Original article

Prognostic predictors in patients with cardiopulmonary arrest: a novel equation for evaluating the 30-day mortality

Shunichi Imamura (MD) [a], Masaaki Miyata (MD, PhD)[a], Kento Tagata (MD)[a], Tatsuo Yokomine (MD)[a], Kenta Ohmure (MD)[a], Mariko Kawasoe (MD)[a], Hideaki Otsuji (MD)[a], Hideto Chaen (MD, PhD)[a], Naoya Oketani (MD, PhD)[a], Masakazu Ogawa (MD, PhD)[a], Kentaro Nakamura (MD)[b], Satoshi Yoshino (MD, PhD)[d], Yasuyuki Kakihana (MD, PhD)[c], Mitsuru Ohishi (MD, PhD)[d]

[a]Department of Cardiovascular Medicine, Kagoshima City Hospital, Kagoshima, Japan

[b]Department of Emergency Medicine, Ohshima Prefectural Hospital, Kagoshima, Japan

[c]Department of Emergency Medicine, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan

[d]Department of Cardiovascular Medicine and Hypertension, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan

Correspondence to: Shunichi Imamura

Department of Cardiovascular Medicine, Kagoshima City Hospital,

37-1 Uearata-cho, Kagoshima City, 890-8760, Japan

Tel: +81-99-230-7000; Fax: +81-99-230-7070

E-mail address: www.haruichi.vs.syunichi@gmail.com

Keywords: resuscitation, cardiopulmonary arrest, 30-day mortality, predictor

Word count: Manuscript, 3576 words

Abbreviations

AMI, acute myocardial infarction

CI, confidence interval

CPA, cardiopulmonary arrest

CPR, cardiopulmonary resuscitation

CT, computed tomography

ECG, electrocardiogram

ECLS, extracorporeal life support

EEG, electroencephalography

EPD, estimated probability of death

GCS, Glasgow Coma Scale

MRI, magnetic resonance imaging

OHCA, Out-of-hospital cardiac arrest

OR, odds ratio

ROC, receiver operating characteristic

ROSC, return of spontaneous circulation

VF, ventricular fibrillation

Abstract

Background: Early prediction of outcomes after cardiopulmonary arrest (CPA) is important for considering the best support. Our purpose was to evaluate predictors of the 30-day mortality in patients with CPA after return of spontaneous circulation (ROSC) and to assess an equation for calculating the 30-day mortality using clinical parameters.

Methods: We retrospectively analyzed the data of 194 consecutive patients with CPA and ROSC in a derivation study (2015–2022). We compared clinical parameters between the survived (n = 78) and dead (n = 116) patients. We derived an equation for estimated probability of death based on clinical parameters, using multivariate logistic regression analysis. The reliability of the equation was validated in 80 additional patients with CPA.

Results: The 30-day mortality was associated with sex, witnessed cardiac arrest, bystander cardiopulmonary resuscitation (CPR), CPA due to acute myocardial infarction, pupil diameter, Glasgow Coma Scale score (GCS), presence of light reflex, arterial or venous pH, lactate levels, initial ventricular fibrillation (VF), CPA time and age. The derived logistic regression equation was as follows: Estimated probability of death = $1 / (1 + e^{-x})$, x = (0.25 × bystander CPR) + (0.44 × pupil diameter) – (0.14 × GCS) + (0.09 × lactate) – (1.87 × initial VF) + (0.07 × CPA time) + (0.05 × age) - 7.03. The cut-off value for estimated probability of death calculated by this equation was 54.5%, yielding a sensitivity, specificity, and accuracy of 86.2%, 80.8%, and 84.5%, respectively. In the validation model, these values were 81.8%, 85.7%, and 82.5%, respectively.

Conclusions: The 30-day mortality may be calculated after ROSC in patients with CPA using simple clinical parameters. This equation may facilitate further best support for patients with CPA.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a common cause of death, with an average incidence of 55 per 100,000 person-year globally, and a survival rate of 2–11% [1]. With the revision of cardiopulmonary resuscitation (CPR) guidelines and implementation of high-quality CPR procedures, minimization of interruptions, and standardized post-cardiac arrest care, the survival rate of OHCA patients has improved [2–6]. In the Cardiac Arrest Registry to Enhance Survival (CARES), the rate of hospital discharge increased from 2.1% to 3.9% in non-shockable rhythms, and from 16.1 to 21.1% in shockable rhythms, during 2005–2012 [7,8]. However, the mortality of OHCA patients remains high, particularly in patients without bystander cardiopulmonary resuscitation (CPR) and those with ventricular fibrillation (VF) as the initial rhythm [1,9].

Despite concerted and extended CPR efforts, patients who do not have a rapid return of spontaneous circulation (ROSC) do not survive with good functional outcomes [10,11]. Longer durations of CPR are associated with lower ROSC and higher mortality rates, even in patients with in-hospital cardiac arrest [11,12]. In addition, when shifting to other procedures after the failure of conventional CPR, such as to extracorporeal life support (ECLS), it results in an undesirable situation both from a personal and a global perspective [6,13–15].

In most situations, appropriate management for cardiopulmonary arrest (CPA) patients remains challenging, because of the lack of knowledge concerning their background, functional status, underlying disease, and collapse time [16,17]. Although laboratory measurements of some factors, such as neuron-specific enolase, a protein soluble in 100% ammonium sulphate, and interleukin-8, were considered to predict

neurological outcomes, these tests cannot always be obtained in daily clinical situations [17–19]. Some studies have reported that neurological or diagnostic imaging approaches, such as electroencephalography, brain computed tomography (CT), and magnetic resonance imaging (MRI), implemented several hours after ROSC could predict the neurological outcome [19–21]. However, neurological findings in comatose patients do not always predict the neurological outcome. Furthermore, the appropriate time to evaluate hypoxic brain damage with CT or MRI has not been established [20], and this could detrimentally delay decisions regarding the optimal management for patients after ROSC.

Therefore, early prediction of outcomes in patients with CPA is important to consider the further best support. However, to our knowledge, there have been no reports that have clarified the predictors of in-hospital mortality immediately after ROSC in OHCA patients. It may be necessary to evaluate useful clinical parameters that can be obtained easily and rapidly at the time of ROSC. The purpose of this study was to evaluate prognostic predictors of the 30-day mortality and to assess an equation for calculating the 30-day mortality in OHCA patients using clinical simple parameters.

Methods

Study design and patient population

The study consisted of two retrospective cohort studies: the derivation and the validation studies. The derivation study was performed in Kagoshima City Hospital, while the validation study was performed in Kagoshima University Hospital and Ohshima Prefectural Hospital. We analyzed data of OHCA patients who

received CPR according to American Heart Association guidelines for CPR by emergency medical staff and who achieved ROSC [22,23]. All patients were aged ≥ 18 years and were admitted to each hospital to receive intensive treatment after ROSC from April 2015 to March 2022. All patients received respiratory tract control with an appropriate device and were treated with infusion solution and adrenaline. We surveyed their clinical data, including age, sex, body mass index, medical history, initial rhythm on electrocardiogram (ECG), presence of a witness to the CPA, bystander CPR, time from CPR to arrival at hospital, time from CPR to ROSC, physical and neurological examinations, arterial or venous pH, laboratory data, and therapeutic procedures after ROSC. The pupil diameter was measured by two emergency medical doctors using a ruler and the blood gas analysis was performed within 5 min of ROSC. Initial abnormal rhythms on ECG were classified as asystole, pulseless electrical activity, pulseless ventricular tachycardia, or VF. CPA was defined as receiving chest compressions performed by emergency medical staffs or electrical shock administered using automated external defibrillator. The CPA time was defined as the time from collapse to the achievement of ROSC. Acute myocardial infarction (AMI) was defined according to the universal definition of myocardial infarction [24]. Patients with AMI had acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cardiac troponin values, with at least one value above the 99th percentile upper reference limit and at least one of the following findings: symptoms of myocardial ischemia, new ischemic ECG changes, development of a pathological Q wave, new loss of viable myocardium, or new regional wall motion abnormality, and identification of a coronary thrombus by angiography [24]. The Glasgow Coma Scale (GCS) is scored between 3 and 15 points, with 3 being the worst and 15 being the best. It is composed of three parameters: best eye

opening (spontaneous = 4, response to verbal command = 3, response to pain = 2, no eye opening = 1), best verbal response (oriented = 5, confused = 4, inappropriate words = 3, incomprehensible sounds = 2, no verbal response = 1), and best motor response (obeys commands = 6, localizing response to pain = 5, withdrawal response to pain = 4, flexion to pain = 3, extension to pain = 2, no motor response = 1) [25,26].

All patients discharged from hospital were assessed for functional status using the modified Rankin Scale (mRS) score at discharge. Scores were defined as follows: mRS 0, no symptoms at all; mRS 1, no significant disability; mRS 2, slight disability; mRS 3, moderate disability; mRS 4, moderately severe disability; mRS 5, severe disability; and mRS 6, death. [27] Good recovery to moderate disability were considered favorable neurological outcomes, which were defined as mRS scores of 0–3 points.

We compared the pre-hospital clinical course and the clinical parameters immediately after ROSC between the 30-day survival and dead groups. We defined the clinical parameters as prognostic predictors for the 30-day mortality if the parameter differed significantly between these groups. For the consecutive variables considered as prognostic predictors, we evaluated the cut-off value for predicting the 30-day mortality of each clinical parameter and then calculated the estimated probability of death (EPD) using logistic regression analysis.

We defined patients in Kagoshima City Hospital as the derivation cohort and those in Kagoshima University Hospital and Ohshima Prefectural Hospital as the validation cohort. We performed the validation study to assess the reliability of EPD in our hospital. Then, we compared clinical parameters and the accuracy of the EPD between the derivation and validation datasets.

The institutional review boards of Kagoshima City Hospital, Kagoshima University Hospital, and

Ohshima Prefectural Hospital approved this study. We presented the study protocol for all participants with opt-out consent.

Statistical analysis

Categorical data are presented as numbers (%) and continuous data are presented as means ± standard deviations or medians with 25th and 75th percentiles. The chi-square test was used for comparisons between groups, and the unpaired *t*-test or Mann–Whitney U test was used for comparison of consecutive variables. Multiple logistic regression analysis was performed to assess the odds ratio (OR) for the 30-day mortality and to derive the equation for EPD based on clinical parameters. We selected age, CPA time, pupil diameter, and lactate levels as the explanatory variables of the logistic regression model for calculating the EPD. Receiver operating characteristic (ROC) curves were constructed to calculate the cut-off value of each clinical parameter for prediction of in-hospital death. Pearson's correlation coefficient was used to evaluate the relationship between clinical parameters and EPD. p values < 0.05 indicated statistical significance. All statistical analyses were performed with R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) and JMP version 16 (SAS Institute, Cary, NC, USA).

Results

Derivation Study

We analyzed the data of 251 consecutive OHCA patients admitted to Kagoshima City Hospital after ROSC, from April 2015 to March 2022. We excluded 13 patients with traumatic CPA, 25 patients who achieved

ROSC at other hospitals, three patients who had undergone cataract surgery (which could influence pupil diameter and light reflex), and 16 patients without essential clinical data. Finally, the clinical data of 194 patients were included in the derivation study (Fig. 1). The mean age of the 194 patients was 70 years, 74% were male, and the survival rate at 30 days was 59.8%. We divided these patients into the survival (n = 78) and dead groups (n = 116) within 30 days (Fig. 1).

The clinical characteristics of these two groups are presented in Table 1. There were no significant differences in body mass index, use of physician-staffed car or helicopter, time from CPR to arrival at hospital, use of percutaneous cardiopulmonary support, and comorbidities (Table 1). On the other hand, there were significantly differences in age, sex, witnessed cardiac arrest, bystander CPR, CPA due to AMI, pupil diameter, GCS, presence of a light reflex, arterial or venous pH, lactate levels, initial VF, and CPA time (Table 1). Male had more AMI as a cause of CPA than female (male vs female: 25.2% vs 7.8%, $p = 0.008$).

Table 2 demonstrates the ORs of each parameter for the 30-day mortality, adjusted by age. The 30-day mortality was associated with sex ($p = 0.026$), witnessed cardiac arrest ($p = 0.019$), bystander CPR ($p = 0.039$), CPA due to AMI ($p = 0.013$), pupil diameter ($p < 0.001$), GCS ($p < 0.001$), present of a light reflex ($p < 0.001$), arterial or venous pH ($p < 0.001$), lactate levels ($p < 0.001$), initial VF ($p < 0.001$), and CPA time ($p < 0.001$).

We performed ROC analysis for the 30-day mortality using age, GCS, pupil diameter, CPA time, arterial or venous pH, and lactate levels. The cut-off values for predicting the 30-day mortality of these parameters are presented in Table 3. Although the pupil diameter, CPA time, arterial or venous pH, and lactate levels demonstrated fair areas under the ROC curve (AUC), it would be difficult to predict the 30-day mortality

by using a single clinical parameter; moreover, the predictors have complicated connections.

Therefore, we derived an equation for the EPD using bystander CPR, pupil diameter, GCS, lactate levels, initial VF, CPA time, and age. By logistic regression analysis, EPD was calculated using the equation:

EPD = $1 / (1+e^{-x})$, where x was represented as follows: x = (0.25 × bystander CPR) + (0.44 × pupil diameter) – (0.14 × GCS) + (0.09 × lactate) – (1.87 × initial VF) + (0.07 × CPA time) + (0.05 × age) – 7.03. In this equation, the nominal variables are changed into categorical variables as follows: bystander CPR (present = 1, absent = 0), and VF in initial rhythm (yes = 1, no = 0). The reliability of this equation was excellent by statistical analysis ($p < 0.001$). After calculating and comparing the EPD between the survival and dead groups, the EPD was significantly higher in the dead group than in the survival group (80.8% [61.9, 93.6] vs 19.5% [12.4, 47.1], $p < 0.001$). The ROC curve revealed an AUC of 0.9 and that an EPD cut-off value of 54.5% yielded 86.2% sensitivity, 80.8% specificity, 84.5% accuracy, 87.7% positive-predictive value, and 80.0% negative-predictive value. (Fig. 2).

Figure 3 shows the scatter plot between EPD and each clinical parameter with continuous variables in the survival and dead groups. There was a significant correlation between the EPD and CPA time ($r = 0.551$, $p < 0.001$), GCS ($r = -0.517$, $p < 0.001$), lactate levels ($r = 0.431$, $p < 0.001$), pupil diameter ($r = 0.501$, $p < 0.001$), and age ($r = 0.261$, $p = 0.021$) in the survival group. Moreover, there was a significant correlation between the EPD and CPA time ($r = 0.469$, $p < 0.001$), GCS ($r = -0.213$, $p = 0.022$), lactate levels ($r = 0.263$, $p < 0.001$), and pupil diameter ($r = 0.465$, $p < 0.001$) in the dead group. However, there was no significant correlation between the EPD and age in the dead group.

Validation study

To certify the reliability of the EPD, we performed a validation study, in which we analyzed 80 consecutive patients with CPA in Kagoshima University Hospital and Ohshima Prefectural Hospital during the same period. Table 4 shows the comparison of clinical characteristics between the derivation and validation dataset. There were no significant differences in age, sex, AMI, initial situation of CPA, therapeutic procedures, physical examination on arrival at hospital, the 30-day mortality, and favorable neurological outcomes at discharge between the derivation and validation dataset (Table 4). The sensitivity, specificity, and accuracy of the EPD at a cut-off of 54.5% in the validation model were 81.8%, 85.7%, and 82.5%, respectively. Furthermore, the AUC derived from the ROC curve was excellent (AUC = 0.931). Using EPD, the favorable accuracy of derivation and validation dataset represented the good reproducibility to evaluate the 30-day mortality after ROSC.

Discussion

In the present study, we demonstrated that the 30-day mortality was associated with age, sex, witnessed cardiac arrest, bystander CPR, CPA due to AMI, pupil diameter, GCS, presence of a light reflex, arterial or venous pH, lactate levels, initial VF, and CPA time. Male tended to survive more than female. The reason was considered that the male had more AMI as a cause of CPA than female, which is a treatable disease. We selected bystander CPR, pupil diameter, GCS, lactate levels, initial VF, CPA time, and age as the explanatory variables of the logistic regression model to calculate the EPD because data on these parameters are easy to obtain after

ROSC and present fair AUC in the ROC curve. The light reflex, witnessed cardiac arrest, definite AMI, and pH were not selected because they are similar to pupil diameter, bystander CPR, initial VF, and lactate levels, respectively. Furthermore, we proposed an equation for predicting the EPD using these clinical parameters as determined immediately after ROSC. A cut-off value of the EPD of 54.5% yielded 86.2% sensitivity, 80.8% specificity, and 84.5% accuracy for predicting the 30-day mortality. Moreover, the reliability of the EPD was verified by a validation study. The main novelty of this research is that we showed the probability of 30-day mortality using simple clinical parameters after ROSC. EPD may become a reference for provision of further support.

Some clinical trials, with subsequent guideline updates, have refined CPR quality, defibrillation timing, and pharmacological treatment for patients with CPA over the past decades [27–32]. Despite the tremendous efforts made for OHCA patients, resuscitation was successful in only 1/3 of OHCA patients, and only 10% of those patients can be discharged from hospital, many of whom have neurological disabilities [13,31-34]. If resuscitation is successful, rapid prediction of the prognosis after ROSC and deciding on an appropriate treatment are difficult. Little evidence is available for predicting the 30-day mortality immediately after ROSC. Reynolds et al. reported that a longer CPR duration was associated with poor neurological outcomes and that the probability of good functional recovery falls to under 2% if CPA time exceeds 15 min [10]. They suggested that intensive treatment, such as ECLS, should be considered if the conventional CPR fails in the first 10–15 min [10]. However, ECLS is effective only for selected patients, such as those with in-hospital CPA or cardiogenic CPA, and it can prolong the state of hypoxic brain injury or increase medical costs [8,35]. Adequate

treatment needs to be selected to avoid unethical treatment.

To predict the outcome after ROSC in patients with OHCA, the Null-PLEASE score, consisting of scores for the 10 items—a non-shockable rhythm, unwitnessed cardiac arrest, no bystander CPR, ≥ 30 min until ROSC, pH < 7.2, lactate > 7, end-stage kidney disease, age ≥ 85 years, CPR even after arriving at the hospital, and extra-cardiac cause—can be calculated, and the mortality rate is three times higher in patients with scores ≥ 5 than in those with scores ≤ 4 [36]. In this previous work, 547 OHCA patients were included and presented a useful score to predict the outcome. Although our study included only 194 OHCA patients, the pupil diameter, and GCS which are important predictors of brain injury [37], were identified as a predictor. In addition, we used logistic regression analysis to evaluate the OR and rough mortality to refer to consider the best support in such patients.

Using the CREST score, the five items of pre-existing coronary artery disease, non-shockable rhythm, ejection fraction < 30% on admission, shock at the time of admission, and CPA time > 25 min are associated with a mortality rate of 0–50% with each score of 0 to 5 points. [38] Although the CREST score may be useful to determine which patients may benefit from interventions after ROSC, the score did not include the physical or neurological findings. The present study demonstrated that bystander CPR, VF in the initial rhythm, and CPA time were associated with prognosis in patients with CPA after ROSC. In addition, we showed that the pupil diameter, the presence of a light reflex, arterial or venous pH, lactate levels, and GCS, which can be easily measured after ROSC, might evaluate factors for high-risk OHCA patients. Pupil diameter, light reflex, arterial or venous pH, lactate levels, and GCS after ROSC may represent the condition of the patient. Therefore, we

adopted bystander CPR, pupil diameter, GCS, lactate levels, initial VF, CPA time, and age when we calculated the EPD.

Hayakawa et al. reported an equation that calculates neurological prognosis after ROSC, using a logistic regression model that incorporates age and CPA time [39]. This study presented a useful equation that could easily predict the 1-month neurological outcomes after ROSC. Furthermore, in this study, accurate CPA time was used because study participants were witnessed and cardiogenic patients with CPA. As our study included a lot of non-witnessed OHCA cases, the CPA time might not be accurate. However, in an aging society, the number of patients who suffer non-cardiogenic CPA or unwitnessed CPA at home may increase [6,14,40,41], which limits the number of patients for whom the equation can be used. Moreover, their report did not consider the quality of CPR. Our equation involved the quality of CPR by incorporating pupil diameter, GCS, and lactate levels after ROSC. As the present study included all patients with CPA of medical origin, our equation would be suited to current circumstances, in which non-cardiogenic patients with CPA are common [6,13].

We propose that an EPD of 54.5% may be a cut-off value for evaluating high-risk OHCA patients. Although the neurological prognosis of patients with CPA has been discussed in many studies [10–12,16–20,42], there is usually limited information available concerning the patients at hospital arrival, and their families are usually confused by the sudden unexpected situation. Therefore, we should evaluate the patients with high mortality and provide them with further appropriate treatments as soon as possible. Although the appropriate treatment for patients with CPA remains challenging, suitable treatment should be provided, considering respect for and the dignity of the patient. Using EPD introduced herein, it may be possible to recognize high-risk OHCA

patients immediately after ROSC and to consider further best support.

Limitations

There were some limitations in this study. First, this study included a small sample size in the derivation and validation examinations, and the prediction model did not have feasible performance for use in real clinical settings. Therefore, a future large clinical study is needed to validate this prediction model. Until then, it should not be used for decision-making. Second, this was a retrospective multicenter study. Therefore, a prospective multicenter study, involving a large sample size, is needed to investigate the reliability of the EPD. Third, as we did not use an automated pupilometer in daily clinical settings, the findings of the pupil diameter and light reflex were based on the subjective evaluation of emergency medical doctors. Fourth, we used the presumed time from collapse to ROSC as the CPA time because our study included a lot of unwitnessed patients with CPA. Fifth, there might be unmeasured confounding factors, such as the location of cardiac arrest or the post-cardiac arrest treatment. Sixth, as we excluded the patients with a history of cataract surgery based only on the information obtained from patients' families, some patients with cataract surgery might have been included in this study. Finally, the accuracy of EPD in this study was not 100%. This probability should not be presented to patients' families considering whether to provide invasive treatment or planning advance care, and physicians should interpret EPD results carefully in clinical settings.

Conclusions

In this study, we showed that the 30-day mortality in OHCA patients was associated with age, sex,

witnessed cardiac arrest, bystander CPR, CPA due to AMI, pupil diameter, GCS, presence of a light reflex, arterial or venous pH, lactate levels, initial VF, and CPA time. Using bystander CPR, pupil diameter, GCS, lactate levels, initial VF, CPA time, and age, we might be able to estimate the 30-day mortality using an equation. However, since the equation of EPD was derived from a small sample size and showed modest accuracy, this equation should not be used in a clinical setting. Therefore, further examination is necessary to verify the EPD.

Acknowledgments

The authors thank Dr. Nami Uchiyama for her assistance to receive approval of the ethical review board of Kagoshima University Hospital. In addition, the authors are indebted to all of the emergency medical system personnel and concerned physicians in Kagoshima City Hospital, Kagoshima University Hospital and Ohshima Prefectural Hospital.

Funding

This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

Disclosures

The authors declare that there is no conflict of interest

References

[1] Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. Resuscitation. 2010;81:1479–87. https://doi.org/10.1016/j.resuscitation.2010.08.006.

[2] Neumar RW, Shuster M, Callaway CW, Gent LM, Atkins DL, Bhanji F, et al. Part 1: Executive summary: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132 (Suppl 2):S315–67. https://doi.org/10.1161/CIR.0000000000000252.

[3] Monsieurs KG, Nolan JP, Bossaert LL, Greif R, Maconochie IK, Nikolaou NI, et al. European Resuscitation Council guidelines for resuscitation 2015: Section 1. Executive summary. Resuscitation. 2015;95:1–80. https://doi.org/10.1016/j.resuscitation.2015.07.038.

[4] Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2010;3:63–81. https://doi.org/10.1161/CIRCOUTCOMES.109.889576.

[5] Daya MR, Schmicker RH, Zive DM, Rea TD, Nichol G, Buick JE, et al. Out-of-hospital cardiac arrest survival improving over time: results from the Resuscitation Outcomes Consortium (ROC). Resuscitation. 2015;91:108–15. https://doi.org/10.1016/j.resuscitation.2015.02.003.

[6] Okubo M, Kiyohara K, Iwami T, Callaway CW, Kitamura T. Nationwide and regional trends in survival from out-of-hospital cardiac arrest in Japan: A 10-year cohort study from 2005 to 2014. Resuscitation. 2017;115:120–8. https://doi.org/10.1016/j.resuscitation.2017.03.036.

[7] Nagao K, Kikushima K, Watanabe K, Tachibana E, Tominaga Y, Tada K, et al. Early induction of hypothermia during cardiac arrest improves neurological outcomes in patients with out-of-hospital cardiac arrest who undergo emergency cardiopulmonary bypass and percutaneous coronary intervention. Circ J. 2010;74:77–85. https://doi.org/10.1253/circj.cj-09-0502.

[8] Tanno K, Itoh Y, Takeyama Y, Nara S, Mori K, Asai Y. Utstein style study of cardiopulmonary bypass after cardiac arrest. Am J Emerg Med. 2008;26:649–54. https://doi.org/10.1016/j.ajem.2007.09.019.

[9] Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008;300:1423–31. https://doi.org/10.1001/jama.300.12.1423.

[10] Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies? Circulation. 2013;128:2488–94. https://doi.org/10.1161/CIRCULATIONAHA.113.002408.

[11] Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S, Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;67:203–10. https://doi.org/10.1212/01.wnl.0000227183.21314.cd.

[12] Nagao K, Nonogi H, Yonemoto N, Gaieski DF, Ito N, Takayama M, et al. Duration of prehospital resuscitation efforts after out-of-hospital cardiac arrest. Circulation. 2016;133:1386–96. https://doi.org/10.1161/CIRCULATIONAHA.115.018788.

[13] Chan PS, McNally B, Tang F, Kellermann A, Recent trends in survival from out-of-hospital cardiac arrest in the United States. Circulation. 2014;130:1876–82. https://doi.org/10.1161/CIRCULATIONAHA.114.009711.

[14] Druwé P, Monsieurs KG, Piers R, Gagg J, Nakahara S, Alpert EA, et al. Perception of inappropriate cardiopulmonary resuscitation by clinicians working in emergency departments and ambulance services: The REAPPROPRIATE international, multi-centre, cross sectional survey. Resuscitation. 2018;132:112–9. https://doi.org/10.1016/j.resuscitation.2018.09.006.

[15] Goto Y, Funada A, Maeda T, Okada H, Goto Y. Field termination-of-resuscitation rule for refractory out-of-hospital cardiac arrests in Japan. J Cardiol. 2019;73:240–6. https://doi.org/10.1016/j.jjcc.2018.12.002.

[16] Granfeldt A, Wissenberg M, Hansen SM, Lippert FK, Torp-Pedersen C, Christensen EF, et al. Location of cardiac arrest and impact of pre-arrest chronic disease and medication use on survival. Resuscitation. 2017;114:113–20. https://doi.org/10.1016/j.resuscitation.2017.02.026.

[17] Tanaka H, Ong MEH, Siddiqui FJ, Ma MHM, Kaneko H, Lee KW et al. Modifiable Factors Associated With Survival After Out-of-Hospital Cardiac Arrest in the Pan-Asian Resuscitation Outcomes Study. Ann Emerg Med. 2018;71:608–617.e15. https://doi.org/10.1016/j.annemergmed.2017.07.484.

[18] Oda Y, Tsuruta R, Fujita M, Kaneda K, Kawamura Y, Izumi T, et al. Prediction of the neurological outcome with intrathecal high mobility group box 1 and S100B in cardiac arrest victims: a pilot study. Resuscitation. 2012;83:1006–12. https://doi.org/10.1016/j.resuscitation.2012.01.030.

[19] Ekmektzoglou KA, Xanthos T, Papadimitriou L. Biochemical markers (NSE, S-100, IL-8) as predictors of

neurological outcome in patients after cardiac arrest and return of spontaneous circulation. Resuscitation. 2007;75:219–28. https://doi.org/10.1016/j.resuscitation.2007.03.016.

[20] Madl C, Grimm G, Kramer L, Yeganehfar W, Sterz F, Schneider B, et al. Early prediction of individual outcome after cardiopulmonary resuscitation. Lancet. 1993;341:855–8. https://doi.org/10.1016/0140-6736(93)93061-5.

[21] Saltuari L, Marosi M. Coma after cardiac arrest: will he recover all right? Lancet. 1994;343:1052–3. https://doi.org/10.1016/s0140-6736(94)90176-7.

[22] Neumar RW, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, et al. Part 8: Adult advanced cardiovascular life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2010;122 (Suppl 3):S729–67. https://doi.org/10.1161/CIRCULATIONAHA.110.970988.

[23] Link MS, Berkow LC, Kudenchuk PJ, Halperin HR, Hess EP, Moitra VK, et al. Part 7: Adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132 (Suppl 2):S444–64. https://doi.org/10.1161/CIR.0000000000000261.

[24] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of myocardial infarction. Circulation. 2018;138:e618–51. https://doi.org/10.1161/CIR.0000000000000617.

[25] Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2:81–4. https://doi.org/10.1016/s0140-6736(74)91639-0.

[26] Mullie A, Verstringe P, Buylaert W, Houbrechts H, Michem N, Delooz H et al. Predictive value of Glasgow Coma Score for awakening after out-of-hospital cardiac arrest. Cerebral Resuscitation Study Group of the Belgian Society for intensive Care. Lancet. 1988;1:137–40.

[27] van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604–7. https://doi.org/10.1161/01.str.19.5.604.

[28] Hostler D, Everson-Stewart S, Rea TD, Stiell IG, Callaway CW, Kudenchuk PJ, et al. Effect of real-time feedback during cardiopulmonary resuscitation outside hospital: prospective, cluster-randomised trial. BMJ. 2011;342:d512. https://doi.org/10.1136/bmj.d512.

[29] Ong ME, Machey KE, Zhang Zc, Tanaka H, Ma MH, Swor R, et al. Mechanical CPR devices compared to manual CPR during out-of-hospital cardiac arrest and ambulance transport: a systematic review. Scand J Trauma Resusc Emerg Med 2012; 20-39.

[30] Stiell IG, Nichol G, Leroux BG, Rea TD, Ornato JP, Powell J, et al. Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. N Engl J Med. 2011;365:787–97. https://doi.org/10.1056/NEJMoa1010076.

[31] Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: A randomized trial. JAMA. 2009;302:2222–9. https://doi.org/10.1001/jama.2009.1729.

[32] Tenney JW, Yip JHY, Lee RHY, Wong BCY, Hung KKC, Lam RPK, et al. Retrospective evaluation of resuscitation medication utilization in hospitalized adult patients with cardiac arrest. J Cardiol. 2020;76:9–13.

https://doi.org/10.1016/j.jjcc.2020.02.004.

[33] Hatakeyama T, Kiguchi T, Kobayashi D, Nakamura N, Nishiyama C, Hayashida S, et al. Effectiveness of dispatcher instructions-dependent of independent bystander cardiopulmonary resuscitation on neurological survival among patients with out-of-hospital cardiac arrest. J Cardiol. 2020;75:315–22. https://doi.org/10.1016/j.jjcc.2019.08.007.

[34] Wong MK, Morrison LJ, Qiu F, Austin PC, Cheskes S, Dorian P, et al. Trends in short- and long-term survival among out-of-hospital cardiac arrest patients alive at hospital arrival. Circulation. 2014;130:1883–90. https://doi.org/10.1161/CIRCULATIONAHA.114.010633.

[35] Herlitz J, Andersson E, Bång A, Engdahl J, Holmberg M, Lindqvist J, et al. Experiences from treatment of out-of-hospital cardiac arrest during 17 years in Goteborg. Eur Heart J. 2000;21:1251–8. https://doi.org/10.1053/euhj.2000.2150.

[36] Potpara TS, Mihajlovic M, Stankovic S, Jozic T, Jozic I, Asanin MR, et al. External validation of the simple NULL-PLEASE clinical score in predicting outcome of out-of-hospital cardiac arrest. Am J Med. 2017;130:1464e13-e21. https://doi.org/10.1016/j.amjmed.2017.05.035.

[37] Couret D, Boumaza D, Grisotto C, Triglia T, Pellegrini L, Ocquidant P et al. Reliability of standard pupillometry practice in neurocritical care: an observational, double-blinded study. Crit Care. 2016;20:99. https://doi.org/10.1186/s13054-016-1239-z.

[38] Bascom KE, Dziodzio J, Vasaiwala S, Mooney M, Patel N, Mcpherson J, et al. Derivation and Validation of the CREST model for very early prediction of circulatory etiology death in patients without ST-segment-

elevation myocardial infarction after cardiac arrest. Circulation. 2018;137:273–82. https://doi.org/10.1161/CIRCULATIONAHA.116.024332.

[39] Hayakawa K, Tasaki O, Hamasaki T, Sakai T, Shiozaki T, Nakagawa Y, et al. Prognostic indicators and outcome prediction model for patients with return of spontaneous circulation from cardiopulmonary arrest: the Utstein Osaka Project. Resuscitation. 2011;82:874–80. https://doi.org/10.1016/j.resuscitation.2011.02.045.

[40] Eisenburger P, Sterz F, Haugk M, Scheinecker W, Holzer M, Koreny M, et al. Cardiac arrest in public locations-an independent predictor for better outcome? Resuscitation. 2006;70:395–403. https://doi.org/10.1016/j.resuscitation.2006.02.002.

[41] Nehme Z, Andrew E, Bray JE, Cameron P, Bernard S, Meredith IT, et al. The significance of pre-arrest factors in out-of-hospital cardiac arrests witnessed by emergency medical services: a report from the Victorian Ambulance Cardiac Arrest Registry. Resuscitation. 2015;88:35–42. https://doi.org/10.1016/j.resuscitation.2014.12.009.

[42] Shannon MF, Alexandre T, Wei C, Bram R, Monica T, Christian V, et al. Pre-arrest and intra-arrest prognostic factors associated with survival after in-hospital cardiac arrest: systemic review and meta-analysis. BMJ. 2019;367:I6373.

Figure legends

Fig. 1. Study flow chart in the derivation group

ROSC, return of spontaneous circulation

Fig. 2. Receiver operating characteristic curve for the estimated probability of death using the derivation dataset

Fig. 3. A comparison of scatter plots of the dead and survival groups

EPD, estimated probability of death; CPA, cardiopulmonary arrest; GCS, Glasgow coma scale

○ Dead group. △ Survival group

Table 1 Comparison of clinical characteristics between survival and dead groups.

	Survival group (n=78)	Dead group (n=116)	P-value
Age (years)	65±19	73±14	<0.001
Male, n (%)	65 (83)	78 (67)	0.013
Body mass index (kg/m²)	21.4±6.1	21.4±5.0	0.954
Witnessed cardiac arrest, n (%)	64 (82)	77 (66)	0.012
Bystander CPR, n (%)	48 (62)	52 (45)	0.028
Use of physician-staffed car or helicopter, n (%)	44 (56)	54 (47)	0.190
Time from CPR to arrival at hospital (min)	36.4±14.9	35.8±16.0	0.843
Definite AMI, n (%)	23 (29)	17 (15)	0.018
Therapeutic hypothermia, n (%)	51 (69)	24 (21)	<0.001
PCPS, n (%)	10 (13)	15 (3)	0.648
Hypertension, n (%)	29 (37)	39 (34)	0.647
Dyslipidemia, n (%)	9 (12)	11 (9)	0.639
Diabetes mellitus, n (%)	20 (26)	35 (30)	0.520
Renal insufficiency	39 (50)	60 (52)	0.884
History of coronary artery disease, n (%)	10 (13)	21 (18)	0.425
Old cerebral vascular disease, n (%)	10 (13)	10 (9)	0.348
Pupil diameter (mm)	3.5±1.3	4.8±1.4	<0.001
GCS	5.0±3.7	3.2±0.7	<0.001
Present of light reflex, n (%)	36 (46)	8 (7)	<0.001
Arterial or venous pH	7.14±0.21	6.95±0.17	<0.001
Lactate levels (mmol/L)	8.74±4.92	12.57±4.85	<0.001
Initial VF, n (%)	41 (53)	19 (16)	<0.001
CPA time (min)	27.2±17.2	43.1±19.8	<0.001

Abbreviations: CPR - cardiopulmonary resuscitation, AMI - acute myocardial infarction, PCPS - percutaneous-cardiopulmonary support, Renal insufficiency - defined as glomerular filtration- rate < 60 ml/minutes/1.73cm², GCS - Glasgow coma scale, VF - ventricular fibrillation, CPA - cardiopulmonary arrest.

Table 2 Odds ratio for the 30-day mortality, adjusted by age.

	Odds ratio	95% CI	P-value
Sex (male)	0.436	0.209-0.907	0.026
Witnessed cardiac arrest (absent)	2.380	1.150-4.920	0.019
Bystander CPR	0.532	0.292-0.970	0.039
Definite AMI (present)	0.400	0.194-0.824	0.013
Pupil diameter (/0.5mm dilatation)	2.010	1.570-2.570	<0.001
GCS	0.624	0.480-0.812	<0.001
Light reflex (present)	0.088	0.037-0.209	<0.001
Arterial or venous pH	0.003	0.0004-0.029	<0.001
Lactate levels	1.230	1.130-1.330	<0.001
Initial VF (present)	0.212	0.106-0.423	<0.001
CPA time (/min)	1.070	1.050-1.100	<0.001
Age	1.030	1.0100-1.050	0.001

Abbreviations: CPR – cardiopulmonary resuscitation, AMI – acute myocardial infarction, GCS – Glasgow coma scale, VF – ventricular fibrillation, CPA – cardiopulmonary arrest.

Table 3 Receiver-Operating Characteristic analysis for the 30-day mortality

	Cut-off value	Sensitivity (%)	Specificity (%)	AUC
Age	74	58.5	58.8	0.58
GCS	5	5.7	70.6	0.35
Pupil diameter (mm)	4.0	83.0	70.6	0.79
CPA time (min)	27	81.1	64.7	0.75
pH	7.04	69.8	67.6	0.71
Lactate levels (mmol/L)	9.4	71.4	65.5	0.74

Abbreviations: GCS - Glasgow coma scale, CPA - cardiopulmonary arrest , AUC – area under the curve

Table 4　Comparison of clinical characteristics between derivation and validation dataset

	Derivation data (n = 194)	Validation data (n = 80)	P-value
Age (years)	69.5±17.4	66.2±19.2	0.17
Male, n (%)	143 (74)	54 (68)	0.304
Definite AMI, n (%)	40 (21)	20 (25)	0.426
Witnessed CPA, n (%)	141 (73)	61 (76)	0.651
Bystander CPR, n (%)	100 (52)	44 (55)	0.69
Initial VF, n (%)	60 (31)	26 (33)	0.886
Time from CPA to arrival at hospital (min)	36±16	36±20	0.814
CPA time (min)	37±20	41±23	0.144
PCPS, n (%)	32 (16)	7 (9)	0.127
Therapeutic hypothermia, n (%)	75 (39)	32 (40)	0.892
GCS	3.9±2.6	3.4±1.6	0.107
Pupil size (mm)	4.3±1.5	4.5±1.4	0.232
Presence of light reflex, n (%)	44 (23)	16 (20)	0.748
Arterial or venous pH	7.25±0.21	7.01±0.23	0.537
Survival at discharge, n (%)	78 (40)	24 (30)	0.131
Modified Rankin scale score 0-3 at discharge, n (%)	38 (19)	12 (19)	0.491

Abbreviations: AMI – acute myocardial infarction, CPA - cardiopulmonary arrest, CPR - cardiopulmonary resuscitation, VF - ventricular fibrillation, PCPS – percutaneous cardiopulmonary support, GCS - Glasgow coma scale.

Fig. 1.

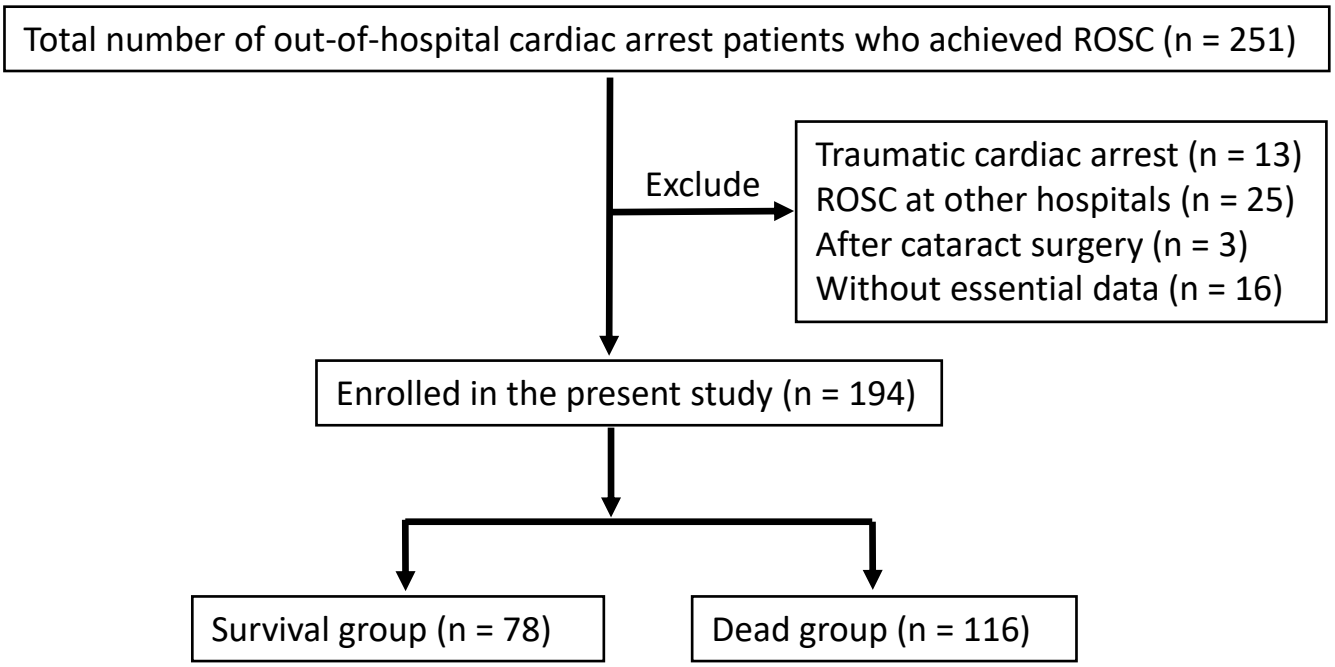

Total number of out-of-hospital cardiac arrest patients who achieved ROSC (n = 251)
Exclude
Traumatic cardiac arrest (n = 13)
ROSC at other hospitals (n = 25)
After cataract surgery (n = 3)
Without essential data (n = 16)
Enrolled in the present study (n = 194)
Survival group (n = 78)
Dead group (n = 116)

Fig. 2.

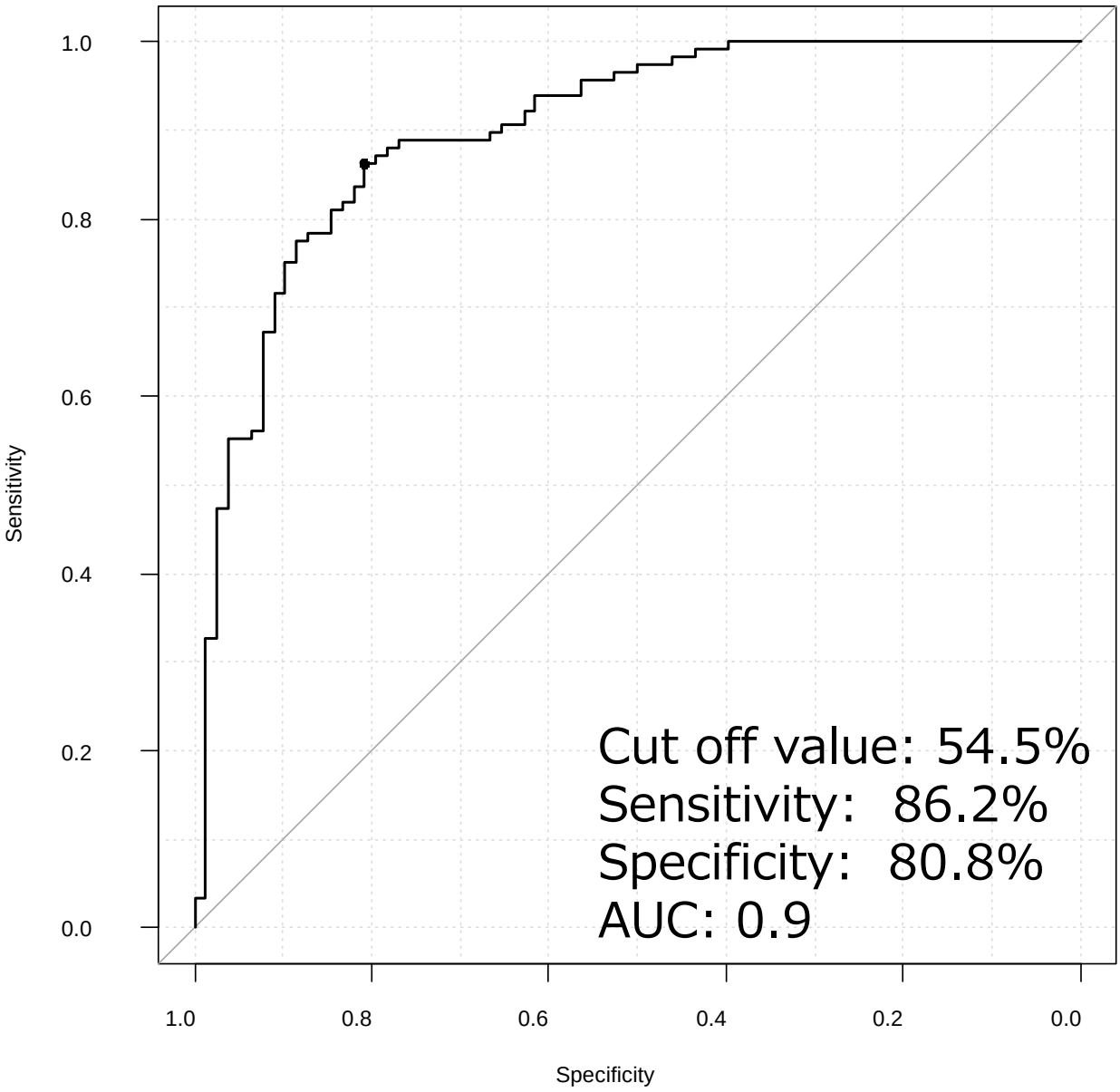
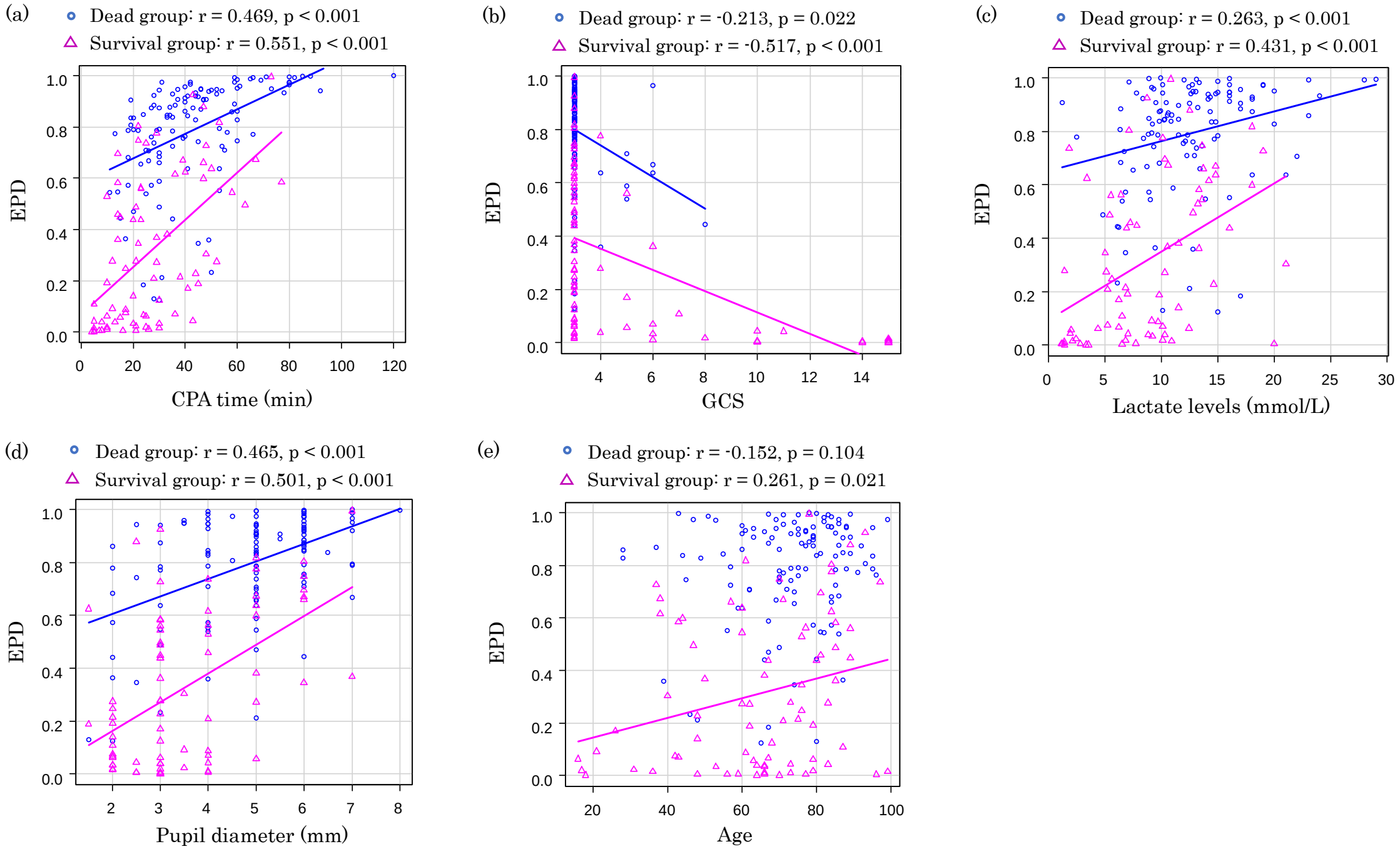

1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
Specificity
Cut off value: 54.5%
Sensitivity: 86.2%
Specificity: 80.8%
AUC: 0.9

Fig. 3.


(a)
Dead group: r = 0.469, p < 0.001
Survival group: r = 0.551, p < 0.001
EPD
CPA time (min)
(b)
Dead group: r = -0.213, p = 0.022
Survival group: r = -0.517, p < 0.001
EPD
GCS
(c)
Dead group: r = 0.263, p < 0.001
Survival group: r = 0.431, p < 0.001
EPD
Lactate levels (mmol/L)
(d)
Dead group: r = 0.465, p < 0.001
Survival group: r = 0.501, p < 0.001
EPD
Pupil diameter (mm)
(e)
Dead group: r = -0.152, p = 0.104
Survival group: r = 0.261, p = 0.021
EPD
Age