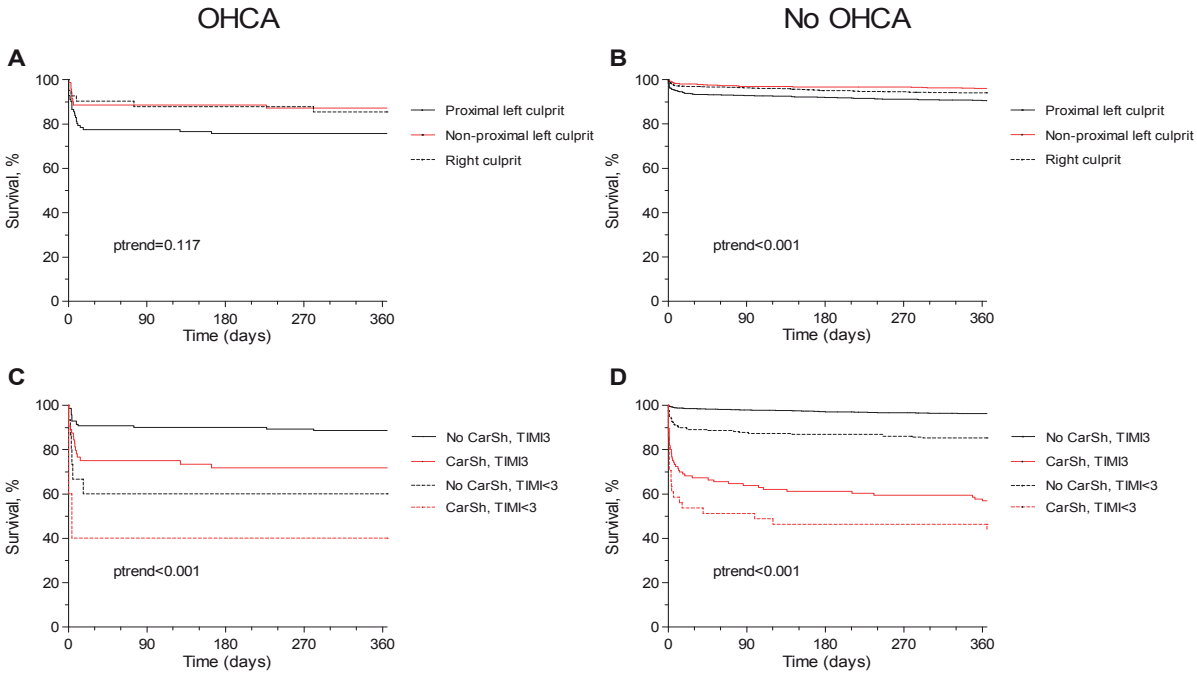

Figure 3. Survival in patients with and without OHCA according to **A)** and **C)** culprit lesion, **B)** and **D)** cardiogenic shock and TIMI flow after PCI.

Discussion

The present multicenter registry identified an association between angiographic culprit location and the occurrence of OHCA in STEMI patients: left proximal coronary lesions were associated with the highest risk for OHCA and right coronary lesions with the lowest. Moreover, culprit location was associated with cardiogenic shock and sub-optimal reperfusion after PCI, both of which were driving factors of prognosis after OHCA.

Attempts to improve the historically poor prognosis of OHCA led to investigation of revascularization techniques for OHCA patients.[2] While thrombolysis during resuscitation failed to prove beneficial, coronary angiography with angioplasty showed promise from early on.[3,4] At present, extensive networks of care make PPCI readily available for patients suffering an OHCA due to STEMI. In the current STEMI population, symptom-to-balloon times were strongly reduced in OHCA patients, a finding also observed by others, possibly reflecting the severity of symptoms leading to early initiation of professional care by either patient or bystanders.[5,6] In contrast, the prolonged door-to-balloon times in OHCA patients were likely related to time needed for in-hospital patient stabilization. Patients presenting with OHCA were more frequently in cardiogenic shock on arrival, due to impaired coronary perfusion during cardiac arrest and culprit lesion location. Culprit location varied between OHCA and non-arrest patients and was found to be associated with occurrence of OHCA. Left coronary lesions resulted in the highest and right coronary artery lesions in the lowest risk for OHCA. Moreover, proximally located culprit lesions within the left coronary artery were associated with higher risk of OHCA compared to non-proximally located lesions. This is likely explained by the larger area of myocardium-at-risk in proximal left lesions, which was supported by the finding that left main and proximal left anterior descending artery culprits were also associated with cardiogenic shock.[11] The lower percentage of right coronary artery culprit lesions is possibly explained by the commonly occurring vagal reaction in inferior MI, which may have a protective effect against VF.[12] However, it cannot be completely ruled out that inferior MI may have caused more severe ischemia, preventing ROSC and thus inclusion in this registry.

In-hospital and 1-year outcome rates stratified according to culprit lesion were similar in OHCA patients. Nevertheless, location of culprit lesions contributed indirectly to mortality due to the association with cardiogenic shock and sub-optimal reperfusion. Left main lesions were the highest risk lesions for STEMI patients, due to the strong association with OHCA, cardiogenic shock and sub-optimal reperfusion, which is supported by other reports.[13] Also, bypass graft culprit lesions were associated with reperfusion failure. The no-reflow phenomenon in setting of STEMI has multiple mechanisms, among which distal embolization and ischemic injury.[14] The occurrence of distal embolization is notorious in PCI of saphenous vein grafts and remains a challenge for operators.[15] The importance of optimal reperfusion in OHCA patients was stressed by the lower survival rates for sub-optimally reperfused OHCA patients without cardiogenic shock during PCI compared to optimally reperfused OHCA patients with cardiogenic shock during PCI. No-reflow possibly reflects the duration of ischemia prior to PCI in OHCA patients and the effect on prognosis may therefore also be explained by a prolonged resuscitation. In contrast, presence of cardiogenic shock was a stronger factor than failed reperfusion in patients without OHCA. This was likely explained by a smaller area of myocardium at risk in these patients due to the different distribution of culprit lesions.

Using a combined treatment strategy of primary PCI and TH, 77% of the OHCA population was discharged with acceptable neurological outcome and 1-year survival was 81%. The combination of PPCI and TH was previously investigated in the PROCAT registry, where the investigators reported an overall in-hospital survival rate of 40%, rising to 54% in STEMI patients after successful PCI which predicted improved prognosis.[7] Furthermore, the positive influence of both PCI and TH on long term survival was established in a cohort of OHCA patients, which included a large percentage of STEMI patients.[16] Also, a recent smaller study focusing specifically on use of TH in STEMI complicated by OHCA reported a neurological recovery rate comparable to the rate observed in the population treated with TH in the current study, supporting the accuracy of our findings.[17]

Limitations

Our investigation represents one of the largest studies covering outcomes in OHCA patients due to STEMI. However, our study was observational and thus shares the limitations of all observational analyses. Because the registry only included STEMI patients with ROSC, no data was available on OHCA patients without ROSC or patients not referred for PPCI. Data covering these patients may have provided more insight into the full community experience.

Conclusions

Location of angiographic culprit lesion was associated with the occurrence of OHCA in the current STEMI population. Moreover, angiographic culprit location predicted cardiogenic shock and success of reperfusion, both of which were associated with the prognosis of OHCA patients.

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