Title Page

Cerebral Oximetry During Cardiac Arrest: A Multicenter Study of Neurologic Outcomes and Survival

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Abstract:

Objective: Cardiac arrest (CA) is associated with morbidity and mortality due to cerebral ischemia. We therefore tested the hypothesis that higher regional cerebral oxygenation (rSO2) during resuscitation is associated with improved return of spontaneous circulation (ROSC), survival and neurological outcomes at hospital discharge. We further examined the validity of rSO2 as a test to predict these outcomes.

Design: Multicenter prospective study of in-hospital CA (IHCA).

Setting: Five medical centers in the United States and United Kingdom

Patients: Inclusion criteria: IHCA, age≥18 years, Prolonged cardiopulmonary resuscitation (CPR)≥5 minutes. Patients were recruited consecutively during working hours between 08/2011-09/2014. Survival with a favorable neurological outcome was defined as a Cerebral Performance Category (CPC)1-2.

Measurements and Main Results: Among 504 IHCA events, 183 (36%) met inclusion criteria. Overall 62/183 (33.9%) achieved ROSC, while 13/183(7.1%) achieved CPC1-2 at discharge. Higher mean±SD rSO2 was associated with ROSC vs. no ROSC (51.8±11.2% vs. 40.9±12.3%) and CPC1-2 vs. CPC3-5 (56.1±10.0% vs. 43.8±12.8%), both P<0.001. Mean rSO2 during the last 5 minutes of CPR best predicted ROSC (area under the curve [AUC]=0.76:95% [confidence intervals] CI:0.69-0.83); rSO2≥25% provided 100% sensitivity (95%CI:94%-100%), 100% negative predictive value (NPV) (95%CI:79%-100%); rSO2 ≥65% provided: 99% specificity (95%CI:95%-100%), 93% positive predictive value (PPV) (95%CI:66%-100%) for ROSC. Time with rSO2>50% during CPR best predicted CPC1-2 (AUC=0.79: 95%CI:0.70-0.88). Specifically, ≥60% CPR time with rSO2>50% provided 77% sensitivity (95%CI:46%-95%), 72% specificity (95%CI:65%-79%) and 98% NPV (95%CI: 93%-100%) for CPC1-2.

Conclusions: Cerebral oximetry allows real-time, non-invasive cerebral oxygenation monitoring during CPR. Higher cerebral oxygenation during CPR is associated with ROSC and neurologically favorable survival to hospital discharge. Achieving higher rSO2 during resuscitation may optimize the chances of CA favorable outcomes.

Key words: cardiac arrest, resuscitation, cerebral oximetry, near-infrared spectroscopy (NIRS), Cardiopulmonary Resuscitation (CPR).

1. Introduction

Ischemic brain injury following cardiac arrest (CA) is a major health burden. Among CA survivors, neurological, cognitive and functional deficits are common, with only 3-7% recovering to their prior functional status[1-4]. Cerebral ischemia contributes to morbidity and mortality through a two-step process; ischemia during CA is followed by reperfusion injury after ROSC, culminating in organ failure and death in the hours/days after cardiopulmonary resuscitation (CPR) [5-7]. As the magnitude of reperfusion injury is determined by the magnitude of ischemia during CA[5-7], the ability to detect, quantify and ameliorate cerebral ischemia in real-time during CA is of vital clinical importance. Nevertheless, one of the main hurdles to improving CA outcomes to date has been the lack of a real-time detection system capable of identifying cerebral ischemia and the quality of oxygen delivery during CPR.

Cerebral oximetry using near infra-red spectroscopy (NIRS) is a non-invasive monitoring system that transmits and detects near infrared light through forehead sensors and continually measures regional cerebral oxygen saturation (rSO2) in the frontal lobe of the brain[8]. It determines the ratio of oxyhemoglobin/deoxyhemoglobin, and it provides a measure of rSO2 with normal values close to venous saturation (70%)[8]. NIRS does not rely on pulsatile flow, enabling it to be used during CA[8]. Although validated and utilized in many settings[8-10], few studies have examined its use during CA[11-16]. While a number of small studies have indicated that ROSC is associated with higher rSO2 during CPR in out-of-hospital CA (OHCA) and IHCA [11-16], they lacked the power to determine the accuracy and clinical utility of rSO2 as a predictor of ROSC. Recently, a single rSO2 measured on arrival to the emergency department (ED) was found to predict survival with favorable neurological outcomes at 90 days after OHCA[17-18]. However, a single rSO2 is unlikely to reflect the overall balance between cerebral ischemia and oxygen delivery throughout CPR. Furthermore, as OHCA comprises a largely different population to IHCA, the applicability of these findings to IHCA remains unknown. Consequently, the optimal level of cerebral oxygen delivery during CPR, as well as the optimal read-out measure that is associated with ROSC and survival with favorable neurological outcomes following CA, remains unknown.

Therefore, we conducted a prospective multi-center study to test the hypothesis that sustained ROSC (ROSC), and survival with favorable neurological outcomes at hospital discharge after IHCA are associated with higher cerebral oxygenation/delivery during CPR. The primary objective was to examine the relationship between rSO2 and sustained ROSC. The secondary objective was to determine the relationship between rSO2 and survival with favorable neurological outcomes at hospital discharge as well as the accuracy, clinical utility and optimal rSO2 measure to predict sustained ROSC, survival and neurological outcomes at hospital discharge.

2. Materials and Methods

Study Population and Enrollment:

We studied IHCA patients in five hospitals across the United States (Stony Brook University Medical Center) and United Kingdom (Southampton University Hospital, Southampton, Hammersmith Hospital, London, Queen Alexandra Hospital, Portsmouth and Heart of England NHS Foundation Trust, Birmingham). All study data were sent to a Data Coordinating Center at Stony Brook University. Participants were enrolled between 08/2011-09/2014. Patients who met inclusion and exclusion criteria were recruited consecutively during working hours (mostly 0800-1700 weekdays). Inclusion criteria were IHCA, age≥18 years, CPR lasting ≥5 minutes. Exclusion criteria were OHCA. We chose CA ≥5 minutes, as short CA is not associated with the same adverse outcomes as CA lasting ≥5 minutes [19]. The research protocol received ethics committee approval prior to enrolling the first participant. Written informed consent was obtained from all CA survivors; a waiver of consent was approved to use data for non-survivors. Patients who survived the initial CA were followed until hospital discharge or death.

Study Definitions and Outcome Measures

CA was defined as absent heartbeat and respirations requiring CPR. Initial return of spontaneous circulation (ROSC) was defined as the presence of a palpable pulse elicited after interruption of CPR. Sustained ROSC was defined as ROSC lasting ≥20 minutes[a]. Survival with a favorable neurological outcome was defined as a Cerebral Performance Category (CPC)1-2. Unfavorable outcomes were defined as CPC3-5. The five CPC categories are; 1: good cerebral performance

[a] For the purpose of our calculations, only rSO2 values up to the point of initial ROSC were used, as rSO2 values during the 20 minute period after initial ROSC reflect cardiac contractility rather than CPR itself.

(normal life with possible minor psychological and/or neurological deficits), 2: moderate cerebral disability (independent activities of daily life), 3: severe cerebral disability (neurological damage and dependence on others but preserved consciousness), 4: coma or vegetative state, and 5: death[22].

Patient Characteristics

Data corresponding with potential confounders and effect modifiers for initial and sustained ROSC, or survival and neurological outcomes to hospital discharge were collected. Demographic data was collected, including patient gender, age, ethnicity, severity of critical illness score using the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system, chronic disease burden using the Charlson comorbidity index (a scale from 0-33, with higher scores indicating greater burden of coexisting conditions)[21]. We further examined variables that could impact oxygenation: hemoglobin, and PaO_2[b], CPR-related factors (initial rhythm, CPR duration, hospital site), and post-resuscitation factors (hypothermia, mean arterial pressure [MAP], glucose, PaO_2, PaCO2][5] in patients who survived beyond sustained ROSC.

The Use of Cerebral Oximetry

Patients received CPR in accordance with Advanced Cardiac Life Support (ACLS) recommendations (2010)[20.] Dedicated research staff at participating sites were provided with a pager and attended all CA events announced through the pager and established cerebral oximetry monitoring. Each clinical site was provided with the same oximetry equipment to minimize measurement errors (Equanox 7600, Nonin Medical, Plymouth, MN, USA). This equipment is capable of measuring cerebral oxygenation during low-flow states with an rSO2 range between 0-100%. An adhesive sensor with two near-infrared light sources and detectors, was placed on the forehead of each CA patient for cerebral oximetry monitoring. A single sensor on either side of the forehead was considered sufficient to measure rSO2, since cerebral perfusion during CA is predominantly dependent on the quality of the circulation. This was determined during a pre-pilot study where rSO2 values were compared on both sides of the forehead during CA and found to be equal. The oximeter measured the rSO2 at 4-second intervals. Artifact values were recognized by values that were three standard deviations away from the mean. Incomplete data, comprising <5% of overall data per patient was defined as any missing or

[b] Pulse oximetry and hence peripheral oxygen saturation measurements were not feasible as pulse oximetry relies on pulsatile flow, which is typically absent during CA. We thus used PaO2 as an indirect marker of the quality of peripheral oxygenation based on the known relationship between PaO2 and oxygen saturation of hemoglobin according to the oxygen dissociation curve.

incomplete values during each 4-second sampling period. It was not possible to blind clinical staff to rSO2 values as research staff needed to observe the monitor continuously during CPR for the purpose of identifying any potential sensor or measurement defects. However the rSO2 values were not used to manage patients by clinical staff, who did not have prior knowledge of the potential utility of this technology during CPR.

Prior to data collection, the research staff was certified in the collection of cerebral oximetry data, the completion of study case report forms and data entry into REDCap, a web-based data entry system prior to study commencement. Study protocols were reinforced during monthly teleconference meetings conducted for the length of data collection. All rSO2 data were recorded and automatically stored on the equipment without the need for further input from research staff, thus minimizing operator bias errors. Staff marked the time of initial ROSC, sustained ROSC or the end of CPR using dedicated event-marking buttons on the oximeter. Data were downloaded onto a designated study computer and transmitted to the Data Coordinating Center using REDCap. All rSO2 data were managed at Stony Brook University by a dedicated data coordinator. Two dedicated statisticians (blinded to the patients' histories) analyzed all rSO2 data. In order to minimize instrument bias, the oximeters were calibrated according to the manufacturer's instructions.

Statistical Analysis

Fisher's exact and Chi-square tests with exact P-values using Monte Carlo simulation were used for categorical variables. Student's t-tests or Wilcoxon rank sum tests were utilized to compare continuous variables. One-way ANOVA was used to compare rSO2 during CPR in patients without ROSC, those with ROSC who subsequently died and those with ROSC who survived with CPC 1-2. A log-binomial regression and a multivariable log-binomial regression model was used to estimate relative risks of ROSC after adjusting for possible confounders. Logistic regression models and receiver operating characteristic (ROC) curves were used to evaluate the rSO2's classification performance for predicting ROSC and CPC1-2. Using the clinical determination of ROSC [20] and the CPC scoring system at hospital discharge as standards, we compared the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the AUC of six pre-determined rSO2 variables. Three of these variables related to cerebral oxygenation throughout CPR: (mean rSO2, median rSO2, % time with rSO2>50% during CPR). The other variables relate to the last 5 minutes of CPR as they relate to initial ROSC or termination of CPR: mean, median and % time with rSO2>50%. Five minutes was chosen to

assess the state of cerebral oxygenation during the last two cycles of CPR for every documented case of ROSC. The percentage of time with rSO2>50% was chosen based on our prior experience[13-16]. While using sustained manual or mechanical CPR may raise rSO2 up to 50-55%, achieving levels>60% even with sustained high quality CPR in accordance with current ACLS standards is often not feasible. We therefore chose an rSO2 target with generalizable applicability. The accuracy of each test was summarized by AUC values and their 95% CIs. Sensitivity, specificity, PPV and NPV with their 95% CIs were reported for a series of pre-selected cut-off values rising in 5% increments from rSO2 (25%-65%) for each rSO2 variable except for % time with rSO2>50% (reported as %time) to further describe the classification performance of rSO2.

Statistical significance was set at 0.05 and analyses were conducted using SAS 9.3 (SAS Institute, Inc., Cary, NC).

3. Results

Demographics and Clinical Characteristics

There were 504 IHCA events, among which 183 (36.3%) patients met inclusion criteria. Mean age was 68.6 years (SD=15.0); 60.7% were men; and 80.9% were white. Pulseless electrical activity (PEA) was the most common presenting rhythm (66.7%). The patients' demographic and clinical characteristic data are summarized in Tables 1 and 2. Research staff typically arrived at the site of CA after 6-8 minutes of CA onset (Table 1).

ROSC, Survival & Neurological Outcomes

Overall 62/183 patients (33.9%) achieved sustained ROSC, while 13/183 (7.1%) survived with CPC1-2. Among the CPC3-5 patients, 4/170 (2.4%) had CPC3; none CPC4 and 166/170 (97.6%) CPC5. Of 166 CPC5 patients, 121 (72.9%) were declared dead after unsuccessful CPR (no ROSC), while 45 (27.1%) initially survived CPR but died prior to hospital discharge (Figure 1). Among this group of 45 patients, 30 (66.7%) died ≤1day after ROSC; the remaining 15 (33.3%) died in-hospital between 2-57 days after ROSC.

Patients with sustained ROSC had higher rSO2 during CPR (Figure 2a) Mean±SD of rSO2 (mean/patient) during CPR: 51.8 ± 11.2% vs. 40.9 ± 12.3%, P< 0.0001). All six tested rSO2 variables were higher in those with ROSC (all P <0.001) (Table 3a).

Patients with CPC1-2 had higher a mean rSO2 during CPR vs. CPC3-5 patients (Figure 2b). The Mean±SD rSO2 (mean/patient) during CPR was: 56.1±10.0% vs. 43.8±12.8%, P<0.001). Significant differences were noted in all six measured rSO2 variables (P < 0.01 for all) (Table 3b).

A stepwise increase in mean rSO2 was noted in patients with no ROSC (40.9±12.3%), vs. those who died in hospital after sustained ROSC (50.6±11.8%) vs. those who survived with CPC1-2 at discharge (56.1±10.0%) (P<0.001)[c]. Patients with CPC1-2 had a non-significant 5.5% higher mean rSO2 (95%CI: 3.4-14.3%) than those who died after sustained ROSC. In turn this group had a 9.7% higher mean rSO2 during resuscitation (95%CI 4.8-14.6%) than those who died without achieving ROSC (P <0.001) (Figure 3).

The Clinical Utility of rSO2 as a Test to Determine ROSC

The prediction accuracy of all six rSO2 variables (mean rSO2; median rSO2; % time with rSO2>50% during CPR; and mean; median and % time with rSO2>50% in the last 5 minutes of CPR) provided similar results for ROSC (Table 4a). The parameter with the highest AUC was mean rSO2 during the last 5 minutes of CPR (AUC=0.76, 95%CI: 0.69-0.83) (Table 4a). For every 5% increase in mean rSO2 in the last 5 minutes of CPR, there was 18% higher probability of achieving ROSC (RR=1.18 with 95%CI:1.13-1.23, P <0.001) (Table 5a). After adjusting for CPR duration, every 5% increase in mean rSO2 in the last 5 minutes of CPR was associated with 7% higher probability of achieving ROSC (RR=1.07 with 95%CI:1.03-1.12, P <0.001) (Table 5a). The sensitivity, specificity, PPV, and NPV and for each of the pre-selected cut-off values of mean rSO2 in the last 5 minutes of CPR are summarized (Table 6a). An rSO2 ≥25% provided 100% sensitivity (95%CI: 94%-100%) and 100% NPV (95%CI: 79%-100%), while an rSO2≥65% provided 99% specificity (95%CI:95%-100%)

[c] We did not analyze the 4 patients with CPC3 due to the low numbers.

and 93% PPV (95% CI:66%-100%) for the prediction of ROSC.

The Clinical Utility of rSO2 to Determine Survival with Favorable Neurological Outcomes at Hospital Discharge.

The rSO2 variable with the highest AUC value to predict CPC1-2 was %time with rSO2>50% throughout CPR (AUC=0.79 with 95%CI:0.70-0.88) (Table 4b). Every 5% increase in %time with rSO2>50% provided 15% higher probability of achieving CPC1-2 (RR=1.15, with 95%CI:1.06-1.26, P=0.002) (Table 5b). The sensitivity, specificity, PPV, and NPV for %time with rSO2>50% during CPR are summarized (Table 6b). Spending >24% time during CPR with rSO2>50% provided 100% sensitivity (95% CI:75%-100%), 55% specificity (95% CI:47%-62%), 14%PPV (95% CI:8%-23%) and 100% NPV(95%CI:96%-100%) for CPC1-2. On the other hand spending ≥60% CPR time with rSO2>50% provided 77% sensitivity (95% CI:46%-95%), 72% specificity (95% CI:65%-79%), 18% PPV (95% CI: 9%-30%) and 98% NPV 95% CI: 93%-100%) for predicting CPC1-2.

Repeated analysis of the rSO_2 data to examine for potential cases of CA with unrecognized underlying cardiac output.

Patients in CA with PEA may include two distinct populations; a) those with a true no cardiac output state (cardiac standstill), b) those with a very low cardiac output state (severely weakened cardiac contractions without a palpable pulse). From a practical perspective, only real-time echocardiography during CA can distinguish between these two states, yet this is not routinely feasible or available during CA. Nonetheless, patients in the latter group may be expected to have higher rSO_2 levels after starting CPR on a background of a very low cardiac output, compared to those with true cardiac standstill. We thus further compared rSO_2 levels in patients known to have cardiac standstill (asystole and VF) with those in PEA. No significant difference in rSO_2 was observed between the PEA and the asystole/VF groups (mean±SD rSO_2: 45±12.9 vs. 42±13 respectively) suggesting that the observed differences in rSO_2 during CPR in our study largely reflected the effect of CPR on oxygen delivery rather than presence or absence of cardiac contractility.

Furthermore, as cardiac contractility typically leads to a steep rise in rSO_2[25], the observed gradual rise in rSO_2 in the final five minutes of CPR in patients with ROSC (Figure 2) did not appear consistent with the impact of a sudden resumption of cardiac contractility. Nonetheless, we re-examined the relationship between rSO_2, sustained ROSC and CPC1-2 outcomes after omitting the last two minutes of rSO_2 data to account for the possibility that cardiac contractility may have preceded the clinical detection of ROSC between 2-minute CPR cycles. This revealed similar results for all six rSO_2 variables for ROSC (all P<0.001), and CPC1-2 outcomes (all P<0.005). The AUC for the prediction of ROSC using rSO_2 in the final 5 minutes CPR changed to 0.72 (95% CI: 0.64, 0.7976) and for CPC1-2 outcomes using rSO_2>50% changed to 0.76 (95%CI: 0.64-0.87).

4. Discussion

Our results indicate that ROSC and neurologically favorable survival following IHCA are associated with cerebral oxygenation and that cerebral oximetry can be used to assess the quality of cerebral oxygenation during CA.

The main strength of this study is that rSO2 data were collected throughout CPR for the purpose of studying the association between cerebral oxygenation with ROSC[11-16] and survival with favorable neurological outcomes[17-18]. The clinical utility of this study lies in identifying a real-time, non-invasive method to quantify cerebral oxygen delivery.

While the overall period of time during CPR with rSO2>50% best predicted survival with favorable neurological outcomes, peak rSO2 best predicted ROSC. Thus, higher cerebral oxygenation maintained throughout CPR may effectively attenuate cerebral ischemic and subsequent reperfusion injury, while a high peak rSO2 may facilitate ROSC. Progressive increases in coronary perfusion pressure (CPP) from 15 to 60mmHg have been shown to lead to an increased likelihood of ROSC[23], while CPP<15mmHg or an end tidal CO2 (ETCO2) <10mmHg are largely incompatible with ROSC[23-24]. While these observations mirror our findings, the advantage of rSO2 is that it also reflects the quality of cerebral oxygenation; a key factor in determining neurological outcomes. Another practical advantage of rSO2 is that it is non-invasive.

Even though our results suggest that a low rSO_2 during CPR may predict poor outcomes, care should be exercised in interpreting these data. Cerebral oxygenation as measured by NIRS is a dynamic, not a static measure, and therefore a

low rSO_2 may suggest a poor outcome where interventions aimed at improving cerebral perfusion have not been made, or have been ineffective. If despite all interventions rSO_2 remains <25% then a poor outcome may be inevitable. However, there is potential to improve rSO_2 during CPR [14 24].

Our study had limitations. Most nightime/weekend IHCA events were not included, limiting the generalizability of our findings. It remains unclear whether higher rSO2 is a marker of less severity of critical illness, or is an independent factor in CA outcomes. We had a reasonable sample, however the low numbers of CPC1-2 survivors (likely reflecting the impact of prolonged CA)[25] limited our ability to examine whether rSO2 is an independent predictor for CPC 1-2 outcomes. Larger studies are needed to explore the utility of monitoring rSO2 to predict survival with favorable neurological outcomes in all IHCA cases, as well as other CA populations.

5. Conclusion

Cerebral oximetry is a real-time, non-invasive monitor for use during CPR. Increasing rSO2 to ≥65% favors ROSC, while rSO2<25% strongly favors the inability to achieve ROSC/survival or CPC1-2. Higher rSO2 during CPR may optimize the chances of achieving survival with favorable neurological outcomes.

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sponsor did not participate in study design, analysis and interpretation of results or the writing of the manuscript. The cerebral oximetry equipment was provided by Nonin Medical, however the company had no other role in the study.

ETHICAL APPROVAL STATEMENT

The research protocol was approved by the UK multicenter national research ethics committee (MREC reference 11/EE/0003) and the Stony Brook Hospital institutional review board prior to the start of recruitment and data collection.

DATA SHARING

All authors either had access to all the de-identified data or had the opportunity to review all aggregate data during analysis

TRANSPARENCY DECLARATION

I Sam Parnia as lead author affirm that the manuscript is an honest, accurate, and transparent account of the study results being reported and that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Disclosures

None

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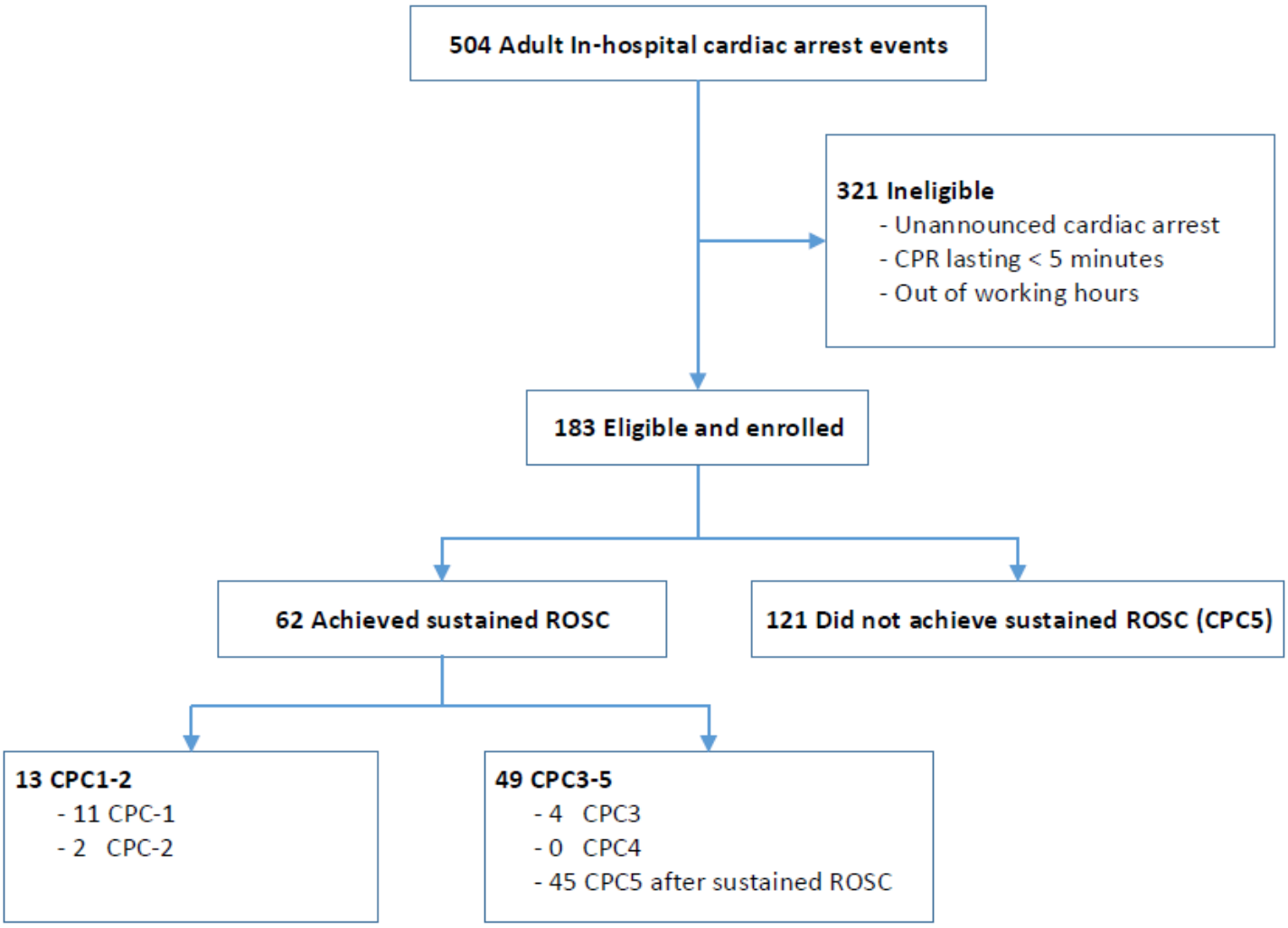

Figure 1

Summary of Study Enrollment and Outcomes.

Key: ROSC= Return of spontaneous circulation. CPC= Cerebral performance category

Figure 2a

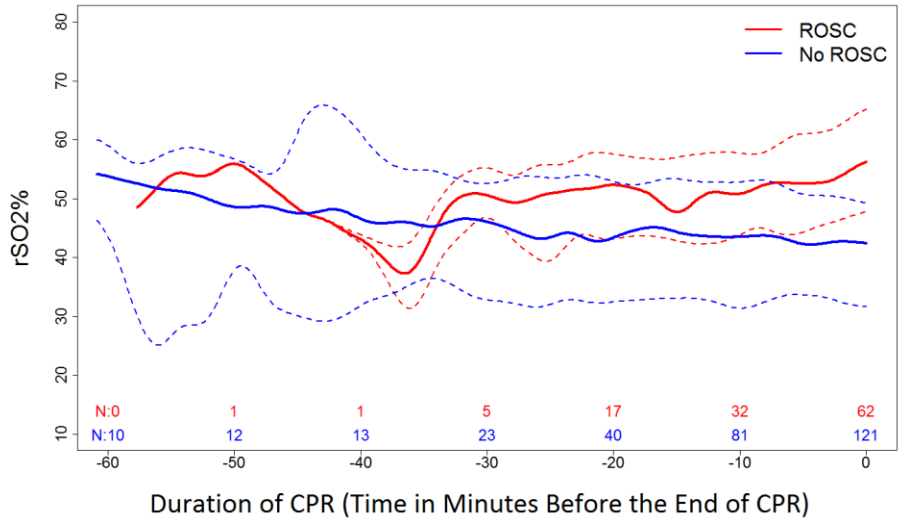

Figure 2b

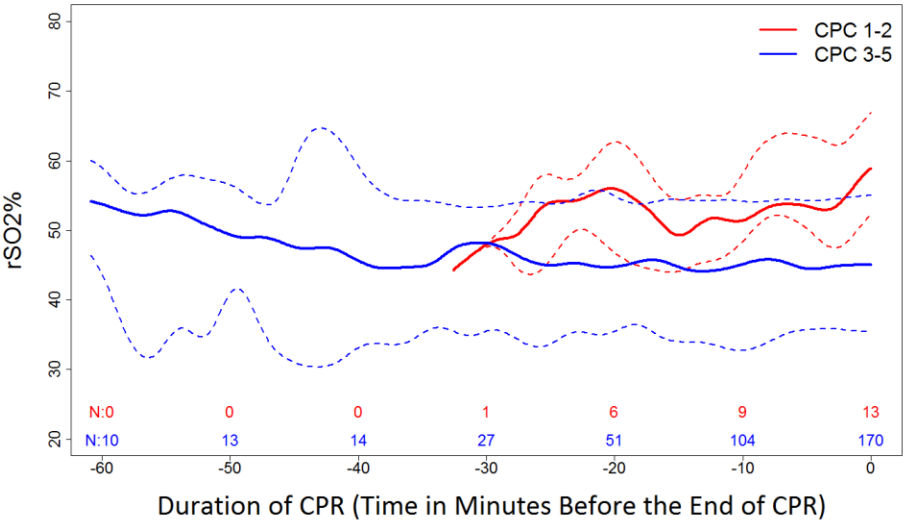

Figure 2: Changes in Cerebral Oxygenation (rSO2) during Cardiopulmonary Resuscitation (CPR) based on (a) ROSC and (b) CPC1-2 vs. CPC3-5 outcomes. The duration of CPR is presented as time before the end of CPR (in t -10 minute increments). Key: Solid lines = median rSO2% value every 4 seconds. Dashed lines = 25th and 75th percentile rSO2% values. N represents the number of patients undergoing CPR at each 10-minute time interval (up to 60 minutes) before the termination of CPR. Key: ROSC= return of spontaneous circulation. CPC= cerebral performance category

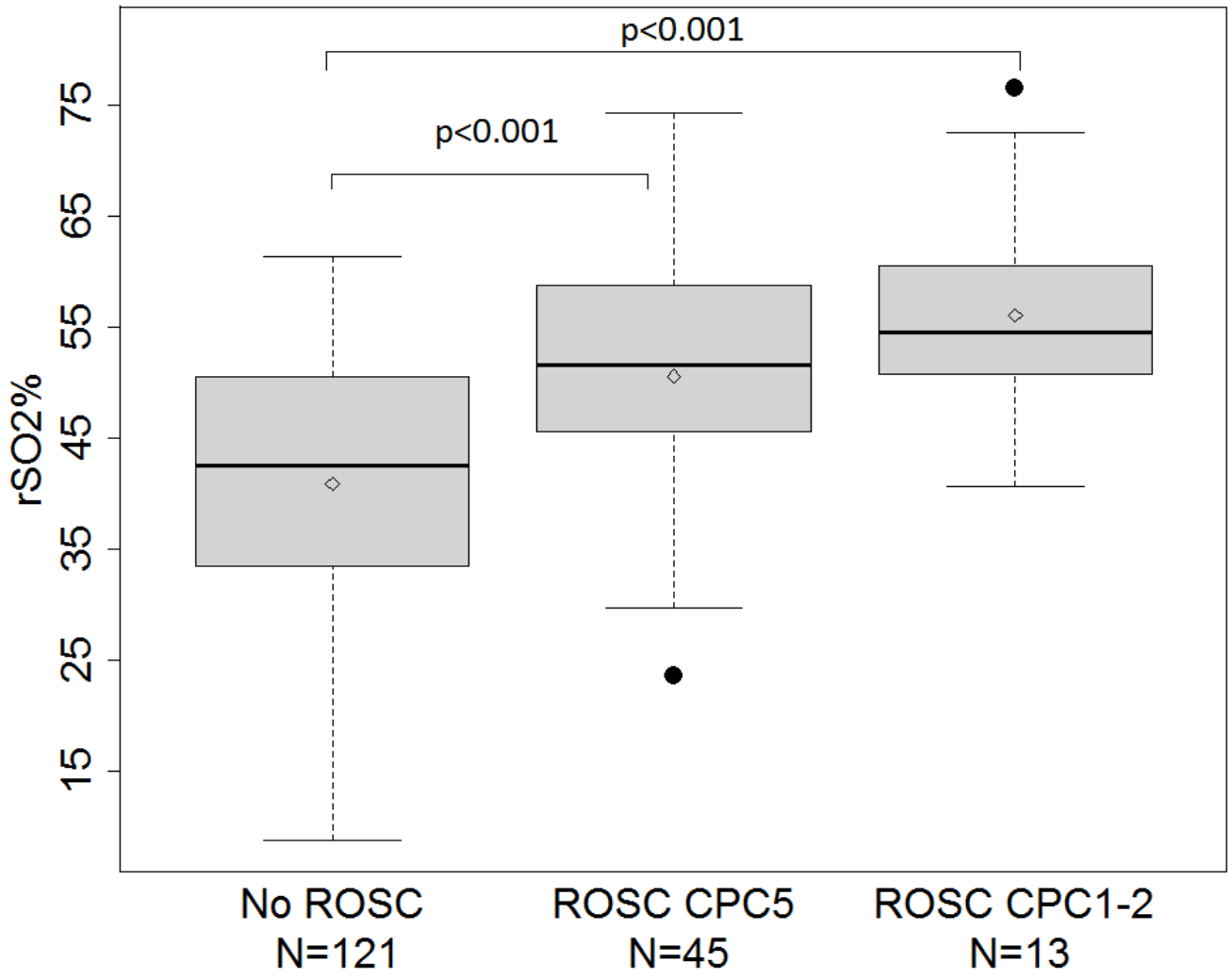

Figure 3: The relationship between rSO2 and (a) Unsuccessful CPR (No ROSC), (b) Successful CPR Followed by Hospital Death (ROSC CPC 5) and (c) Successful CPR with Hospital Survival and Favorable Neurological Outcomes (ROSC CPC1-2). Analysis carried out using one-way ANOVA. Key: ROSC= return of spontaneous circulation. CPC= cerebral performance category

Table 1. Demographic and clinical characteristics of all cardiac arrest patients based on return of spontaneous circulation (ROSC) status			
Variable	**ROSC (N=62)**	**No ROSC (N=121)**	**P-value**
Intra-cardiac arrest characteristics			
Sex			
Male	38(61%)	73(60%)	1.00
Female	24(39%)	48(40%)	
Age (mean ± SD)	66.63±15.13	69.64±14.83	0.20
Ethnicity			
Caucasian	47(76%)	101(83%)	0.41
Asian/South Asian	8(13%)	7(6%)	
African descent	4(6%)	7(6%)	
Hispanic/Latino	3(5%)	6(5%)	
Initial rhythm			
PEA	41(66%)	81(67%)	0.24
Asystole	12(19%)	31(26%)	
VF/VT	9(15%)	9(7%)	
Clinical Site			
Site 1	18(29 %)	21(17%)	0.49
Site 2	27(44%)	58(48%)	
Site 3	5(8%)	12(10%)	
Site 4	5(8%)	12(10%)	
Site 5	7(11%)	18(15%)	
Charlson Co-Morbidity Score (mean ± SD)	5.47±2.53	5.75±2.76	0.48
APACHE II* Score (Pre-Cardiac Arrest) (mean ± SD)†	21.68±11.61	22.38±11.00	0.78
Hemoglobin (g/dL) prior to cardiac arrest (mean ± SD)‡	10.76±2.00	10.79±2.49	0.94
$PaCO_2$ during CPR* (mean ± SD)§	58.35±20.89	64.08±29.57	0.23
PaO_2 during CPR* (mean ± SD)§	138.02±140.44	88.72±113.78	0.06
Duration of CPR (min) (mean ± SD)	23.37±17.77	31.31±26.26	0.02
Time to placement of oximeter sensor (minutes) (mean ± SD)	6.15±7.23	8.21±8.04	0.08
Duration of oximetry monitoring during ACLS (minutes) (mean ± SD)	17.23±14.13	23.09±24.18	0.04

*APACHE: Acute Physiology and Chronic Health Evaluation

†APACHE II scores were not available for 92 patients as arterial blood gases and other laboratory tests needed to calculate the score were not available prior to cardiac arrest.

‡Hemoglobin was not available for 41 patients prior to cardiac arrest.

§Intra-arrest $PaCO_2$ and PaO_2 were not available on 73 patients.

Table 2: Demographic and clinical characteristics of all cardiac arrest patients based on cerebral performance category (CPC) status: (CPC1-2 vs. CPC3-5)

Variable	CPC1-2 (N=13)	CPC3-5 (N=170)	P-value
Intra-cardiac arrest characteristics			
Sex			
Male	11(85%)	100(59%)	0.08
Female	2(15%)	70(41%)	
Age (mean ± SD)	60.69±18.21	69.22±14.57	0.09
Race/Ethnicity			
Caucasian	9(69%)	139(82%)	
Asian/South Asian	2(15%)	13(8%)	0.80
African descent	1(8%)	10(6%)	
Hispanic/Latino	1(8%)	8(5%)	
Initial rhythm			
PEA	8(7%)	114(93%)	0.02
Asystole	1(2%)	42(98%)	
VF/VT	4(22%)	14(78%)	
Clinical Site			
Site 1	3(23%)	36(21%)	
Site 2	9(69%)	76(45%)	0.34
Site 3	0(0%)	17(10%)	
Site 4	0(0%)	17(10%)	
Site 5	1(2%)	24(14%)	
Charlson Co-Morbidity Score (mean ± SD)	5.23±2.68	5.69±2.69	0.72
APACHE II* Score (Pre-Cardiac Arrest) (mean ± SD)†	14±8.67	22.74±11.10	0.04
Hemoglobin (g/dL) prior to cardiac arrest (mean ± SD)‡	10.98±1.88	10.76±2.36	0.77
$PaCO_2$ during CPR (mean ± SD)§	53.67±14.56	62.48±27.29	0.51
PaO_2 during CPR (mean ± SD)§	129.67±99.60	105.16±127.27	0.22
Duration of CPR (min) (mean ± SD)	28.85±24.33	28.6±24.02	0.62
Time to placement of rSO2 sensor (min) (mean ± SD)	8.62±10.73	7.43±7.59	0.80
Duration of rSO2 monitoring during ACLS (min) (mean ± SD)	20.23±17.64	21.17±21.76	0.81
Post resuscitation characteristics‖			
Targeted Temperature Management ¶ (32-34° C)			
Yes	5(29.41%)	12(70.59%)	1.00
No	7(28.00%)	18(72.00%)	
Glucose 24 hour post resuscitation (mg/dL) (mean ± SD) **	183.56±71.54	218.23±147.11	1.00
MAP† 24 hour post resuscitation (mmHg) (mean ± SD)‡‡	76.31±5.83	75.64±14.01	0.97
$PaCO_2$ 24 hour post resuscitation (mmHg) (mean ± SD) §§	57.38±34.78	45.89±11.66	0.34
PaO_2 24 hour post resuscitation (mmHg) (mean ± SD) §§	117.95±41.54	120.52±60.12	0.68

*APACHE: Acute Physiology and Chronic Health Evaluation

†APACHE II scores were not available for 92 patients as arterial blood gases and other laboratory tests needed to calculate the score were not available prior to cardiac arrest.

‡Hemoglobin was not available for 41 patients prior to cardiac arrest.

§Intra-arrest $PaCO_2$ and PaO_2 were not available on 73 patients.

‖Among the 62 patients who achieved ROSC, some could not receive all aspects of standardized post resuscitation care due to the high number (n=30) of early deaths (<24 hours) post ROSC.

¶Targeted temperature management data was missing on 20 patients.

** 24 hour post resuscitation glucose data was missing on 22 patients.

††MAP: Mean arterial pressure

‡‡24 hour post resuscitation MAP data was missing on 23 patients.

§§ 24 hour post resuscitation $PaCO_2$ and PaO_2 data was missing on 24 patients.

Table 3a: A comparison of the six different rSO_2 measures between patients with ROSC vs. without ROSC			
Variable	**ROSC (N=62)**	**No ROSC (N=121)**	**P-value**
Mean rSO_2 during resuscitation			
Mean ± SD	51.82±11.21	40.93±12.33	<0.001
Median (min, max)	52.07(23.60,76.52)	42.52(8.76,61.37)	
Median rSO_2 during resuscitation			
Mean ± SD	52.42±11.68	41.38±12.6	<0.001
Median (min, max)	53.00(24.00,77.00)	42.00(9.00,62.00)	
Mean rSO_2 in the last 5 minutes of resuscitation			
Mean ± SD	53.94±11.6	41.59±13.35	<0.001
Median (min, max)	53.30(25.2,76.52)	42.46(7.71,80.61)	
Median rSO_2 in the last 5 minutes of resuscitation			
Mean ± SD	54.02±12.24	41.93±13.47	<0.001
Median (min, max)	53.75(24.00,77.00)	43.00(8.00,80.00)	
Percentage of time with rSO_2 above 50%			
Mean ± SD	56.59±35.39	24.29±33.84	<0.001
Median (min, max)	62.85(0.00,100.00)	0.00(0.00,100.00)	
Percentage of time in the last 5 minutes with rSO_2 above 50%			
Mean ± SD	59.68±40.66	24.83±39.19	<0.001
Median (min, max)	66.45(0.00,100.00)	0.00(0.00,100.00)	

Table 3b: A comparison of the six different rSO_2 measures between patients with CPC1-2 vs. CPC 3-5.			
Variable	**CPC1-2 (N=13)**	**CPC3-5 (N=170)**	**P-value**
Mean rSO_2 during resuscitation			
Mean ± SD	56.05±9.98	43.75±12.81	<0.001
Median (min, max)	54.55(40.66,76.52)	45.22(8.76,74.29)	
Median rSO_2 during resuscitation			
Mean ± SD	56.77±10.98	44.23±13.10	0.001
Median (min, max)	54.00(42.00,77.00)	46.00(9.00,74.00)	
Mean rSO_2 in the last 5 minutes of resuscitation			
Mean ± SD	56.82±10.18	44.93±13.95	0.001
Median (min, max)	54.82(46.29,76.52)	45.58(7.71,80.61)	
Median rSO_2 in the last 5 minutes of resuscitation			
Mean ± SD	57.35±10.62	45.16±14.14	0.001
Median (min, max)	54.00(42.00,77.00)	45.00(8.00,80.00)	
Percentage of time with rSO_2 above 50%			
Mean ± SD	70.98±26.64	32.50±36.91	<0.001
Median (min, max)	76.99(24.35,100.00)	16.00(0.00,100.00)	
Percentage of time in the last 5 minutes with rSO_2 above 50%			
Mean ± SD	65.74±33.15	34.41±42.82	0.006
Median (min, max)	67.11(0.00,100.00)	0.00(0.00,100.00)	

Table 4a: Summary Table for area under the curve (AUC) and 95% confidence intervals values derived from receiver operating characteristics (ROC) curves to evaluate rSO_2%'s classification performance for predicting ROSC	
Measures	AUC (95% CI)
Mean rSO_2 in the last 5 minutes	0.76 (0.69-0.83)
Mean rSO_2	0.74 (0.66-0.82)
Median rSO_2 in the last 5 minutes	0.75 (0.67-0.82)
Median rSO_2	0.74 (0.66-0.81)
Percentage of time with rSO_2 above 50%	0.75 (0.68-0.82)
Percentage of time in the last 5 minutes with rSO_2 above 50%	0.74 (0.67-0.81)

Table 4b: Summary Table for area under the curve (AUC) and 95% confidence intervals values derived from receiver operating characteristics (ROC) curves to evaluate rSO_2%'s classification performance for predicting CPC score 1-2	
Measures	AUC (95% CI)
Mean rSO_2 in the last 5 minutes	0.75 (0.64-0.85)
Mean rSO_2	0.77 (0.66-0.88)
Median rSO_2 in the last 5 minutes	0.75 (0.64-0.86)
Median rSO_2	0.76 (0.64-0.88)
Percentage of time with rSO_2 above 50%	0.79 (0.70-0.88)
Percentage of time in the last 5 minutes with rSO_2 above 50%	0.70 (0.59-0.81)

Table 5a: The relative risk associated with a 5% increase in rSO2% in predicting return of spontaneous circulation (ROSC).					
Measures	**Unit**	**Unadjusted**		**Adjusted**	
		Relative Risk (%95 CI)	**P**	**Relative Risk (%95 CI)**	**P**
Percentage of time with rSO2 above 50%	5	1.07(1.04,1.1)	<.0001	1.07 (1.04,1.09)	<.0001
Mean rSO2 in the last 5 minutes	5	1.18(1.13,1.22)	<.0001	1.07 (1.03,1.12)	0.0002
Mean rSO2	5	1.15(1.07,1.24)	<.0001	1.05 (1.02,1.09)	0.0014

Table 5b: The relative risk associated with a 5% increase in rSO_2% in predicting CPC1-2.			
Measures	**Unit**	**Relative Risk (95% CI)**	**P-value**
Percentage of time with rSO_2 above 50%	5	1.15 (1.06-1.26)	0.002
Mean rSO_2 in the last 5 minutes	5	1.42 (1.12-1.81)	0.004
Mean rSO_2 during CPR	5	1.60 (1.20-2.13)	0.002

Table 6a: The prediction accuracy of using mean rSO_2 in the last 5 minutes of CPR with different cut-off values to predict Return of Spontaneous circulation (ROSC) among all cardiac arrest patients.							
Measures	**Cutoff ≥ rSO2%**	**No. patients**	**Sensitivity (95%CI)**	**Specificity (95%CI)**	**PPV* (95%CI)**	**NPV† (95%CI)**	**Misclassification (95%CI)**
Mean rSO_2% in the last 5 minutes CPR	25.19	167	1.00 (0.94-1.00)	0.13 (0.08-0.21)	0.37 (0.30-0.45)	1.00 (0.79-1.00)	0.57 (0.50-0.65)
	30	158	0.98 (0.91-1.00)	0.20 (0.13-0.28)	0.39 (0.31-0.47)	0.96 (0.80-1.00)	0.54 (0.46-0.61)
	35	143	0.9 (0.80-0.96)	0.28 (0.20-0.37)	0.39 (0.31-0.48)	0.85 (0.70-0.94)	0.51 (0.43-0.58)
	40	127	0.9 (0.80-0.96)	0.41 (0.32-0.51)	0.44 (0.35-0.53)	0.89 (0.78-0.96)	0.42 (0.35-0.50)
	45	99	0.84 (0.72-0.92)	0.61 (0.52-0.70)	0.53 (0.42-0.63)	0.88 (0.79-0.94)	0.31 (0.25-0.38)
	50	70	0.61 (0.48-0.73)	0.74 (0.65-0.81)	0.54 (0.42-0.66)	0.79 (0.70-0.86)	0.31 (0.24-0.38)
	55	45	0.42 (0.30-0.55)	0.84 (0.77-0.90)	0.58 (0.42-0.72)	0.74 (0.66-0.81)	0.30 (0.24-0.37)
	60	29	0.29 (0.18-0.42)	0.91 (0.84-0.95)	0.62 (0.42-0.79)	0.71 (0.64-0.78)	0.30 (0.24-0.37)
	65	14	0.21 (0.12-0.33)	0.99 (0.95-1.00)	0.93 (0.66-1.00)	0.71 (0.64-0.78)	0.27 (0.21-0.34)
	70	9	0.13 (0.06-0.24)	0.99 (0.95-1.00)	0.89 (0.52-1.00)	0.69 (0.62-0.76)	0.30 (0.24-0.37)
	75	2	0.02 (0.00-0.09)	0.99 (0.95-1.00)	0.50 (0.01-0.99)	0.66 (0.59-0.73)	0.34 (0.27-0.41)
	80	1	0.00 (0.00-0.06)	0.99 (0.95-1.00)	0.00 (0.00-0.98)	0.66 (0.59-0.73)	0.34 (0.28-0.42)

Table 6b: The prediction accuracy of using the percentage of time with rSO_2% above 50% during cardiopulmonary resuscitation (CPR) to predict CPC1-2 with different cut-off values among all cardiac arrest patients.							
Measures	**Cutoff ≥ rSO2%**	**No. patients**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV* (95%CI)**	**NPV† (95%CI)**	**Misclassification (95% CI)**
Percentage of time with rSO_2 above 50%	24.34	90	1.00 (0.75-1.00)	0.55 (0.47-0.62)	0.14 (0.08-0.23)	1.00 (0.96-1.00)	0.42 (0.35-0.50)
	30	86	0.92 (0.64-1.00)	0.56 (0.49-0.64)	0.14 (0.07-0.23)	0.99 (0.94-1.00)	0.41 (0.34-0.48)
	40	79	0.77 (0.46-0.95)	0.59 (0.52-0.67)	0.13 (0.06-0.22)	0.97 (0.92-0.99)	0.39 (0.32-0.47)
	50	69	0.77 (0.46-0.95)	0.65 (0.58-0.72)	0.14 (0.07-0.25)	0.97 (0.93-0.99)	0.34 (0.27-0.41)
	60	57	0.77 (0.46-0.95)	0.72 (0.65-0.79)	0.18 (0.09-0.30)	0.98 (0.93-1.00)	0.27 (0.21-0.34)
	70	40	0.54 (0.25-0.81)	0.81 (0.74-0.86)	0.18 (0.07-0.33)	0.96 (0.91-0.98)	0.21 (0.16-0.28)
	80	34	0.46 (0.19-0.75)	0.84 (0.77-0.89)	0.18 (0.07-0.35)	0.95 (0.91-0.98)	0.19 (0.14-0.26)
	90	26	0.31 (0.09-0.61)	0.87 (0.81-0.92)	0.15 (0.04-0.35)	0.94 (0.89-0.97)	0.17 (0.12-0.23)
	100	16	0.15 (0.02-0.45)	0.92 (0.87-0.95)	0.13 (0.02-0.38)	0.93 (0.89-0.97)	0.14 (0.09-0.20)

*PPV= positive predictive value

†NPV= negative predictive value