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## The Association Between Post Resuscitation Hemoglobin Level And Survival With Good Neurological Outcome Following Out of Hospital Cardiac Arrest

Aiham Albaeni, Shaker M. Eid, Bolanle Akinyele, Lekshmi narayan Kurup, Dhananjay Vaidya, and Nisha Chandra-Strobos

Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, USA

### Abstract

**Aims**—to explore the association between post return of spontaneous circulation (ROSC) hemoglobin level and survival with good neurological outcome following out-of-hospital cardiac arrest.

**Methods**—We studied adults with non-traumatic out-of-hospital cardiac arrest who achieved ROSC within 50 minutes of collapse. We quantified the association between post ROSC hemoglobin level and good neurological outcome (defined as Cerebral Performance Category score of 1 or 2), using multivariate logistic regression analyses. The impact of Post ROSC hemoglobin level  $\geq 10$  g/dl and time varying hemoglobin level  $\geq 10$  g/dl on time to Survival with good outcome was assessed using Cox proportional hazard models.

**Results**—Of 931 cardiac arrest patients, 146 (16%) achieved ROSC and 30 survived to discharge with a good neurological outcome. Of those with post ROSC hemoglobin level  $\geq 10$  g/dl, 28% (27/98) had good outcome, whereas of those with level  $< 10$  mg/dl only 6% (3/48) had good outcome (CPC  $< 3$ ,  $p=0.003$ ). The use of blood transfusions and therapeutic hypothermia were comparable in both good and bad outcome groups. An immediate post ROSC hemoglobin level  $\geq 10$  g/dl was significantly associated with good neurological outcome (AOR 8.31 95% CI 1.89–36.52  $p=0.005$ ). Patients with post ROSC hemoglobin  $\geq 10$  g/dl were more likely to achieve good outcome earlier (HR 6.02 95% CI 1.75–20.72  $p=0.004$ ).

**Conclusions**—Post ROSC hemoglobin level  $\geq 10$  g/dl is associated with survival with good neurological outcome. The importance of time to achieve such level and the role of blood transfusion warrants further investigation.

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Please send all correspondence to: Aiham Albaeni, MD, FACP, Assistant Professor of Medicine, Johns Hopkins University School of Medicine, Johns Hopkins Bayview Medical Center, 5200 Eastern Ave, MFL west 6<sup>th</sup> floor, Baltimore MD, 21224, Phone: 410 550 5018, Fax: 410 550 2972, aalbaen1@jhmi.edu.

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## Keywords

Cardiopulmonary resuscitation; cardiac arrest; sudden death; Hemoglobin

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## 1. Introduction

The International resuscitation committee has recommended comprehensive therapeutic strategies to improve outcome following cardiac arrest, including therapeutic hypothermia, percutaneous coronary intervention, early hemodynamic optimization and supportive care.<sup>1-5</sup> The quintessential goal of such therapies is to achieve neurologically intact survival by maintaining adequate balance between oxygen delivery and consumption, thus alleviating the impact of ischemia and hypoxia on the brain tissue following arrest.

Cardiac arrest is a severe ischemic event that will eventually lead to the failure of organs' defense mechanisms in the absence of adequate supportive therapies. The cerebrovascular system responds to hypoxia by increasing production of nitric oxide and stimulating sympathetic B2 receptors to achieve adequate vasodilatation that will maintain cerebral blood flow.<sup>6,7</sup> However, in the setting of severe anemia, such increase in cerebral blood flow will eventually be insufficient to compensate for the decrease in arterial oxygen content caused by low hemoglobin levels.<sup>8</sup> Moreover, in cardiac arrest as compared to other brain ischemic events, severe hypotension, myocardial dysfunction and lactic acidosis will further complicate the picture and decrease the chance of successful defense.

The optimal neuro-protective hemoglobin level following cardiac arrest has not yet been determined. Two studies maintained hemoglobin level above 9–10 g/dl in a post cardiac arrest protocol to improve survival.<sup>9,10</sup> The SOS-KANTO study group demonstrated an association between higher hemoglobin level and favorable neurological outcome.<sup>11</sup> However, there was no general agreement on the best hemoglobin level and whether such level will impact time to achieve neurologically intact survival following arrest. Hence the goal of this study was to explore the association between post arrest hemoglobin level 10 g/dl with survival with good neurological outcome, and the time to achieve good neurological outcome following arrest.

## 2. Methods

### 2.1. Setting and Study design

This study was approved by the Johns Hopkins Institutional Review Board. We performed a retrospective review of all adult patients over 18 years of age with non-traumatic out-of-hospital cardiac arrest who achieved ROSC within 50 minutes, and admitted to an academic medical center between 2004 and 2010. We excluded patients with traumatic cardiac arrest and those who died upon arrival to the emergency department. Out of 210 patients who achieved ROSC, 64 patients were excluded; 9 patients due to missing data, 10 patients were not comatose upon hospital admission and 45 did not achieve ROSC within 50 minutes. Those 45 patients were excluded as no one with ROSC > 50 minutes survived with good outcome (Fig. 1)

## 2.2. Study variables and patient data

Primary outcome was survival with good neurological outcome defined as Cerebral Performance Category score (CPC) of 1 or 2, secondary outcome was time to achieve good neurological outcome in hours from the time of arrest. Patient demographics, cardiac arrest and post cardiac arrest variables were collected according to Utstein guidelines.<sup>12,13</sup> Cardiac catheterization and percutaneous coronary intervention (PCI) were performed in select patients based on the decision of the cardiology attending. Similarly, therapeutic hypothermia was started in select patients according to a pre-defined hospital wide protocol that is based on the American Heart Association guidelines.<sup>2,3</sup> Fluids and vasopressors were used as needed to maintain a mean arterial pressure  $\geq 65$  mmHg, and Propofol or Midazolam were used for sedation. Intensive care unit neurological assessments were performed by nursing staff, resident physicians, the ICU attending physician and often the consulting neurologist. Sedation was interrupted each morning to assess for recovery. In rare cases of discrepancy between observers, the report of the attending/neurologist was selected to reflect the status of the patient. Neurological outcome was assessed according to Glasgow-Pittsburgh Cerebral Performance Categories scale (CPC): CPC 1 is conscious and normal; CPC 2 conscious with moderate cerebral disability; CPC 3 conscious with severe cerebral disability; CPC 4 coma or vegetative state; and CPC 5 death.<sup>13</sup> Patients with CPC 1 or 2 were considered to have good neurological outcome while those with CPC 3, 4 or 5 were considered to have bad neurological outcome.

## 2.3. Repeated measures

Hemoglobin levels were measured as follows for patients who met inclusion criteria: Post ROSC, every 6 hours for the first 24 hours and then every 24 hours until reaching good neurological outcome (CPC 1, 2) or bad outcome (CPC 3,4,5). For patients who achieved good outcome on a specific day, the immediate preceding 24 hour hemoglobin level was considered the last hemoglobin measured. Then survival analysis was performed to look at the impact of post ROSC hemoglobin level  $\geq 10$  g/dl and time varying hemoglobin level  $\geq 10$  g/dl on time to achieve good neurological outcome following cardiac arrest.

## 2.4. Statistical analysis

After the exclusion of patients who did not meet inclusion criteria, 146 patients entered the analyses and were divided by neurological outcome at the time of hospital discharge into patients with good (CPC 1 or 2) or bad (CPC 3, 4, or 5) neurological outcome (Fig. 1). Baseline demographics, clinical characteristics and cardiac arrest variables were studied in all 146 patients using simple statistics. Categorical variables were compared using Chi-squared test, and continuous variables were studied using unpaired t-test if normally distributed and non-parametric Wilcoxon rank-sum (Mann-Whitney) test when data were not normally distributed. The receiver operating characteristic (ROC) curve was used to evaluate the association between post ROSC hemoglobin levels and survival with good neurological outcome.

Univariate analyses were performed on all variables of interest (time to ROSC in minutes, initial rhythm VF/VT, the presence of shock requiring pressors, post ROSC hemoglobin  $\geq 10$  g/dl, age, the presence of multi-organ failure, post ROSC blood PH  $< 7$ , post ROSC lactic

acid level  $\geq 10$  mmol/L, congestive heart failure, cancer, ESRD on hemodialysis, brainstem reflex score within 24–3) to explore association with favorable neurological outcome (CPC 1 or 2) using Chi square test. Multivariate logistic regression with stepwise backward-elimination was used to adjust for covariates that were found in univariate analyses to impact good neurological outcome with a P value of less than 0.05. Sensitivity analyses were used to evaluate the model performance following the exclusion of patients who had care withdrawal. Collinearity between variables was checked with the variation inflation factor (VIF), and the final model goodness of fit was checked using pseudo- $R^2$  and Pearson  $\chi^2$ . Time to achieve good neurological outcome was assessed by Cox-proportional hazard models, censoring events were death and care withdrawal. Two different models were evaluated, one with only baseline hemoglobin as the predictor, and another with hemoglobin levels as a time-varying predictor. The proportional hazard assumption was tested based on Schoenfeld residuals (Phtest).

### 3. Results

#### 3.1 Patient characteristics

Of 931 non-traumatic out of hospital cardiac arrest patients, 146 patients (16%) achieved ROSC within 50 minutes and met inclusion criteria. Of these 77 (53%) were male, 106 (73%) were Caucasian and 40 (27%) were black. The median age was 64.5 years IQR (53–77). Of 146 patients, 30 patients (21%) survived with good neurological outcome (CPC of 1 or 2), and 116 patients (79%) had bad outcome (CPC  $\geq 3$ ); of those 116 patients, 76 (65%) had care withdrawal. Therapeutic hypothermia was used in 71 patients (49%) with comparable use in patients with good and bad neurological outcome (57% vs.47%  $p=0.32$ ). Among patients who underwent cardiac catheterization, only 3 patients had percutaneous coronary intervention (PCI); blood transfusion during hospital stay was performed in a total of 34 patients (23%) with comparable use in both groups (20% vs. 24%  $p=0.63$ ) (Table 1). The association between different post ROSC hemoglobin levels and survival with good neurological outcome was assessed using the receiver operating characteristic (ROC) curve, AUC 0.65 95% CI (0.55–0.75). And post ROSC hemoglobin level  $\geq 10$  g/dl has a sensitivity of 90% and specificity of 39% (supplement table 1 and supplement figure 1).

#### 3.2 Univariate analysis

**Good versus bad neurological outcome**—Patients with good neurological outcome were more likely to have VF/VT as an initial rhythm compared to those with bad outcome (40% vs. 14%,  $p= 0.001$ ). They were also more likely to have shorter time to return of spontaneous circulation [ROSC 9.5 minutes [4, 13] vs. 28.5 minutes [16.5, 40],  $P< 0.0001$ ], higher median post ROSC hemoglobin level (12.5 [11.2, 13.5] vs. 10.8 [8.9, 13.1],  $p= 0.01$ ), and more patients with post ROSC hemoglobin level  $\geq 10$  g/dl (90% vs. 61%,  $p =0.003$ ). Twenty eight percent (27/98) of patients with hemoglobin  $\geq 10$  had a good neurologic outcome while only six percent (3/48) of patients with hemoglobin  $<10$  had a good neurologic outcome ( $p=0.003$ , Supplement table 2). In addition, patients with good neurological outcome were less likely to have shock requiring pressors (20% Vs 59%  $P<0.0001$ ); they were also less likely to have post ROSC lactic acid level  $\geq 10$  mmol/L or PH  $<7$  (Table 2).

### 3.3 Multivariable analysis

In multivariable logistic regression model with backward elimination, post ROSC hemoglobin level  $\geq 10$  g/dl was associated with survival with good neurological outcome (CPC of 1 or 2) (AOR 8.31, 95% CI 1.89–36.52), (Model 1-Table 3). After excluding patients who underwent care withdrawal, sensitivity analysis revealed a significant association between post ROSC hemoglobin level  $\geq 10$  g/dl and survival with good neurological outcome (AOR 9.19, 95% CI 1.72–49.1), (Model 2-Table 3). Sensitivity analyses also revealed similar results when we included patients who had ROSC  $>50$  minutes.

### 3.4 Survival analysis

Out of 30 patients who eventually achieved good neurological outcome (CPC 1 or 2), 27 patients had post ROSC hemoglobin  $\geq 10$  g/dl. Patients with post ROSC hemoglobin  $\geq 10$  g/dl were more likely to achieve good neurological outcome earlier than patients with post ROSC hemoglobin  $<10$  g/dl (HR 6.02, 95% CI 1.75–20.72) (Table 4–Figure 2A). Further changes in hemoglobin during hospital stay were not associated with early neurological recovery (HR 1.74, 95% CI 0.78–3.88) (Table 4–Figure 2B). All 30 patients received sedation for a median of 2 days IQR (1–4).

## 4. Discussion

In this study, we found that post ROSC hemoglobin level  $\geq 10$  g/dl was associated with good neurological outcome following out of hospital cardiac arrest. Patients with post ROSC hemoglobin level  $\geq 10$  g/dl were more likely to achieve good outcome earlier than those with hemoglobin level less than 10 g/dl. Further changes in hemoglobin during hospital stay were not associated with early favorable outcome, and this might reflect the importance of time to achieve such neuro-protective level.

Our results are consistent with literature reports of neurologically intact survival association with higher hemoglobin levels following cardiac arrest.<sup>11,14,15</sup> The SOS-KANTO study group reported favorable short-term neurological outcome in patients with higher post arrest hemoglobin level. Study patients in the good neurological outcome group had a median hemoglobin level of 14.4 g/dl vs. 12.8 g/dl in the bad outcome group.<sup>11</sup> Similarly, Ryu et. al. reported a significant association between favorable outcome and higher hemoglobin levels before extracorporeal cardiopulmonary resuscitation. Patients in the good outcome group had a median pre-ECMO hemoglobin level of 11.9 g/dl vs. 10.7 g/dl in the bad outcome group.<sup>15</sup> Therefore, anemia correction might be neuroprotective.<sup>15</sup>

In similar ischemic neurologic injury models such as in animal stroke models, penumbral oxygenation in an ischemic brain had the best oxygen utilization at hematocrit of 31%.<sup>16</sup> Inadequate oxygen utilization was shown at hemoglobin levels less than 10 g/dl,<sup>16</sup> and with profound hemodilution to a hematocrit level of 26%.<sup>17</sup> In addition, clinical stroke studies have also shown a U or J-shaped relationship between hemoglobin level and adverse outcome, where both high and low levels were associated with bad outcome;<sup>18,19</sup> however, optimal oxygen delivery was achieved at a hematocrit level of 40–45%.<sup>20</sup>

Blood transfusion seems to be a reasonable treatment option to prevent further damage; however, this has never been studied following cardiac arrest. Most of the clinical trials that recommend the conservative approach of lower hemoglobin threshold for transfusion excluded patients with severe ischemic events like myocardial infarction.<sup>21,22,23</sup> Similarly, the International Surviving Sepsis Campaign guidelines recommend maintaining a hematocrit of more than 30% (hemoglobin 10 g/dl) in the presence of hypoperfusion in the first 6 hours. After that, the transfusion threshold should be at a hemoglobin level less than 7 g/dl to achieve a level between 7 and 9 g/dl in patients who do not have myocardial ischemia, severe hypoxia, acute hemorrhage, or ischemic coronary artery disease.<sup>24</sup> More recently, Salisbury et. al. reported lower risk of in-hospital mortality among acute myocardial infarction patients who received transfusion, and suggested that the observation of increased mortality reported in previous studies might have been influenced by selection bias, given the inability to match transfused and non-transfused patients.<sup>25</sup>

The current study also demonstrated that patients with post ROSC hemoglobin level 10 g/dl were more likely to achieve survival with good neurological outcome earlier as compared to those who had post ROSC hemoglobin <10 g/dl. This observation did not sustain with subsequent hemoglobin levels measured 6 hours later and thereafter during the hospital stay, as further changes in hemoglobin level did not associate with early neurological recovery (HR 1.74, 95% CI 0.78–3.88). This finding might fall in the same realm of the Sepsis Campaign recommendations of keeping the hematocrit level above 30% in the first 6 hours of hypoperfusion. It also raises an important question to be answered; whether there is a golden hour for transfusion following cardiac arrest. Prospective studies designed to answer this specific question are currently lacking.

## 5. Limitations

This study should be interpreted with the following limitations. First, this study reflects a single institution experience with a small sample size which may limit the generalizability of the results. However, our finding of the beneficial impact of higher hemoglobin level is consistent with literature reports. Second, the small number of patients with post ROSC hemoglobin level <10 g/dl who eventually achieved survival with good neurological outcome, limits the interpretation of the impact of post ROSC hemoglobin on time to achieve this outcome. Third, PCI was only performed in three patients, so we were not able to account for its impact on survival. Finally, we could not identify the impact of hemodilution on hemoglobin and hematocrit levels as it is common that post arrest patients will receive liberal amounts of fluids during resuscitation that would likely decrease these levels. However, the association of purposeful hemodilution and blood transfusion with neurologically intact survival following cardiac arrest has not been previously studied and warrants further investigations.

## 6. Conclusion

Post ROSC hemoglobin level 10 g/dl is associated with survival with good neurological outcome. Time to good neurologic outcome was shorter in patients with hemoglobin level

10. The importance of time to achieve such level and the role of blood transfusion warrants further investigation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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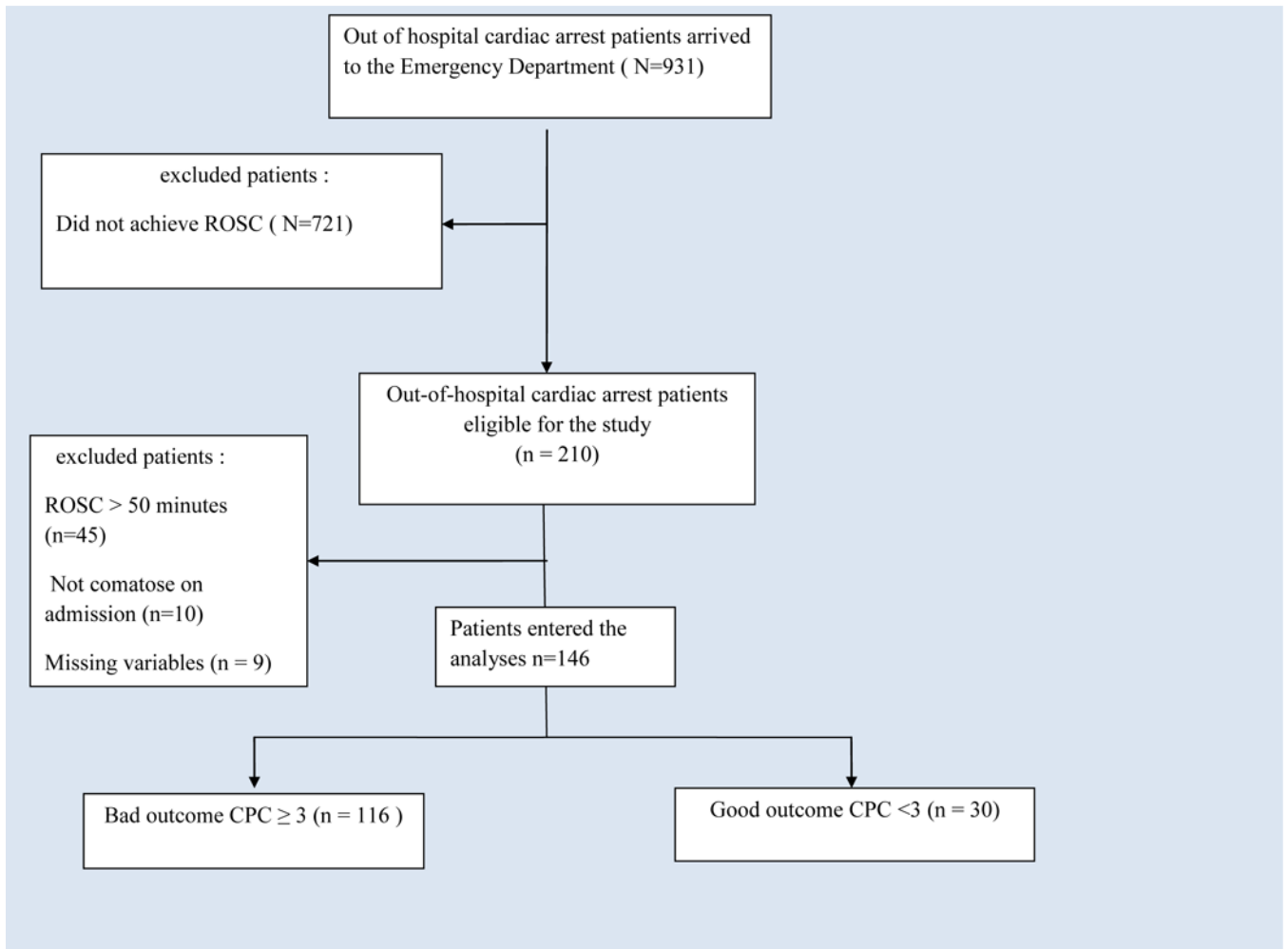
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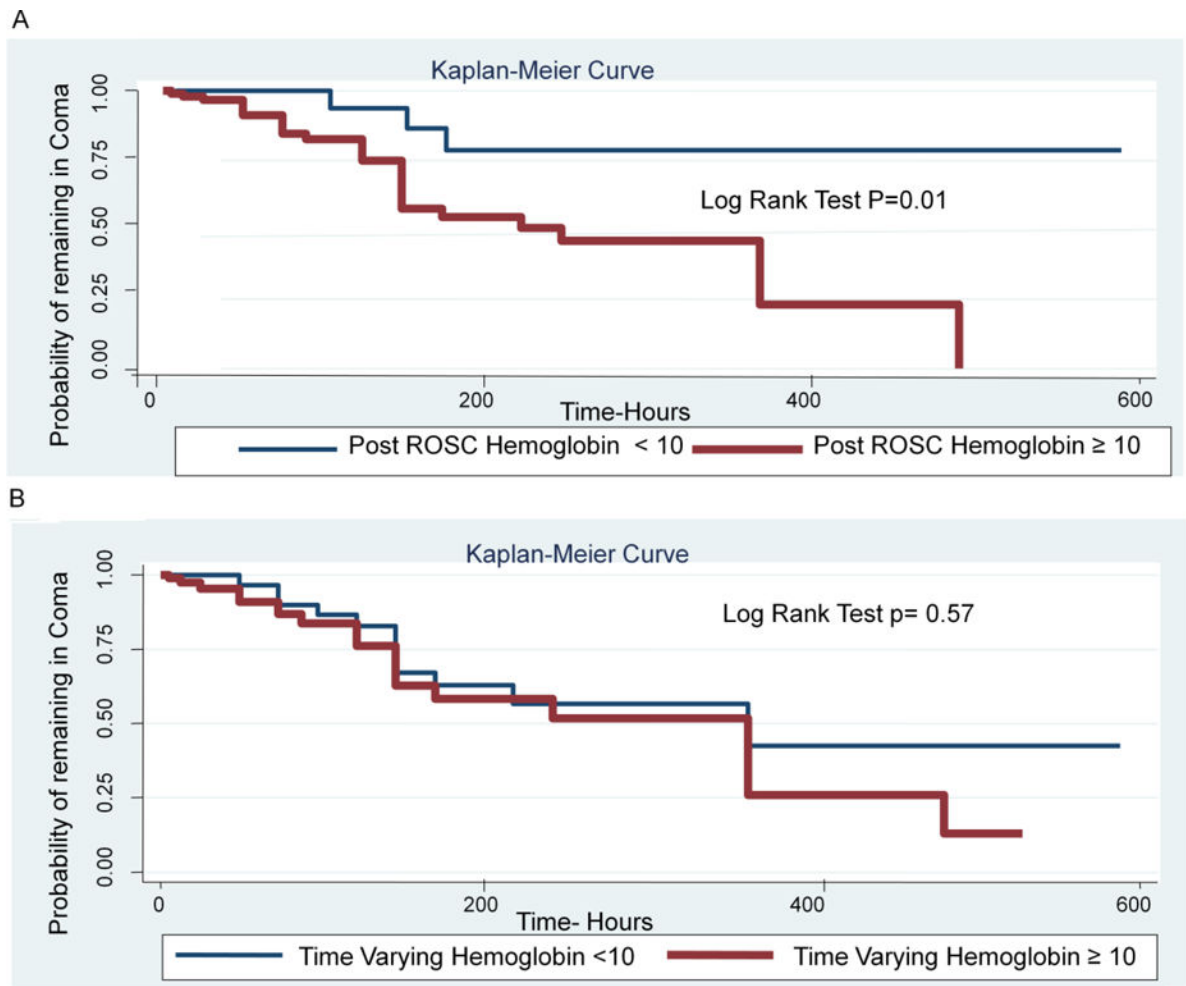
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**Fig. 1.** Study Flow Diagram. CPC: cerebral performance category, ROSC: return of spontaneous circulation.



**Fig. 2.**

A: Post ROSC hemoglobin level and time to survival with good neurological outcome.

B: Time Varying Hemoglobin level and time to survival with good neurological outcome.

**Table 1**

## Patients Characteristics

<b>Demographics, cardiac arrest characteristics and therapies</b>				
	<b>All patients N=146</b>	<b>Good Outcome N=30</b>	<b>Bad Outcome N = 116</b>	<b>P value</b>
Age, median (range)	64.5 (53–77)	57 (52–68)	66.5 (56–78)	0.03
Male gender	77 (53)	14 (47)	63 (54)	0.46
Race				
Caucasians	106 (73)	21 (70)	85 (73)	0.72
Black	40 (27)	9 (30)	31 (27)	
Co morbidities				
Diabetes Mellitus	53 (36)	10 (33)	43 (37)	0.70
Hypertension	110 (75)	25 (83)	85 (73)	0.26
Coronary artery disease	58 (40)	12 (40)	46 (40)	0.97
Congestive heart failure	55 (38)	15 (50)	40 (34)	0.12
CVA/TIA	25 (17)	4 (13)	21 (18)	0.54
ESRD on HD	14 (10)	6 (20)	8 (7)	0.03
COPD	44 (30)	8 (27)	36 (31)	0.64
History of Cancer	24 (16)	9 (30)	15 (13)	0.03
Co morbidity 2	105 (72)	24 (80)	81 (70)	0.27
Arrest characteristics				
Witnessed arrest	113 (77)	26 (87)	87 (75)	0.17
Bystander CPR	46 (32)	9 (30)	37 (32)	0.84
BRS 3 at 24 hours	35 (24)	15 (50)	20 (17)	<0.0001
Initial rhythm VF/VT	28 (19)	13 (40)	16 (14)	0.001
Care withdrawal	76 (52)	0 (0)	76 (65)	<0.0001
Interval collapse to ROSC, min	21.5 (12–35)	9.5 (4–13)	28.5 (16.5–40)	<0.0001
Post arrest Hemoglobin g/dl	11.4 (9.4–13.2)	12.5 (11.2–13.5)	10.8 (8.9–13.1)	0.01
Post arrest Hemoglobin 10 g/dl post arrest therapies	98 (67)	27 (90)	71 (61)	0.003
Hypothermia	71 (49)	17 (57)	54 (47)	0.32
Transfusion	34 (23)	6 (20)	28 (24)	0.63
PCI	3 (2)	2 (7)	1 (1)	0.05

Data are: n (%), median (range). CVA/TIA: cerebrovascular accident/transient ischemic attack, ESRD On HD: end stage renal disease on hemodialysis, COPD: chronic obstructive lung disease, CPR: cardiopulmonary resuscitation, BRS: brain stem reflex score, VF/VT: ventricular fibrillation/ventricular tachycardia, ROSC: return of spontaneous circulation, PCI: percutaneous coronary intervention.

**Table 2**

## Clinical Characteristics During Hospitalization

	All patients N=146	Good Outcome N=30	Bad Outcome N = 116	P value
Clinical findings				
Sepsis	70 (48)	10 (33)	60 (52)	0.07
Septic shock	46 (32)	4 (13)	42 (36)	0.02
Cardiac shock	38 (26)	5 (17)	33 (28)	0.19
Shock requiring pressors	75 (51)	6 (20)	69 (59)	<0.0001
MOF	79 (54)	11 (37)	68 (59)	0.03
Myocardial infarction	27 (18)	9 (30)	18 (15)	0.07
Pneumonia	48 (33)	11 (37)	37 (32)	0.62
ARDS	15 (10)	2 (7)	13 (11)	0.47
Pulmonary Embolism	10 (7)	1 (3)	9 (8)	0.39
Acute renal failure	106 (73)	19 (63)	87 (75)	0.20
Seizure (presentation)	24 (16)	3 (10)	21 (18)	0.29
Post ROSC PH< 7	44 (30)	3 (10)	41 (35)	0.007
Post ROSC Lactic acid 10 mmol/L	78 (53)	8 (27)	70 (60)	0.001

Data are: n (%), median (range). MOF: multi-organ failure, ARDS: Acute respiratory distress syndrome, ROSC: return of spontaneous circulation.

**Table 3**

Multivariable analysis for factors associated with good neurological outcome.

**Model 1: all patients N=146**

Factors	OR	95% Conf.interval	P value	Pseudo R <sup>2</sup>
Post ROSC Hemoglobin 10 g/dl	8.31	1.89–36.52	0.005	0.45
Time from collapse to ROSC minutes	0.87	0.81–0.92	<0.0001	
Initial Rhythm VF/VT	6.40	1.72–23.87	0.006	
Shock requiring pressors	0.18	0.05–0.60	0.005	

**Model 2: Sensitivity analysis excluding patient with care withdrawal, N=70**

Factors	OR	95% Conf.interval	P value	Pseudo R <sup>2</sup>
Post ROSC Hemoglobin 10 g/dl	9.19	1.72–49.1	0.009	0.45
Time from collapse to ROSC minutes	0.91	0.85–0.98	0.009	
Initial Rhythm VF/VT	2.92	0.59–14.37	0.19	
Shock requiring pressors	0.10	0.03–0.42	0.001	

OR: Odds ratio, ROSC: return of spontaneous circulation, VF/VT: ventricular fibrillation/Ventricular tachycardia Goodness of fit P value tested using Pearson  $\chi^2 = 0.99$

OR: Odds ratio, ROSC: return of spontaneous circulation, VF/VT: ventricular fibrillation/Ventricular tachycardia Goodness of fit P value tested using Pearson  $\chi^2 = 0.85$

**Table 4**

Multivariable analysis for factors associated with time to survival with good neurological outcome.

**Model 1: Post ROSC hemoglobin, all patients N=146.**

Factors	HR	95% Conf.interval	P value
Post ROSC Hemoglobin 10	6.02	1.75–20.72	0.004
Time from collapse to ROSC minutes	0.92	0.88–0.96	<0.0001
Active seizure on presentation	0.22	0.06–0.78	0.02
Shock requiring pressors	0.37	0.14–0.94	0.04

**Model 2: Time varying hemoglobin, all patients N=146.**

Factors	HR	95% Conf.interval	P value
Time varying Hemoglobin 10	1.74	0.78–3.88	0.18
Time from collapse to ROSC minutes	0.92	0.88–0.97	0.001
Active seizure on presentation	0.28	0.08–0.92	0.04
Shock requiring pressors	0.52	0.21–1.31	0.17

HR: Hazard ratio, ROSC: return of spontaneous circulation.