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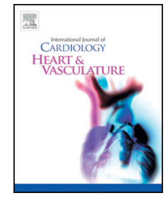

Long-term survival in patients presenting with STEMI complicated by out of hospital cardiac arrest

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ABSTRACT

Background: There is limited data regarding long-term survival in patients who present with STEMI and out of hospital cardiac arrest (OHCA).

Methods: We prospectively analysed outcomes in 3521 consecutive patients who were diagnosed with STEMI and underwent primary percutaneous coronary intervention (PPCI) or coronary artery bypass surgery from 2004 to 2017. They were divided into two groups according to the presence of cardiac arrest (group I, patients with cardiac arrest; $n = 156$ group II, patients without cardiac arrest; $n = 3365$).

Results: Patients with OHCA had higher in hospital mortality (27.7% vs 2.9%, $p < 0.01$), sustained VT or VF (44.6% vs 4.3%, $p < 0.01$) and cardiogenic shock (22.9% vs 6.8%, $p < 0.01$). 30-day mortality (excluding death within first 24 h) was also higher in the OHCA group (24.6% vs 3.3%, $p < 0.01$). There was no significant difference in recurrent AMI, TVR, stroke, major bleeds or new onset heart failure. After a mean follow-up of 18.6 months, mortality was higher in patients with OHCA (7.9% vs 3.8%, p 0.04). This was driven mainly by an increase in cardiac mortality (5% vs 1.1%, $p < 0.01$). OHCA was a significant predictor of mortality beyond 30 days (HR – 2.5, 95% CI 0.99–6.3). Kaplan–Meier curves and the log-rank test revealed that patients with OHCA had significantly lower survival ($p < 0.01$).

Conclusions: Patients with STEMI complicated by OHCA remain a high-risk group associated with high in hospital mortality. Beyond 30 days the occurrence of cardiac arrest was a significant predictor of all-cause and cardiac mortality.

1. Background

Out of hospital cardiac arrest (OHCA) is a major complication associated with patients presenting with STEMI and is associated with poor outcomes [1]. The proportion of patients presenting with resuscitated cardiac arrest before admission is relatively rare accounting for <5% of all AMI patients [2]. Significant efforts have been made to improve outcomes in patients with myocardial infarction and OHCA. Emergency percutaneous coronary intervention (PCI) may improve survival in this group of patients [3–6] and this is reflected in current guidelines [7]. Knowledge about outcomes in these patients is limited mainly due to the fact that they are difficult to recruit and hence excluded from clinical trials. Previous studies have demonstrated OHCA to be associated with increased short-term mortality [8,9]. The influence of OHCA on long-term survival is however unclear with some studies showing worsened long-term survival [9,10] while others showing no difference in patients who have survived cardiac arrest [8,11,12]. The aim of this study was hence to prospectively evaluate long-term clinical outcomes of patients with ST elevation myocardial infarction (STEMI) and OHCA undergoing emergency PCI.

2. Methods

2.1. Study population

3521 consecutive patients who presented with ST elevation myocardial infarction and underwent primary percutaneous coronary intervention (PPCI) or coronary artery bypass surgery from 2004 to 2017 were recruited. Recruitment occurred in a prospective fashion and after informed consent. The patients either presented directly to Westmead Hospital (Tertiary centre) or were transferred after referral by four associated regional hospitals. The diagnosis of STEMI was confirmed on angiogram in all patients and all patients were transferred to the cardiac catherization laboratory with the purpose of undergoing PPCI. All the patients were commenced on guideline based optimal medical therapy.

The patients were divided into two groups, those who had experienced out-of- hospital cardiac arrest (OHCA) and those who had not

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(no OHCA). Out-of-hospital cardiac arrest was identified according to the definition provided by the European Resuscitation Council [13]. Patients were followed at 1, 6, and 12 months. Subsequent follow-up was carried out on a yearly basis, unless symptoms intervened. Telephone contact, clinics, and review of hospital medical records were methods used for follow-up.

Ethics approval for the study was given by the Western Sydney Local Health District Human Ethics Committee. Patients were followed at 1, 6, and 12 months. Subsequent follow-up was carried out on a yearly basis, unless symptoms intervened.

2.2. Outcomes

In hospital outcomes included death on arrival, in hospital death (excluding death on arrival), ventricular tachycardia or fibrillation, cardiogenic shock, acute renal impairment, cerebrovascular accident, major bleed (bleeding that was fatal or overt bleeding with a drop in haemoglobin level of at least 20 g/L or requiring transfusion of at least 2 units packed blood cells, or haemorrhage into a critical anatomical site), new onset heart failure and repeat myocardial infarction.

Long-term outcomes included death, myocardial infarction, TVR/TLR, stroke, CABG and (TVR: defined as repeat revascularization of the treated vessel, TLR: Target lesion revascularization was defined as either repeat percutaneous or surgical revascularization for a lesion anywhere within the stent or the 5-mm borders proximal or distal to the stent). Three local investigators blinded to BMI category were responsible for adjudication of the cause of death (Cardiac vs Non-Cardiac). Information collected from witnesses, relatives, inpatient records and death certificates from the Registry of Births, Deaths, and Marriages were used to make a decision regarding the cause of death.

2.3. Statistical analysis

We used the Statistical Package for the Social Sciences for Windows (SPSS release 15.0, SPSS, Inc., Chicago, IL, USA) for analysis. Chi-square test was used to test for association between categorical variables and One-way ANOVA for the association between categorical and continuous variables. The cumulative risk of mortality was estimated using the Kaplan–Meier procedure and log rank Chi-square tests. We used Cox regression multivariable analysis to derive independent predictors of the mortality using the variables listed in Table 3. A p value of <0.05 was considered significant.

3. Results

A total 3521 STEMI patients treated with PPCI or CABG were recruited. Patients were classified according to whether or not they presented with out of hospital cardiac arrest. A total of 156 patients (4.4%) presented with OHCA. The mean follow-up was for 18.6 (SD ± 19.5) months. Baseline characteristics are shown in Table 1. Patients who presented with OHCA were significantly less likely to have a history of smoking (59.7% vs 64.2%, $p < 0.01$) and family history of ischemic heart disease (24.8% vs 42.1%, p < 0.01). There was no difference in the other traditional risk factors including diabetes, hypertension and dyslipidaemia. Both groups received standard treatment for acute myocardial infarction with no difference between the groups in this regard. Procedural and angiographic characteristics are mentioned in Table 1. Symptom to door time was significantly less in patients with OHCA (98.31 ± 82.2 min vs 170 ± 366 min, p-0.02). Patients with OHCA were more likely to have LAD territory infarct (52.9% vs 43,6%, p 0.01), had lower mean LVEF (43.18% vs 48.97%, $p < 0.01$) (Table 2).

Table 1
Baseline characteristics in patients with STEMI, with and without out of hospital cardiac arrest (OHCA).

	Group I ($n = 156$)	Group II ($n = 3365$)	P Val
Demographics			
Mean age	60.65 ± 12.07	60.59 ± 12.89	0.94
Male gender	127(81.4%)	2664(79.2%)	0.79
Medical history			
History of smoking	74 (59.7%)	2110 (64.2%)	<0.01
Hypertension	58(45%)	1767(53.4%)	0.16
Diabetes	42(31.8%)	964 (29.3%)	0.97
Renal impairment	26 (17%)	403(12.1%)	0.18
COPD	11(9.5%)	337(11.9%)	0.26
Hyperlipidemia	66 (50.8%)	1521 (46.2%)	0.17
Family history	30 (24.8%)	1365(42.1%)	<0.01
Previous CVA	4(3.2%)	161(4.9%)	0.66
Prev IHD	35 (26.9%)	780 (23.7%)	0.23
Previous PTCA	19 (14.6%)	390 (11.8%)	0.77
Previous CABG	6(4.7%)	111 (3.4%)	0.84
Signs and symptoms on presentation			
Mean SBP (mm of Hg)	115 ± 29	131 ± 37	<0.01
Mean DBP (mm of Hg)	73 ± 19	78 ± 17	<0.01
Mean heart rate	91 ± 25	78 ± 20	<0.01
Pulmonary EDEMA	67(43.2%)	366(11%)	<0.01
Mean LVEF ± S.D. (%)	43.18 ± 13.4	48.97 ± 11.8	<0.01
Mean CK	3603	2324	<0.01
Mean troponin	2689	1957	0.5
Medications			
Aspirin	104(81.3%)	2625 (79.8%)	0.39
Clopidogrel	119 (93.1%)	3088 (94%)	0.86
ACE inhibitors/ARB	117 (91.4%)	2846 (87.1%)	0.36
Beta blockers	116(90.6%)	2834 (86.5%)	0.39
Calcium channel blockers	11(6.9%)	18(9.9%)	0.57
Statins	97(75.8%)	2472 (75.2%)	0.98
Angiographic characteristics			
Symptom to door time (min)	98.31 ± 82.2	170 ± 366	0.02
Door to table time (min)	91.7 ± 72.4	95.5 ± 94.8	0.59
Table to 1st inflation time (min)	39.5 ± 18	37.6 ± 19.3	0.25
LAD territory	83(52.9%)	1471(43.6%)	0.01
RCA territory	46(29.3%)	1333(39.5%)	<0.01
CxTerritory	16(10.2%)	392(11.6%)	0.35
Left main disease	0(0%)	0(0%)	0.07
Single vessel disease	75(47.8%)	1574(46.7%)	0.43
Double vessel disease	37(23.6%)	940(27.9%)	0.14
Triple vessel disease	42(26.8%)	789(23.4%)	0.19
Pre-intervention TIMI 0	120(76.4%)	2446(72.5%)	0.16
Procedural success	137(89%)	3032(90.6%)	0.66
Treatment strategy			
PCI	138(90.8%)	3112 (93.7%)	0.36
CABG	7(4.6%)	106(3.2%)	0.36
Medical Therapy	7(4.6%)	103(3.1%)	0.36

COPD – Chronic Obstructive Pulmonary Disease, CVA – Cerebro Vascular Accident, IHD – Ischemic Heart Disease, PTCA - Percutaneous Transluminal Coronary Angioplasty, CABG - Coronary Artery Bypass Graft, SBP - Systolic Blood Pressure, DBP - Diastolic Blood Pressure, CK – Creatine Kinase, ACE - Angiotensin Converting Enzyme, ARB - Angiotensin Receptor Blocker. LAD – Left Anterior Descending Artery, RCA – Right Coronary Artery, Cx – Circumflex Artery, PCI – Percutaneous Coronary Intervention, CABG – Coronary Artery Bypass Grafts, CK – Creatine Kinase, ACE - Angiotensin Converting Enzyme, ARB - Angiotensin Receptor Blocker.

3.1. Short-term outcomes

Patients with OHCA had higher in hospital mortality even after excluding mortality within 24 h of hospital admission (27.7% vs 2.9%, $p < 0.01$). In addition to this they were more likely to have sustained VT or VF (44.6% vs 4.3%, $p < 0.01$) and cardiogenic shock (22.9% vs 6.8%, p < 0.01). There was no significant difference in the occurrence of acute renal impairment, recurrent AMI and stroke. (See Table 2.)

30-day mortality (excluding death within first 24 h) was also higher in the OHCA group (24.6% vs 3.3%, p < 0.01). There was no significant difference in recurrent AMI, TVR, stroke, major bleeds or new onset heart failure.

Table 2
Short and long-term outcomes in STEMI patients with and without OHCA.

	Group I	Group II	P Val
In-Hospital outcomes			
DOA	22(14.1%)	78(2.3%)	<0.01
In hospital death (excluding DOA)	38(27.7%)	94(2.9%)	<0.01
VT or VF	70(44.6%)	146(4.3%)	<0.01
Cardiogenic shock	36(22.9%)	228(6.8%)	<0.001
Acute renal impairment	0(0%)	31(0.9%)	0.24
CVA	2(1.3%)	17(0.5%)	0.21
AMI	0(0%)	18(0.5%)	0.44
30-Day outcomes (excluding DOA)			
Death	36(26.3)	109(3.3%)	<0.01
MI	2(1.3%)	23(0.7%)	0.31
TVR	0(0%)	23(0.7%)	0.35
Stroke	0(0%)	21(0.6%)	0.38
Major Bleed	0(0%)	16(0.5%)	0.48
CABG	0(0%)	118(3.5%)	<0.01
New onset HF	0(0%)	22(0.7%)	0.37
Long-term outcome			
Patients who survived first hospital admission			
Death	44(32.1%)	225(6.8%)	<0.01
Cardiac death	37(27.1%)	115(3.5%)	<0.01
Sudden cardiac death	5(3.6%)	7(0.2%)	<0.01
Non-cardiac death	1(0.7%)	52(1.6%)	0.38
Repeat AMI	4(3.5%)	135(5%)	0.34
TVR/TLR)	2(1.8%)	178(6.6%)	0.02
Outcomes (beyond 30 days)			
Death	8(7.9%)	122(3.8%)	0.04
Cardiac death	5(5%)	34(1.1%)	<0.01
Sudden cardiac death	1(1%)	2(0.1%)	0.09
Non cardiac death	0(0%)	47(1.5%)	0.23

3.2. Long-term outcomes

After a mean follow-up of 18.6 months and excluding patients who died within the first 30 days after presentation, mortality was higher in patients with OHCA (7.9% vs 3.8%, p 0.04). This was mainly driven by significantly higher rates of cardiac death (5% vs 1.1%, $p < 0.01$). Sudden cardiac death was also higher in patients with OHCA (1% vs 0.1%, p 0.09). Non-cardiac death was similar in both groups. Kaplan–Meier curves and the log-rank test revealed that patients with OHCA had significantly lower survival (p < 0.01). (Fig. 1).

3.3. Predictors of mortality

After adjusting for age, LVEF, renal impairment, hypertension the occurrence of OHCA remained a significant predictor of mortality in patients who survived 30 days post presentation. The hazard ratio for mortality for patients who presented with OHCA in comparison to those who did not was 2.5 (95% CI 0.99–6.3, p 0.05) (Table 3).

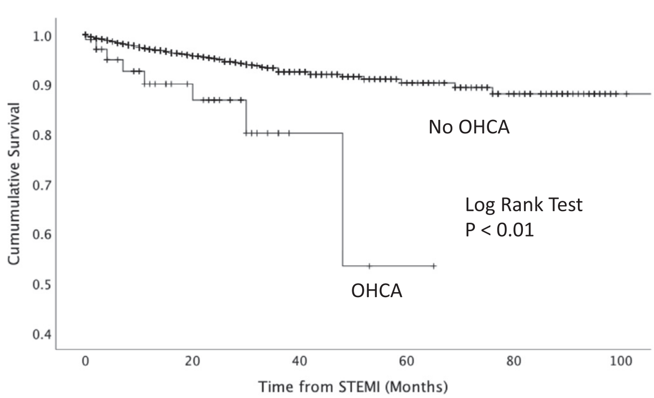

Fig. 1. Kaplan Meier Survival – in patients with and without OHCA (beyond 30 days).

Age, EF and renal impairment were the other significant predictors of mortality.

3.4. Mortality in patients with OHCA

Of the 156 patients who presented with cardiac arrest 22 did not survive the first 24 h. In the remaining 134 patients overall mortality was 30.6%. Patients who did not survive were significantly more likely to be male (64.4% vs 35.6%, $p < 0.01$), older (63.56 ± 11.85 vs 58.87 ± 12.06 years, p – 0.03), have a history renal impairment (25.6% vs 10.8%, p – 0.03), diabetes (50% vs 23.3%, p < 0.01) and ischemic heart disease (53.3% vs 16.9%, p < 0.01) (Supplementary Table 1). They were less likely to have a shockable rhythm (27.6% vs 64.3%, $p < 0.01$). In addition to this they were more likely to have triple vessel disease (40% vs 16.1%, $p < 0.01$. In patients who presented with OHCA on multivariate analysis a history of diabetes (HR 2, 95% CI 1–3.9, p – 0.04) and triple vessel disease (HR 3.2, 95% CI, 1.5–6, p < 0.01) were the significant predictors of mortality (Supplementary Table 2).

3.5. Outcome according to presence or absence of shockable rhythm

In patients with OHCA, mortality was higher in patients who presented with a non-shockable rhythm/PEA (64.3% vs 27.6%, p, 0.01) and was driven primarily by an increase in cardiac death (71.4% vs 26%, p, 0.01) (Supplementary Table 3). This remained true during analysis of patients who survived the first 24 h after admission. The absence of shockable rhythm was not however a predictor of mortality on multivariate analysis.

4. Discussion

In hospital mortality remains extremely high in patients who are admitted with STEMI after being resuscitated from cardiac arrest [8,11]. Cardiac arrest patients are often excluded from clinical trials as a result of which clinical data regarding prognostic factors in this group of patients is limited [11]. Our study adds to the current body of evidence available for this group of patients. The main findings were as follows 1) OHCA was associated with significantly higher risk of in hospital and 30-day mortality. 2) After a mean follow-up of 18.6 months, OHCA was associated with significantly higher all-cause mortality beyond 30 days when compared to non-OHCA patients 3) The increase in all-cause mortality in OHCA patients was driven mainly by a rise in cardiac mortality, there was no significant difference in non-cardiac mortality. 4) In patients with OHCA, diabetes and triple vessel disease were significant predictors of mortality.

So as to assure uniformity in our patient recruitment we excluded patients with in hospital cardiac arrest. In terms of burden of cardiovascular disease OHCA patients were more likely to have LAD and RCA territory disease. LVEF was significantly lower in this group and as expected patients with OHCA were more likely to present with cardiogenic shock. Interestingly symptom to door time was significantly shorter in OHCA compared to non OHCA patients. This may be to the fact that OHCA is usually a rapid and sudden event, hence attracting earlier attention of people nearby and this has been reported in previous studies [10]. All of the patients in the OHCA group underwent urgent coronary angiography. This is in keeping with recommendations from ACC guidelines (Class IB) [7] regarding STEMI patients who present with OHCA and is indicative of improved adherence to evidence-based guidelines. There was no difference between OHCA and non OHCA groups with regards to PCI percentage. Notably there was no significant difference in the procedural success rate in both groups.

In agreement with most [8,9,11] but not all [10] of the previous studies OHCA was associated with higher in hospital mortality in comparison to the non OHCA group. In a study by Siudak et al., in hospital death was not significantly higher in OHCA patients (7.1% vs 3.9% for OHCA and non OHCA patients respectively, p-0.28). There was a trend

Table 3
Predictors of mortality.

Univariate predictors	Hazard ratio (95% CI)	P - Val	Multivariate predictors	Hazard ratio (95% CI)	P - val
Age (per yr increase)	1.07 (1.05–1.08)	<0.01	Age (per yr increase)	1.07 (1.05–1.09)	<0.01
Renal impairment	3.7 (2.5–5.4)	<0.01	Renal impairment	2.1 (1.2–3.6)	<0.01
Hypertension	1.01 (0.64–1.6)	0.97			
Diabetes	1.02 (0.83–1.2)	0.89			
LVEF (for every 1% decrease)	1.04 (1.03–1.06)	0.17	LVEF (For every 1% decrease)	1.05 (1.03–1.06)	<0.01
OHCA	3.3 (1.6—6.9)	0.001	OHCA	2.5 (0.99–6.3)	0.05

towards increase in mortality at 30 days (11.9% vs 5.2%, p-0.054). One potential explanation for the difference in short-term mortality in this study could be the overall low mortality in comparison to other studies. Notably, only patients who were awake following cardiac resuscitation were included in the mentioned study. In agreement with findings of Siudak et al. and Zimmermann et al., long-term mortality was significantly higher in the OHCA patients in our study. Zimmerman et al. demonstrated that 1 year mortality was high in STEMI patients with OHCA when compared to non OHCA patients (34.7% vs 9.5% respectively, $p < 0.001$) [11]. This was however a retrospective study. In the study by Siudak et al. involving 1650 patients with STEMI, one-year mortality was higher in patients who presented with OHCA (19.1% vs 8.1%, p-0.01) [10]. OHCA remained a significant predictor of mortality in patients who survived the first 30 days after STEMI. This was despite the fact that rates of procedural success were similar in both groups. Garot et al. in their study involving 186 patients with cardiac arrest complicating myocardial infarction demonstrated six-month mortality as 46% from hospital admission [2]. After excluding mortality during hospital admission six-month mortality after discharge was only 2.9%. In addition to this, Kaplan–Meier survival estimation showed almost linear probability of survival after 30 days. In hospital mortality in our study was similar this study.

Our findings regarding long-term mortality are in contrast to those demonstrated by Bendz et al. [14]. Mortality in this study was 27.9% in the OHCA vs 7.9% in the non OHCA group. After discharge from hospital there was no significant difference in mortality between the two groups. This may have been influenced by the fact that this was an observational study involving a relatively small population sample (365 patients). In addition to this overall mortality was low in this study as patients who did not survive CPR were not included. Lee et al. in their study involving 7942 patients with STEMI found no residual effect of OHCA beyond 30 days [8]. There may be several possible explanations for this. First, in comparison to their study, a higher (92.4%) proportion of patients overall underwent primary PCI in our study. In addition to this, in our study, there was no significant difference in primary PCI rates between OHCA and non OHCA patients (90.8% vs 93.7%, p-0.36). In the study by Lee et al. patients with OHCA were significantly more likely to have undergone primary PCI compared to those without OHCA (79.5% vs. 74.7%, $p = 0.020$). Lim et al. demonstrated that 1-year survival of patients discharged alive from hospital was similar between patients with and without OHCA (96% vs. 97% $p = 0.8$). In contrast to the study by Lim et al. our study included STEMI patients only. Finally and importantly, in contrast to the studies by Lim et al. and Lee et al., follow-up in our study was longer, with mean follow-up at 18.6 months.

In our study the presence of triple vessel disease and diabetes were significant predictors of mortality in patients with OHCA on multivariate analysis. Barcan et al. [15], in a study involving 78 patients with STEMI and out of hospital cardiac arrest, identified on multivariate analysis, the presence of cardiogenic shock (odds ratio [OR]: 3.17, $p = 0.02$), multivessel disease (OR: 3.0, $p = 0.03$), renal failure (OR: 4.2, $p = 0.004$), anaemia (OR: 4.07, p = 0.02), need for mechanical ventilation >48 h (OR: 8.07, $p = 0.0002$) and a duration of stay in the ICU longer than 5 days (OR: 9.96, p = 0.0002) as the most significant independent predictors for mortality. Zimmermann et al. demonstrated in their study involving 72 patients with STEMI and OHCA undergoing PCI, age adjusted multivariate analysis identified 'unsuccessful PCI', 'vasopressors on admission' and 'start of ACLS after >6 min' as independent predictors of negative long-term outcome [11]. Our study in keeping with previous studies, demonstrates that mortality was influenced by condition of the coronary circulation and the existing comorbidities.

In addition to this we noted that patients with a shockable rhythm had better survival in comparison those without one. This remained true after excluding patients with death within 24 h of arrival. However on multivariate analysis the absence of a shockable rhythm was not a significant predictor of mortality. These findings are in keeping with the findings of Lee et al. In their study patients with initial rhythm as non-shockable showed significantly higher in-hospital mortality than the patients with initial rhythm as shockable before (29.8% vs. 42.7%, p b 0.019) and after excluding the patients who died at the day of hospital arrival (15.3% vs. 30.2%, $p = 0.006$).

Coronary artery disease is the most common cause of OHCA [16]. Recent guidelines recommend urgent PCI in patients with OHCA and myocardial infarction [7]. Our study in agreement with previous studies demonstrates that it is feasible to perform PCI in patients with OHCA. In this study all patients were transferred to the cardiac catheterisation laboratory for the purpose of primary PCI. Successful PCI was achieved in >90% in both OHCA and non OHCA groups with no significant difference between the two. Limited knowledge is available about the prognostic factors in patients with OHCA and STEMI. This is mainly due to the fact that prognosis maybe determined by a multitude of factors some of which may be difficult to assess. Our study emphasises the fact that OHCA is associated with significant morbidity and mortality. Short-term mortality may have been explained by lower LVEF, increased rates of cardiogenic shock and ventricular arrhythmias. Poor angiographic and procedural features including increased incidence of LAD disease and reduced likelihood of post procedural TIMI 0 were additional features which may have contributed to this outcome. There was no difference in guideline-based treatment in the two groups. Unlike most of previous studies we report increased long-term mortality. This finding is significant and indicates that this group of patients may benefit from more stringent follow-up. The data in this group of patients is still limited, therefore we believe our study adds an additional layer of evidence to this topic.

4.1. Limitations

Our study has several limitations. First, we were unable to provide details of resuscitation prior to hospital admission. These included variables like duration of total arrest time, total cardio- pulmonary resuscitation time, and bystander cardiopulmonary resuscitation all of which may have an influence on clinical outcomes. In addition to this factors that may influence outcomes in this group of patients including blood glucose levels and treatment with hypothermia were not analysed as this data was not available. Hence future research on out of hospital cardiac arrest should take into consideration these variables. Finally, ours was a single centre study.

5. Conclusions

Cardiac arrest complicating STEMI was associated with increased in-hospital mortality. After a mean follow-up of 18.6(SD $\pm$ 19.5) months, OHCA remained a significant predictor of all-cause mortality. This group of patients may hence benefit from more meticulous follow-up.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2018.12.001.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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