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Predictors of in-hospital mortality in recovered Out-of-Hospital Cardiac Arrest patients with Coronary Artery Disease

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Abstract

Introduction: Recovered Out-of-Hospital Cardiac Arrest (rOHCA) population is wide and heterogenous. Few studies have focused specifically on outcomes in the rOHCA subgroup with proven significant coronary artery disease (SigCAD). We aimed to further characterize this specific population.

Methods: Retrospective observational study of consecutive rOHCA patients submitted to coronary angiography for presumed Acute Coronary Syndrome (ACS). The finding of significant coronary artery disease, defined as >70% stenosis in the major vessels or >50% in left main and/or need for intervention, established coronary cause of Out-of-Hospital Cardiac Arrest (OHCA). Only patients with SigCAD were included.

Results: 60 patients were included, 85% were male, mean age was 62.6 ± 12.1 years. In-hospital mortality rate was 43.3%. Patients with diabetes (42.3% vs 11.8%, p=0.007) and history of previous stroke (11.5% vs 0%, p= 0.042) were less likely to survive. Regarding to initial presentation, a non-shockable initial rhythm (42.3% vs 8.8%, p=0.002), home or public location of the arrest (88.5% vs 50.0%, p=0.002), a longer time delay from basic life support (BLS) until return of spontaneous circulation (ROSC) (ln- 2.95 ± 0.60 vs 2.15 ± 0.98, p=0.001) and higher doses of adrenaline administered during advanced life support (ALS) (3.6 ± 3.0 vs 1.8 ± 2.3, p= 0.009) were statistical correlated with higher mortality. In-hospital variables revealed that a higher GRACE risk score values at 24 to 48 hours (176.2 ± 33.4 vs 151.2 ± 31.9, p=0.041), higher lactate values at admission (ln- 1.80 ± 0.83 vs 1.28 ± 0.99, p=0.039) and first 6 hours (ln- 1.02 ± 0.80 vs 0.59 ± 0.71, p=0.040), potassium levels at admission (4.10 ± 0.87 vs 3.66 ± 0.70, p=0.05) and first 24 hours (4.20 ± 0.82 vs 3.81 ± 0.48, p=0.028), and lower pH levels at admission (7.17 ± 0.18 vs 7.27 ± 0.19, p=0.011) and first 48 hours (7.32 ± 0.10 vs 7.41 ± 0.05, p<0.001) during in-hospital stay were linked to poor prognostic outcomes. In-hospital complications, as anoxic brain injury (57.7% vs 23.5%, p<0.001), hemodynamic instability (96.2% vs 38.2%, p<0.001), multiorgan dysfunction (76.9% vs 26.5%, p=0.007) had a strict relation with in-hospital mortality.

Conclusion: The presence of specific clinical and biochemical characteristics can be applied to determine in-hospital mortality in rOHCA patients with proven coronary artery disease (CAD).

Keywords

Out-of-Hospital Cardiac Arrest, Return of Spontaneous Circulation, Coronary Artery Disease, Coronary Angiography

Resumo

Introdução: A população de pacientes recuperados após paragem cardiorrespiratória extra-hospitalar (rOHCA) é ampla e heterogénea. Poucos estudos se focaram especificamente nos resultados do subgrupo de pacientes recuperados após paragem cardiorrespiratória extra-hospitalar com doença arterial coronária significante comprovada. O nosso objetivo fora caracterizar esta população específica.

Métodos: Estudo observacional retrospetivo de pacientes rOHCA submetidos a angiografia coronária por presumível Síndrome Coronário Agudo (ACS). A identificação de doença arterial coronária significativa (SigCAD), definida como estenose >70% em vasos major ou >50% no ramo principal esquerdo e/ou a necessidade de intervenção, estabeleceu causa coronária de paragem cardiorrespiratória extra-hospitalar (OHCA). Apenas os pacientes com doença arterial coronária significativa foram incluídos.

Resultados: 60 pacientes foram incluídos, 85% homens, com idade média de 62.6 ± 12.1 anos. A taxa de mortalidade intra-hospitalar foi de 43.3%. Pacientes com diabetes (42.3% vs 11.8%, p=0.007) e história prévia de acidente vascular cerebral (11.5% vs 0%, p=0.042) tiveram uma menor probabilidade de sobreviver. Relativamente à apresentação inicial, um ritmo inicial não-desfibrilhável (42.3% vs 8.8%, p=0.002), paragem em local público ou privado (88.5% vs 50.0%, p=0.002), maior intervalo de tempo entre suporte básico de vida até recuperação da circulação espontânea (ln- 2.95 ± 0.60 vs 2.15 ± 0.98, p=0.001) e doses mais elevadas de adrenalina administradas durante o suporte avançado de vida (3.6 ± 3.0 vs 1.8 ± 2.3, p= 0.009) correlacionaram-se estatisticamente com maior mortalidade. As variáveis intra-hospitalares revelaram que, valores mais elevados do GRACE risk score das 24 até às 48 horas (176.2 ± 33.4 vs 151.2 ± 31.9, p=0.041), valores mais elevados de lactatos à admissão (ln- 1.80 ± 0.83 vs 1.28 ± 0.99, p=0.039) e nas primeiras 6 horas (ln- 1.02 ± 0.80 vs 0.59 ± 0.71, p=0.040), valores de potássio à admissão (4.10 ± 0.87 vs 3.66 ± 0.70, p=0.05) e nas primeiras 24 horas (4.20 ± 0.82 vs 3.81 ± 0.48, p=0.028), e valores baixos de pH à admissão (7.17 ± 0.18 vs 7.27 ± 0.19, p=0.011) e nas primeiras 48 horas (7.32 ± 0.10 vs 7.41 ± 0.05, p<0.001), durante o internamento, estiveram relacionados com maus resultados prognósticos. Complicações intra-hospitalares como, lesão anóxica cerebral (57.7% vs 23.5%, p<0.001), instabilidade hemodinâmica (96.2% vs 38.2%, p<0.001), disfunção multi-órgão (76.9% vs 26.5%, p=0.007) tiveram uma relação estrita com mortalidade intra-hospitalar.

Conclusão: A presença de características clínicas e bioquímicas específicas podem ser aplicadas para determinar mortalidade intra-hospitalar em pacientes rOHCA com doença arterial coronária comprovada.

List of Abbreviations

ACS – Acute Coronary Syndrome
ALS – Advanced Life Support
BLS – Basic Life Support
BMI – Body Mass Index
CA – Coronary Angiography
CABG – Coronary Artery Bypass Graft
CAD – Coronary Artery Disease
CPR – Cardiopulmonary Resuscitation
EKG – Electrocardiogram
GRACE – Global Registry of Acute Coronary Events
HF – Heart Failure
ICU – Intensive Care Unit
INEM – Portuguese National Institute of Medical Emergency
LV – Left Ventricle
OHCA – Out-of-Hospital Cardiac Arrest
PCI – Percutaneous Coronary Intervention
rOHCA – recovered Out-of-hospital Cardiac Arrest
ROSC – Return of Spontaneous Circulation
RV – Right Ventricle
SigCAD – Significant Coronary Artery Disease
VMER – Medical Emergency and Reanimation Vehicle

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Introduction

Out-of-Hospital Cardiac Arrest (OHCA) remains one of the most challenging health care problems in western countries.[1,2] The estimated number of patients with OHCA in Europe is 275.000, annually,[3,4] with an incidence of 84 per 100.000 inhabitants.[2]

Despite recent efforts to improve cardiopulmonary resuscitation (CPR), with the development of evidence-based guidelines, only 30-40% of OHCA patients will attain Return of Spontaneous Circulation (ROSC) and merely 7%, approximately, will survive until hospital discharge.[1,5,6]

Coronary Artery Disease (CAD) represents the main cause of OHCA in adults.[1,7] Given the high incidence of Acute Coronary Syndromes (ACS) in patients with OHCA, current guidelines recommend immediate coronary angiography (CA) to be considered in all recovered OHCA (rOHCA) patients with suspected ACS.[8-10] However, this concept has recently been challenged, in a randomized trial that found that in patients without ST-segment elevation, immediate CA did not improve overall survival when compared to delayed CA.[11]

CA is nevertheless a crucial part of the early approach to post-ROSC patients, considering the clinical importance of the CAD in OHCA' ethiology. Successful treatment stands as an independent predictive factor of survival in OHCA patients without an obvious extra-cardiac cause of arrest, regardless of the post-resuscitation electrocardiographic pattern.[1]

The identification of determined cardiovascular risk factors, symptoms and circumstances in which the cardiac arrest occurred, the promptitude of medical assistance support, as the need of an advanced support, will give a general information on the severity clinical status of the patient at hospital admission. These, complemented with imaging and biochemical data, will allow to determine better outcomes.

A 2014 International Committee consensus statement[12], updated the variables and definitions considered important in understanding the portrait of OHCA, which are the cornerstone for the larger majority of OHCA related studies. Agreement on how and what to measure in cases of OHCA leads to a better understanding of the characteristics associated with mortality, improves management pathways and hopefully survival from this devastating condition.[13]

Multiple studies have explored the predictors of coronary artery disease in the global OHCA population.[14-16] However, few have focused specifically on predictors of in-hospital mortality in the OHCA survivors with proven coronary artery disease by coronary angiography.[17] In this subset of OHCA patients, consistent data regarding to their specific clinical, biochemical and imaging prognostic predicts is still scarce, hence the importance of this study. Establishing predictors of

adverse outcomes in this critical population can provide vital insights to improve clinical approach and management of this selective group of patients.

This study aims to characterize the population of OHCA survivors and non-survivors with proven CAD by coronary angiography and to establish the clinical, biochemical and imaging predictors of in-hospital mortality.

Methods

Retrospective observational study of patients admitted after rOHCA and submitted to coronary angiography in the subsequent 48 hours. The finding of significant CAD (defined as >70% stenosis in the major vessels or >50% in left main and/or need for percutaneous coronary intervention)[18,19] was used to establish coronary cause of OHCA. Only patients with proven CAD admitted at Hospital de Santo António - Centro Hospitalar Universitário do Porto, from October 2006 to July 2018 were included. The study was approved by the Research Ethics Committee – N/REF. ª 2018.237 (207-DEFI/206-CES).

Pre-hospital variables, demographic and clinical characteristics and in-hospital evolution data, including diagnostic tests, therapeutic options and cardiovascular status were analysed by chart review.

Collected data were anonymized by the attribution of a numeric ID to each patient that was saved separately and protected by password. Patients confidentiality was guaranteed.

Descriptive statistics were summarized as percentages for categorical variables and as mean ± standard deviation or median ± interquartile range for continuous variables. Pearson χ^2 test and Student's t-test (Fisher Exact test or Mann-Whitney test when appropriate) were used to compare baseline characteristics and to identify risk factors associated with in-hospital mortality. The primary outcome was in-hospital mortality. Univariate logistic regression analysis was used to determine which variables could predict in-hospital mortality. P values of <0.05 settled statistical significance.

All statistical analyses were performed using IBM SPSS Statistics 25 software.

Results

Between October 2006 to July 2018, 73 patients recovered from OHCA were admitted at Hospital de Santo António - Centro Hospitalar Universitário do Porto and submitted to coronary angiography. Among them, 10 (13.7%) did not present evidence of CAD. Of the remaining 63 (86.3%) patients with documented CAD, 3 (4.8%), did not fulfil the criteria used to define significant CAD and were excluded. A total number of 60 patients with rOHCA and proven CAD were included in this study (Figure 1).

Baseline and clinical characteristics

The studied population (Table I) was composed by 51 men (85.0%) and 9 women (15.0%), with a mean age of 62.6 years old (range 50.5 to 74.7 years).

Relatively to the cardiovascular risk factors, 35 (53.8%) patients had hypertension, 15 (25.0%) diabetes, 34 (56.7%) dyslipidaemia and 9 (15.0%) patients were obese (BMI ≥ 25 kg/m^2). A significant percentage of patients had smoking habits, recent or past (35 patients, 58.3%). Heart failure (HF) symptoms were present before OHCA in 11 (18,3%) cases. 23 (38,3%) patients had previously known CAD. Cerebrovascular disease was found in 5.0% (3 patients) of the population.

Different locations of the cardiac arrest were noted as follows: public place in 27 patients (45.0%), at home in 13 (21.7%), during the transport to the hospital in 3 (5.0%), and at the hospital but before medical attention (waiting room), in 17 (28.3%) cases. Most patients (65.0%) were transported to the hospital by an emergency unit (Medical Emergency and Reanimation Vehicle - *VMER*), and only a small percentage by own means or ambulance (11.7% and 23.3% respectively). The mean time from the beginning of basic life support (BLS) manoeuvres to ROSC was 17.08 ± 13.13 minutes. During advanced life support (ALS) manoeuvres, the mean dose of adrenaline administered was 2.6 ± 2.8 mg.

Most patients presented with a shockable initial rhythm: 46 (76.7%) patients presented with ventricular tachycardia or ventricular fibrillation, contrasting from the remaining 14 (23.3%) patients that demonstrated a non-shockable initial rhythm (Pulseless Electrical Activity/Asystole). Chest pain was present before arrest in 40% of the patients.

On the post-ROSC ECG, an ST-segment elevation pattern was identified in 36 (60%) cases.

Echocardiographic assessment (Table II) was available for 95.0% of patients. Left ventricle disfunction moderate to severe, at 24 hours of hospital admission was present in 40 (66.7%), and in 36 (60.0%) patients during in-hospital stay. Right ventricle disfunction in the first 24 hours of admission was present in only 1 (1.7%) patient.

Predictors of in-hospital mortality

The population was divided in two groups, according to hospital survival (Table I). *rOHCA non-survivors* (Group 1) included all rOHCA patients that did not survive till hospital discharge, and, *rOHCA survivors* (Group 2). In-Hospital mortality was 43.3%. The demographic and clinical baseline characteristics (Table I) of the study population showed that rOHCA non-survivors had a higher incidence of diabetes (42.3% vs 11.8%, p=0.007) and prior stroke history (11.5% vs 0%, p=0.042). No significant differences between Group 1 and 2, with respect to age, gender, and the presence of cardiovascular risk factors prior to OHCA were found. Likewise, there weren't any differences in the two groups according to the mean of transport, clinical history of cardiac arrest relapse prior to hospital admission, presence of chest pain and in the first post-ROSC electrocardiographic pattern. On the other hand, rOHCA non-survivors were more likely to present with an non-shockable initial arrest rhythm (43.3% vs 8.8%, p= 0.002), a longer time delay from BLS to ROSC (ln- 2.95 ± 0.60 vs 2.15 ± 0.98, p=0.001) and to be administered higher doses of adrenaline during ALS (3.6 ± 3.0 vs 1.8 ± 2.3, p= 0.009).

Regarding to coronary angiography (Table II), there were no significant differences related to Percutaneous coronary intervention (PCI), procedural success/failure or type of revascularization (culprit or complete). Echocardiographic data (Table II), didn't show significant differences between groups.

Hospital survival rate was also significantly lower in patients higher GRACE risk score[20] values (Table III) at 24-48 hours after admission (176.2 ± 33.4 vs 151.2 ± 31.9, p=0.041).

In-hospital mortality was strongly correlated with biochemical variables (Table III): higher potassium levels at admission (4.10 ± 0.87 vs 3.66 ± 0.70, p=0.05) and at 24 hours (4.20 ± 0.82 vs 3.81 ± 0.48, p=0.028), as so persistently higher lactates values, in serial measurements, in the first 6 hours, (ln- 1.80 ± 0.83 vs 1.28 ± 0.99, p=0.039 and ln- 1.02 ± 0.80 vs 0.59 ± 0.71, p=0.040, respectively) and lower pH level at admission (7.17 ± 0.18 vs 7.27 ± 0.19, p=0.011) and at 24-48 hours (7.32 ± 0.10 vs 7.41 ± 0.05, p<0.001) had an association with a higher mortality rate.

In-hospital evolution in patients that eventually died was associated with a worse clinical status during hospital stay (Table II). rOHCA non-survivors had a significantly higher incidence of anoxic brain injury (57.7% vs 23.5%, p=0.007), hemodynamic instability, defined as either need for vasopressors more than 48 hours, new severe dysrhythmia or arrest (96.2% vs 38.2%, p<0.001) and multi-organ disfunction (76.9% vs 26.5%, p<0.001).

As expected, the median duration of hospital stay was longer in the rOHCA survivors' group compared to non-survivors' group, due to an lower life time expectancy of the non-survivors' group (15, 6-22 days vs 3, 2-6 days, p<0.001).

Univariate logistic regression analysis

In univariate analysis (Table IV), was found that patients with diabetes (OR 5.50, 95% CI 1.50-20.2; p=0.010) location of the arrest at outside (OR 7.67, 95% CI 1.93-30.4; p=0.004), non-shockable initial rhythm (OR 7.58, 95% CI 1.84-31.3; p=0.005), as a longer time delay from BLS to ROSC (OR 3.29, 95% CI 1.51-7.13; p=0.003) and higher administrated doses of adrenaline during ALS (OR 1.31, 95% CI 1.05-1.62; p=0.017) were related to hospital mortality. A higher GRACE score at 24 to 48 hours (OR 1.03, 95% CI 1.01-1.05; p=0.016) also correlated with a poor in-hospital outcome. The biochemical data, registered during in hospital stay, associated with a lower survival rate were higher potassium levels, at admission (OR 2.15, 95% CI 1.01-4.59; p= 0.048) and at 24 hours (OR 2.81, 95% CI 1.04-7.58; p=0.041), lower pH levels at admission (OR 0.05, 95% CI 0.002-0.942; p=0.046) and 24 to 48 hours (OR 0.0, 95% CI 0.00-0.0001) and constantly elevated lactates levels in the first 6 hours – admission (OR 1.89, 95% CI 1.02-3.51; p=0.045); 1 to 6 hours (OR 2.20, 95% CI 1.01-4.79; p=0.048) of the OHCA. All the identified in-hospital complications: anoxic brain injury (OR 4.43, 95% CI 1.46-13.5; p= 0.009), multi-organ disfunction (OR 9.26, 95% CI 2.82-30.4; p<0.001) and hemodynamic instability (OR 30.39, 95% CI 4.87-335; p=0.001) demonstrated a correlation with worse clinical prognosis.

Discussion

The main findings of our study are the following: First, clinical and demographic features did not relate to mortality, except for diabetes and cerebrovascular disease. Second, variables associated to the circumstances of arrest and its initial management correlate with prognosis. On the other hand, failure of percutaneous coronary intervention and ventricular dysfunction were not linked with mortality. Lastly, we corroborate the prognostic utility, in this specific rOHCA population, of multiple biochemical markers classically used to predict survival.

The main goal of our study was to determine specifically in-hospital mortality predictors in rOHCA patients with proven coronary artery disease, as the identified cause of the arrest. Previous studies have mainly explored the predictors of coronary artery disease in the global OHCA population[15,16,21], which is wide and heterogenous. By focusing only in SigCAD patients, we tried to be more accurate on identifying predictors of in-hospital mortality in this subgroup with a common pathophysiological mechanism leading to OHCA (CAD).

Our study population is similar with other important studies[1,14,17,22] concerning clinical and demographic characteristics. It is defined, essentially by males, with a mean age of 63 years old and characterized by the presence of various cardiovascular risk factors, such as, hypertension, smoking habits, dyslipidaemia and diabetes. In line with previous studies[1,14,17,22-24], we found that in-hospital mortality correlate with different factors: pre-existing comorbidities, characteristics of the cardiac arrest episode, and in-hospital biochemical data and complications. Mortality rates were relatively similar with the same studies, that range from 36% to 68%. Contrasting with higher mortality rates, around 90%, reported in descriptive populational studies.[23,25]

Diabetes was related with a higher mortality rate. Actually, diabetes is a well-established cardiovascular risk factor associated with microvascular and advanced macrovascular heart disease and cardiac autonomic dysfunction. These factors may influence myocardial infarction size or provoke asystole during resuscitation[26]. Diabetes is associated with larger myocardial infarction sizes and reduced reperfusion, decreasing the probability to achieve ROSC, and consequently, leading to an increased mortality after acute myocardial infarction, the most common cause of OHCA.[26,27] Among rOHCA patients, Larsson *et al* also showed that diabetics had a lower in-hospital survival rate.[28]

Cerebrovascular disease, as a marker of cardiovascular risk, is not a widely studied variable as a predictor of in-hospital mortality in rOHCA patients. According to our results, history of a previous stroke is a strong indicator of worst clinical outcome. In fact, all the 3 patients with stroke history died during hospital stay. Our small sample size prevents significant conclusions, but it allows us to comment that previous cerebrovascular disease signals decreased hospital survival.

Several predictors of mortality till hospital discharge in this study are consistent with previous publications.[17,22,23] Most of the cardiac events occurred in a public place or at patients' home. The mean time from the beginning of basic life support (BLS) manoeuvres to ROSC was around 17 minutes. These time intervals are the reflect of Portuguese National Institute of Medical Emergency (INEM)'s effectiveness and particularities of our specific population, like short distances and good access to hospital facilities. However, there are still major opportunities for improvement, specially by interventions directed to the general public. Namely, initiatives to better educate, inform and train the public on BLS and increasing the number of automated external defibrillator available in public places could have a major impact.

Shockable initial rhythm, the location of the arrest and lower time delay from BLS to ROSC were related to an improved likelihood of survival. These predictors of favourable outcomes are explained by the fact that an initial ventricular tachycardia/ventricular fibrillation rhythm can be converted into to an effective perfusing cardiac rhythm, helping establish ROSC. Consequently, a longer delay in the achievement of ROSC, has a higher probability of the initial rhythm turning in a non-shockable one, by itself, linked to worst prognosis. Likewise, Wah *et al* confirmed that an initial non-shockable rhythm, subsequently converted to a shockable rhythm was associated with better post-arrest survival and neurological outcomes.[29] Similarly, an arrest at home/private setting is less likely to be promptly rescued by professionals or people who can perform BLS manoeuvres, compared with an arrest occurred in the transport to/or in the hospital. Therefore, there is a higher probability of deterioration of the patient's status, allied with the probability of existing initial non-shockable rhythms and subsequently poor outcome.[30,31]

Adrenaline is one of the few drugs incorporated in advanced life support algorithms.[9] The advantage of adrenaline resides in the constriction effect of arterioles, mediated by α-adrenergic receptors, which increases aortic diastolic pressure, augmenting coronary blood flow and enhancing the chance of ROSC.[32] In our study, higher doses of adrenaline pre-ROSC were associated with lower survival rate during hospital stay. Previous studies[33,34], also had similar results according to adrenaline dose used and mortality outcomes. Higher dose of adrenaline used during ALS meant that a longer time and efforts were expended achieving ROSC, and as aforementioned, related with poor prognosis. Several observational studies indicate that adrenaline use for OHCA is associated with improved ROSC, but significantly decreased likelihood of survival to hospital discharge and worst neurological outcomes.[33-36] The use of adrenaline has been linked to ischemic lesions provoked by the vasoconstrictor effects on microvascular cerebral circulation[35,37] and correlated to an increased long-term risk of poor neurological outcome. These findings have questioned the role of adrenaline in OHCA resuscitation. In a recent randomized double-blinded trial (PARAMEDIC-2), Perkins *et al*, >8000 randomized patients to either adrenaline or placebo used during ALS efforts,

found that the use of adrenaline in OHCA patients resulted in a significantly higher rate of 30-day survival than the use of placebo, but there was not significant difference between groups (adrenaline vs placebo) concerning the rate of a neurological favourable outcome because more survivors had severe neurological impairment in the adrenaline patients group.[37]

Our study results did not show any relationship between angiographic and echocardiographic data and in-hospital outcome. In fact, a larger majority of studies refers a strict association between in-hospital survival and the performance of immediate CA post-ROSC, as recommended by guidelines[10], and if necessary, consequent PCI[1,17,38], as treatment. In our study, there were no significant differences between the non-survivors and survivors' groups concerning the performance of CA, or even PCI failure.

It is well known that post-cardiac arrest syndrome leads to a post-arrest myocardial dysfunction, an important cause of post-resuscitation circulatory failure. Our results did not display any correlation between the systolic ventricular function, an echocardiographic measure of myocardial dysfunction, and in-hospital mortality. These results are consistent with other studies[5] that refer that systolic function is not an independent predictor of hospital and long-term mortality. Interestingly, Jentzer *et al*, shown that diastolic dysfunction is associated with hospital and long-term mortality, considering it a more important variable in predicting patient outcomes.[39]

The GRACE risk score has been reported to be useful for predicting short and long-term mortalities in patients with ACS.[40] This score has been widely used in risk stratification and guidance of ACS treatment, as well as in-hospital mortality. Age, heart rate, systolic blood pressure, creatinine, cardiac arrest at admission, ST segment deviation on electrocardiogram (EKG), abnormal cardiac enzymes and Killip class are the components of the score.[20,41] According to our study, GRACE risk score values calculated between the first 24 to 48 hours after hospital admission were directly linked with prognostic outcome of rOHCA patients. Recently, Otani *et al*. showed that GRACE risk score predicted the in-hospital mortality outcome of rOHCA patients with shockable initial cardiac rhythm regardless the cause of the arrest.[40] Currently, the information that relates GRACE risk score as an in-hospital mortality predictor of outcome for OHCA patients is sparse. Our results give emphasis to the applicability of GRACE risk score in this population, as useful as a simple tool to help defining prognosis.

Regarding to inflammatory markers, we found that no single variable revealed to have a clear simple relationship with in-hospital mortality, although there were globally elevated levels of all classic markers. During cardiac arrest, the whole-body is exposed to ischemia, and together with reperfusion injury induced after ROSC, an inflammatory response is activated, leading to endothelial activation and systemic inflammation, inducing a sepsis like syndrome, and

consequently tissue injury.[42-44] This mechanism explains the higher values of inflammatory/immune cells, like neutrophils and lymphocytes, observed in early begging of post-ROSC evaluation.

Blood gas analysis provides critical information after rOHCA. The interruption of blood supply to the tissues that occurs during the cardiac arrest is a recognized cause of tissue oxygen deficit, lactate accumulation due to anaerobic metabolism, and metabolic acidosis, thereby leading to high lactate levels and low pH levels in the blood.[45] Several studies[45-47] reported that patients with an unfavourable outcomes presented higher lactate and lower pH levels at admission and during hospital stay, reflecting a longer time body exposure to ischemia. However, the cut-off points of blood lactate and pH levels for determining a poor prognosis in OHCA patients are not well established. Our study demonstrated that higher early lactate values, measured in the first 6 hours of hospital stay, including admission values, were associated with worst clinical prognosis compared to the survivors' group. Inversely, lower pH levels at admission and after 24 to 48 hours in the hospital, were linked to a worst prognosis. pH is influenced by CO2 clearance, HCO3- and anion gap which includes lactates, hence its variation may reflect more broadly on the status of critical organs. pH levels can therefore be a more specific predictor of outcome compared to lactate, as seen in Momiyama *et al*[45].

In our study, higher potassium levels, both at admission and at 24 to 48 hours, were linked to higher in-hospital mortality. Few studies focused on the importance of potassium in the OHCA context, however, Lin *et al* results correlated with ours, stating that higher levels of serum potassium predicted worse outcomes and influence the duration of survival in rOHCA patients.[48] Hyperkalaemia in OHCA reflects abnormal cellular metabolism, cellular death, electrolyte exchange and kidney function. Higher potassium blood levels change the action potential of heart rhythm cells and additional inducing critical cardiac arrhythmias with a important impact on the hemodynamic status.[48]

Overall, our study showed that variables classically used to predict short-term survival in the OHCA population like pH, lactates and potassium retain its prognostic value, in this specific subgroup of rOHCA patients.

Study limitations

We faced some challenges along our work. The retrospective nature of this study and the fact that it was based on medical records meant the existence of some missing information, which make it more prone to be influenced by bias and confounding factors.

Our restrictive study inclusion criteria were defined to better portray a group of patients with very specific features. However, it inevitably led to a smaller sample size, for the time intervals

that we proposed to study, that may have limited our power to detect other characteristics that may be associated with in-hospital mortality. Moreover, the OHCA patients that did not make it to the hospital were not included and this represents an important limitation.

Conclusion

With our work, we suggest that certain clinical, circumstances of arrest and initial management, biochemical markers and in-hospital data are useful predictors of in-hospital mortality in rOHCA patients with SigCAD. These results might help defining a better and more complete approach to these patients, allowing the clinicals to be aware of a possible pattern of status evolution, having in concern that certain events can determine a better or worst clinical development and consequently chance of survival.

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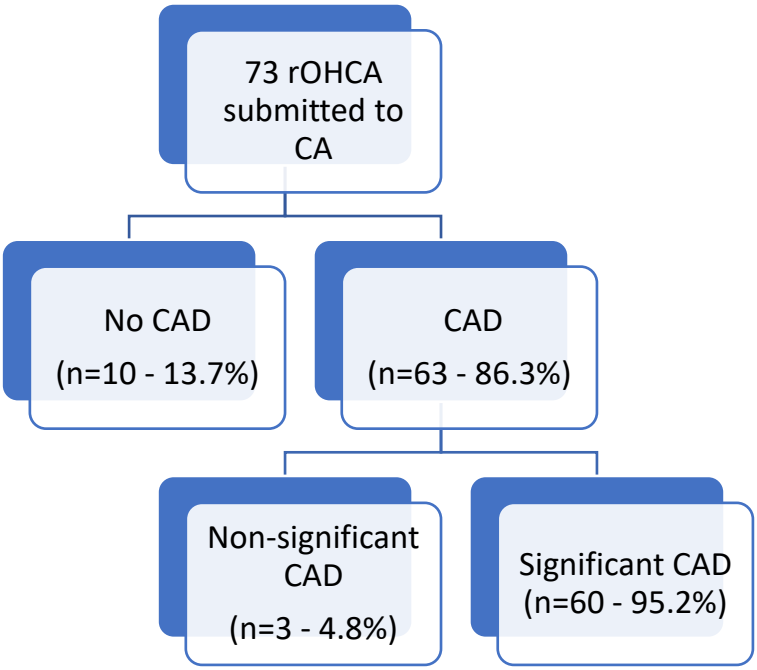
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List of Figures and Tables

Figure 1 - Study inclusion criteria



rOHCA – recovered Out-of-Hospital Cardiac Arrest; CA – coronary angiography; CAD – coronary artery disease

Table I - Baseline and clinical characteristics

rOHCA- recovered Out of Hospital Cardiac Arrest; CV- cardiovascular; pPCI – previous percutaneous coronary intervention; pCABG – previous Coronary Artery Bypass Graft; COPD – Chronic Obstructive Pulmonary Disease; VMER – Medical Emergency and Reanimation Vehicle; BLS – Basic Life Support; ROSC – Return Of Spontaneous Circulation; VT – Ventricular Tachycardia; VF – Ventricular Fibrillation; PEA – Pulseless Electrical Activity; EKG – Electrocardiogram; STEMI – ST-elevation myocardial infarction; NSTEMI – Non ST-elevation myocardial infarction
std dev- standard deviation; ln -logarithm (natural)
¥- 1 missing in group 1; # - Mann-Whitney test

	Overall n=60	Group 1 rOHCA non-survivors n=26 (43.3%)	Group 2 rOHCA survivors n=34 (56.7%)	P value
Age in years, mean (std dev)	62.6 ± 12.1	65.5 ± 10.6	60.3 ± 12.8	0.1
Gender, male	51 (85.0%)	22 (84.6%)	29 (85.3%)	0.9
CV risk factors				
Hypertension	35 (58.3%)	18 (69.2%)	17 (50.0%)	0.1
Smoking	35 (58.3%)	12 (46.2%)	23 (67.6%)	0.1
Dyslipidemia	34 (56.7%)	15 (57.7%)	19 (55.9%)	0.9
previous Coronary Artery Disease	23 (38.3%)	12 (46.2%)	11 (32.4%)	0.3
Myocardial Infarction	19 (31.7%)	7 (26.9%)	12 (35.3%)	0.5
Diabetes	15 (25.0%)	11 (42.3%)	4 (11.8%)	**0.007**
Heart Failure	11 (18.3%)	6 (23.1%)	5 (14.7%)	0.4
pPCI	10 (16.7%)	4 (15.4%)	6 (17.6%)	0.8
Peripheral vascular disease	10 (16.7%)	6 (23.1%)	4 (11.8%)	0.2
Obesity	9 (15.0%)	4 (15.4%)	5 (14.7%)	0.9
pCABG	7 (11.7%)	3 (11.5%)	4 (11.8%)	1.0
COPD	4 (6.7%)	2 (7.7%)	2 (5.9%)	0.8
Stroke	3 (5.0%)	3 (11.5%)	0 (0.0%)	**0.042**
Means of transport				
VMER	39 (65.0%)	20 (76.9%)	19 (55.9%)	0.1
Location of cardiac arrest				**0.002**
Outside/Home	40 (66.7%)	23 (88.5%)	17 (50%)	
Hospital/Transport	20 (33.3%)	3 (11.5%)	17 (50%)	
ln Time from BLS to ROSC, minutes¥ (std dev)	2.49 ± 0.93	2.95 ± 0.60	2.15 ± 0.98	**0.001**
Adrenaline pre-ROSC, mg¥ (std dev)	2.6 ± 2.8	3.6 ± 3.0	1.8 ± 2.3	**0.009#**
New Cardiac Arrest	14 (23.3%)	8 (30.3%)	6 (17.6%)	0.2
Initial arrest rhythm				**0.002**
VT/VF	46 (76.7%)	15 (57.7%)	31 (91.2%)	
PEA/asystole	14 (23.3%)	11 (42.3%)	3 (8.8%)	
Chest pain	24 (40.0%)	7 (26.9%)	17 (50.0%)	0.1
First EKG				
STEMI	36 (60.0%)	15 (57.7%)	21 (61.8%)	0.8

Table II - Imaging and in-hospital complications data

*- Fisher's exact test; # - Median test; IQR- interquartile range
¥¥- 3 missing in group 1; ¥¥¥-6 missing in group1

	Group 1 rOHCA non-survivors n=26 (43.3%)	Group 2 rOHCA survivors n=34 (56.7%)	P value
Percutaneous coronary intervention	17 (65.4%)	26 (76.5%)	0.3
Failure	1 (5.9%)	2 (7.7%)	0.8
Complete revascularization	2 (11.8%)	0 (0.0%)	0.2*
Echocardiogram			
Left ventricle disfunction moderate/severe			
admission¥¥	17 (73.9%)	23 (67.6%)	0.6
in-hospital evaluation¥¥¥	14 (70%)	22 (64.7%)	0.7
Right ventricle disfunction upon admission¥¥	0 (0.0%)	1 (2.9%)	1.0*
In-hospital complications			
Hemodynamic instability	25 (96.2%)	13 (38.2%)	**<0.001**
Multi-organ disfunction	20 (76.9%)	9 (26.5%)	**<0.001**
Anoxic brain injury	15 (57.7%)	8 (23.5%)	**0.007**
Infection	11 (42.3%)	19 (55.9%)	0.3
Median duration of stay, days (IQR)	3 (2-6)	15 (6-22)	**<0.001#**
Median intensive care unit, days (IQR)	3 (2-6)	6 (4-12)	0.1#
Median vasopressor, days (IQR)	2 (0-5)	1 (0-3)	0.1#

Table III - Clinical scores and biochemical data

#- Mann-Whitney test; CK- creatine kinase; PCR- Protein C reactive; std dev- standard deviation; ln- logarithm (natural)
¥- 1 missing in group 1; ¥¥- 3 missing in group 1; µ - 5 missing in group 1; ¥¥¥- 6 missing in group 1; ¥µ-7 missing in group 1; ¥¥¥¥ - 8 missing in group 1;
∞- 1 missing in group 2; ∞∞- 3 missing in group 2; ∑- 4 missing in group 2; ∑∑- 5 missing in group 2; ∞∞∞∞ - 6 missing in group 2

		Group 1 rOHCA non-survivors n=26 (43.3%)	Group 2 rOHCA survivors n=34 (56.7%)	P value
Clinical scores				
Killip score III-IV				
	1-6h	14 (53.8%)	12 (35.3%)	0.2
	24-48h¥¥¥	9 (45.0%)	7 (20.6%)	0.1
GRACE score (mean, std dev)				
	admission¥	174.8 ± 37.8	160.8 ± 32.1	0.1#
	24-48h¥µ	176.2 ± 33.4	151.2 ± 31.9	**0.041#**
Biochemical data (mean, std dev)				
ln Troponin T				
	admission¥¥/∞∞	-0.71 ± 2.16	-1.81 ± 2.25	0.074
	24h¥¥¥¥/∞∞	0.82 ± 1.62	0.50 ± 1.12	0.4
ln CK highest		7.26 ± 1.58	7.60 ± 0.96	0.3
PCR				
	admission∞	15.65 ± 49.22	18.27 ± 53.21	0.6#
	24h¥¥¥/∞	54.29 ± 54.43	57.52 +/- 55.69	0.7#
	48h¥¥¥	158.31 ± 95.42	123.21 ± 84.53	0.2#
Creatinine				
	Admission	1.36 ± 0.53	1.32 ± 0.83	0.2#
	24h-48h¥¥¥	1.32 ± 0.74	1.25 ± 1.27	0.2#
ln Neutrophils				
	Admission	2.15 ± 0.61	2.13 ± 0.62	0.9
	24-48h¥¥¥	2.46 ± 0.55	2.26 ± 0.37	0.1
Lymphocytes				
	Admission	4.39 ± 2.72	3.20 ± 2.10	0.1#
	24-48h¥¥¥	1.22 ± 0.60	1.59 ± 1.06	0.3#
Platelets				
	Admission	193.9 ± 77.7	223.1 ± 57.7	0.1
	24-48h¥¥¥	182.0 ± 72.4	193.7 ± 52.0	0.5
Haemoglobin				
	Admission	13.6 ± 2.1	14.1 ± 2.0	0.2
	24-48h¥¥¥	13.8 ± 2.5	13.0 ± 1.6	0.1
ln Lactates				
	admission∑	1.80 ± 0.83	1.28 ± 0.99	**0.039**
	1-6h¥/∑	1.02 ± 0.80	0.59 ± 0.71	**0.040**
	6-24hµ/∞∞∞	0.87 ± 0.56	0.48 ± 0.56	**0.046**
	24-48h¥¥¥/∞∞∞	0.57 ± 0.73	0.24 ± 0.57	0.084
Potassium				
	Admission	4.10 ± 0.87	3.66 ± 0.70	**0.05#**
	24h¥¥¥	4.20 ± 0.82	3.81 ± 0.48	**0.028**
Calcium	admission∑∑	1.13 ± 0.10	1.12 ± 0.07	0.5
pH				
	admission∞∞	7.17 ± 0.18	7.27 ± 0.19	**0.011#**
	24-48h¥¥¥/∑	7.32 ± 0.10	7.41 ± 0.05	**<0.001#**

Table IV – Univariate logistic regression analysis

ln- logarithm (natural)

	Odds Ratio (95% CI)	P value
Cardiovascular risk factors		
Diabetes	5.50 (1.50-20.2)	**0.010**
Location of Cardiac Arrest		
Outside vs Transport/Hospital	7.67 (1.93-30.4)	**0.004**
Initial Rhythm		
Non-shockable vs Shockable	7.58 (1.84-31.3)	**0.005**
Ln Time from BLS to ROSC	3.29 (1.51-7.13)	**0.003**
Adrenaline pre-ROSC	1.31 (1.05-1.62)	**0.017**
Clinical scores		
Grace score admission	1.01 (1.00-1.03)	0.1
Grace score 24-48h	1.03 (1.01-1.05)	**0.016**
Biochemical data		
ln Neutrophils 24-48h	2.95 (0.76-11.4)	0.1
ln Lactates admission	1.89 (1.02-3.51)	**0.045**
ln Lactates 1-6h	2.20 (1.01-4.79)	**0.048**
ln Lactates 6-24h	2.49 (0.98-6.30)	0.055
ln Lactates 24-48h	2.30 (0.88-6.01)	0.1
Potassium admission	2.15 (1.01-4.59)	**0.048**
Potassium 24h	2.81 (1.04-7.58)	**0.041**
pH	0.05 (0.002-0.942)	**0.046**
pH 24-48h	0.0 (0-0.001)	**0.002**
In-hospital complications		
Anoxic Brain Injury	4.43 (1.46-13.5)	**0.009**
Hemodynamic instability	40.39 (4.87-335)	**0.001**
Multi-Organ disfunction	9.26 (2.82-30.4)	**<0.001**
Duration of stay	0.79 (0.69-0.90)	**<0.001**