Usefulness of the Degree of Blood–brain Barrier Disruption to Predict Neurological Prognosis in Cardiac Arrest Survivors who Wnderwent Target Temperature Management: A Retrospective Study

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Research

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Abstract

Background: This study aimed to compare the day-specific association of blood–brain barrier (BBB) disruption with neurological outcomes in out-of-hospital cardiac arrest (OHCA) survivors treated with target temperature management (TTM).

Methods: This retrospective single-center study included 68 OHCA survivors, who underwent TTM between April 2018 and December 2019. The albumin quotient (Q_A) was calculated as [$albumin_{CSF}$] / [$albumin_{serum}$] immediately (day 1), and at 24 h (day 2), 48 h (day 3), and 72 h (day 4) after return of spontaneous circulation (ROSC). The degree of BBB disruption was weighted using the following scoring system: $0.07 \geq Q_A$ (normal), $0.01 \geq Q_A > 0.007$ (mild), $0.02 \geq Q_A > 0.01$ (moderate), and $Q_A > 0.02$ (severe). This system gave it 0 (normal), 1 (mild), 4 (moderate), and 9 (severe) points. Poor neurological outcome was determined at six months after ROSC and was defined as cerebral performance categories 3–5.

Results: We enrolled 68 patients (males, 48; 71%); 37 (54%) of them had a poor neurological outcome. The distributions of this outcome at six months in patients with moderate and severe BBB disruption versus the other groups were 19/22 (80%) vs. 18/46 (50%) on day 1, 31/37 (79%) vs. 6/31 (32%) on day 2, 32/37 (81%) vs. 5/31 (30%) on day 3, and 32/39 (85%) vs. 5/29 (30%) on day 4 ($P < 0.001$). Using ROC analyses, the optimal cutoff values of Q_A levels for prediction of neurological outcomes were determined as: day 1, > 0.009 (sensitivity 56.8%, specificity 87.1%); day 2, > 0.012 (sensitivity 81.1%, specificity 87.1%); day 3, > 0.013 (sensitivity 83.8%, specificity 87.1%); day 4, > 0.013 (sensitivity 86.5%, specificity 87.1%); sum of all time points, > 0.039 (sensitivity 89.5%, specificity 79.4%); and scoring system, > 9 (sensitivity 91.9%, specificity 87.1%).

Conclusions: Our results suggested that Q_A is a useful tool for predicting neurological outcomes in OHCA survivors treated with TTM. However, the prediction of poor neurological outcome using Q_A showed low sensitivity at 100% specificity. Thus, it could be used as part of a multimodal approach than as a single prognostic prediction tool.

Background

The blood–brain barrier (BBB) is composed of cerebral microvascular endothelial cells, a capillary base membrane, pericytes, and astrocyte end-feet. It regulates the movement of plasma constituents into the brain parenchyma [1–3]. The junctional complexes between endothelial cells comprise tight junctions and adherens junctions [1]. An ischemic/reperfusion injury, such as ischemic stroke and cardiac arrest (CA), increases the permeability of the BBB tight junctions due to microvascular damage induced through oxidative stress, resulting in BBB disruption [1, 4]. With cytotoxic edema that does not produce BBB disruption, the total tissue brain mass will initially remain unchanged. However, vasogenic edema resulting in BBB disruption is compounded through the addition of water from the vascular space, which leads to tissue swelling, tissue movement, and eventually to an increase in intracranial pressure (ICP) [5].

Brain edema and ICP are associated with poor neurological outcome and death in patients who have survived a CA.

The relationship between BBB disruption after CA and neurological prognosis is rare in clinical studies and mostly reported in animal studies. Our previous study was the first clinical study, where we reported that severe BBB disruption and its onset timing were strongly associated with poor neurological outcomes in the out-of-hospital cardiac arrest (OHCA) survivors who had undergone target temperature management (TTM) [6]. However, that study had several limitations. First, it was limited in its generalizability, as it comprised only a small number of patients (n = 21). Second, it did not reveal any relationship between the neurological outcome and the degree of BBB disruption. Third, the study could not predict poor neurological outcome of BBB disruption.

We hypothesized that the degree of BBB disruption was associated with the neurological status in OHCA survivors. Therefore, we investigated the association between the degree of BBB disruption for three days and the neurological status six months after the return of spontaneous circulation (ROSC) in patients with OHCA who had been treated with TTM.

Methods

Study design and patients

In this retrospective observational study, we used prospectively collected data derived from adult comatose OHCA survivors treated with TTM at Chungnam National University Hospital in Daejeon, Republic of Korea, between April 2018 and December 2019. The Institutional Review Board of Chungnam National University Hospital approved this study (CNUH-2020-04-103). This study included 14 patients from our previous studies on severe BBB disruption [6].

We included adult (≥ 18 years) OHCA survivors, who were unconscious (Glasgow Coma Scale score, ≤ 8) after ROSC. They had been treated with TTM using an Arctic Sun® system (Energy Transfer Pads™; Medivance Corp, Louisville, CO, USA). We excluded patients (1) who had experienced a traumatic CA or an interrupted TTM owing to transfer or death, (2) who were ineligible for lumbar puncture (LP), (3) who were receiving extracorporeal membrane oxygenation, (4) who had no next of kin to provide consent for an LP procedure, and (5) whose next of kin did not consent to further treatment. The ineligibility for LP was determined if the brain computed tomography showed severe cerebral edema, obliteration of the basal cisterns, an occult intracranial mass lesion, or coagulopathy with a platelet count < 40×10^3/mL or international normalized ratio > 1.5.

Targeted temperature management

Comatose OHCA survivors underwent TTM in accordance with our previously published TTM protocols [7]. A target temperature of 33°C was maintained for 24 h using an Arctic Sun® feedback-controlled

surface cooling device. Upon completion of the TTM maintenance period, the patients were rewarmed to 37°C at a rate of 0.25°C/h, and the temperature was monitored using a bladder temperature probe.

All patients received sedatives, and a neuromuscular blocking agent was used during TTM. Midazolam (0.05 mg/kg intravenous bolus, followed by a titrated intravenous continuous infusion between 0.05 and 0.2 mg/kg/h) and cisatracurium (0.15 mg/kg intravenous bolus, followed by an infusion up to 5 μg/kg/min) were administered to sedate the patient and to control shivering, respectively. Anesthetic depth was monitored using ADMS™ (Anesthetic Depth Monitor for Sedation, Unimedics Co., Ltd., Seoul, Republic of Korea). An electroencephalography was performed if persistent deterioration in a patient's consciousness level, involuntary movements, or seizures were observed. In case of evidence of electrographic seizures or clinical diagnosis of seizures, we administered an antiepileptic medication, namely, levetiracetam (loading dose, 2 g bolus, intravenously; maintenance dose, 1 g bolus, twice daily, intravenously). All other aspects of patient management involved standard intensive care processes, carried out in accordance with our institutional intensive care unit protocol.

Data collection

We obtained data on the following parameters from hospital records: age, sex, medical history (hypertension, coronary artery disease, diabetes mellitus), witnessed collapse, bystander cardiopulmonary resuscitation (CPR), first monitored rhythm, etiology of CA, time from collapse to CPR (no flow time), time from CPR to ROSC (low flow time), time from ROSC to obtaining ICP via LP (ICP time), and sequential organ failure assessment (SOFA) score within the first 24 h after admission. We assessed the neurological outcomes at three months after OHCA via phone interview, using the cerebral performance category (CPC) scale, as follows: CPC 1, good performance; CPC 2, moderate disability; CPC 3, severe disability; CPC 4, vegetative state; or CPC 5, brain death or death [8, 9].

Measurement of albumin quotient and scoring system

A lumbar catheter insertion was performed using the Hermetic^{TM} lumbar catheter accessory kit (Integra Neurosciences, Plainsboro, NJ, USA) with the patient lying in a lateral decubitus position with hips and knees flexed. CSF albumin and serum albumin samples were obtained at the same time immediately (day 1), and at 24 h (day 2), 48 h (day 3), and 72 h (day 4) after ROSC. The albumin quotient (Q_A) was calculated using the following formula:

albumin quotient (Q_A) = [albumin$_{CSF}$] / [albumin$_{serum}$]

The degree of BBB disruption was defined as follows: $0.07 \geq Q_A$ (normal), $0.01 \geq Q_A > 0.007$ (mild), $0.02 \geq Q_A > 0.01$ (moderate), and $Q_A > 0.02$ (severe). Based on our previous studies, the scoring system weighted the degree of BBB disruption and gave it 0 (normal), 1 (mild), 4 (moderate), and 9 (severe)

points. For example, if normal disruption occurred on day 1, mild disruption on day 2, moderate disruption on day 3, and severe disruption on day 4, then the weighted score would be 0 + 1 + 4 + 9 = 14 points.

Statistical analysis

We described categorical variables as frequencies and percentages and continuous variables as median values with interquartile ranges. We compared categorical variables between groups using the χ^2 test with continuity correction in 2 × 2 tables. We compared continuous variables between groups using the Mann–Whitney *U* test, since all continuous variables showed non-normal distribution. At each time point, the receiver operating characteristic (ROC) curves were plotted and corresponding areas under the curve (AUC) were determined to evaluate the predictive performance of BBB disruption on poor neurological outcome (CPC 3–5). The cutoff value for predicting poor neurological outcomes after six months post-OHCA was determined using the Youden index. Data were analyzed using SPSS software version 18 (SPSS Inc., Chicago, IL, USA). The ROC curves were calculated using MedCalc version 15.2.2 (MedCalc Software, Mariakerke, Belgium). The significance level was set to $P < 0.05$.

Results

Clinical characteristics of the patients

In total, 81 adult comatose OHCA survivors had been treated with TTM during the study period. Of these, 68 patients were enrolled in the study. At six months after ROSC, 31 (45.6%) patients were in the good neurological outcome group, whereas 37 (54.4%) were in the poor neurological outcome group (Fig. 1). Table 1 displays the demographic and OHCA characteristics, stratified according to the neurological outcome at six months. There were no significant differences between the two groups in terms of median age, sex, pre-existing illness, and LP time. Patients with good neurological outcome had a higher incidence of witness arrest and bystander CPR, were more likely to have a shockable rhythm and a cardiac etiology, had shorter no- and low flow times, and had lower SOFA scores.

Table 1
Baseline demographics and clinical characteristics

Characteristics	Total (n=68)	Good neurological outcome (n=31)	Poor neurological outcome (n=37)	*P-value*
Age, years, median (IQR)	55.9 (52.1 – 59.8)	54.7 (48.8 – 60.6)	57.1 (51.8 – 62.5)	0.53
Male, n (%)	53 (73.6)	28 (82.4)	25 (65.8)	0.18
Preexisting illness, n (%)				
DM	25 (34.7)	11 (32.4)	14 (36.8)	0.81
HTN	26 (36.1)	14 (41.2)	12 (31.6)	0.47
Coronary artery disease	11 (15.4)	6 (17.6)	5 (13.2)	0.75
Cardiac arrest				
Witness, n (%),	49 (68.1)	28 (82.4)	21(55.3)	0.02
Bystander CPR, n (%)	49 (68.1)	30 (88.2)	19 (50.0)	< 0.001
Shockable rhythm, n (%)	19 (26.4)	18 (52.9)	1 (2.6)	< 0.001
Cardiac aetiology, n (%)	29 (40.3)	20 (58.8)	9 (23.7)	0.04
No flow time, min, median (IQR)	2.0 (0.0 – 18.5)	0.5 (0.0 – 4.25)	10.5 (1.0 – 31.3)	< 0.001
Low flow time, min, median (IQR)	19.0 (9.0– 30.0)	12.0 (5.8 – 20.0)	28.0 (15.0 – 43.0)	< 0.001
LP time, hour, median (IQR)	4.7 (3.3 – 6.1)	4.3 (3.0 – 5.6)	4.8 (4.3 – 6.4)	0.1
SOFA score	10.0 (7.0– 12.0)	8.0 (7.0 – 11.0)	11.0 (8.0 – 12.0)	0.04

IQR, interquartile range; DM, diabetes mellitus; HTN, hypertension; CPR, cardiopulmonary resuscitation; ROSC, restoration of spontaneous circulation; LP, lumbar puncture; SOFA, sequential organ failure assessment

Serial comparison of Q_A levels between good and poor neurological outcome groups

The Q_A levels were significantly lower in the good neurological outcome group compared with that in the poor neurological outcome group at each time point ($P < 0.001$). On days 1–4, the Q_A values between the good and poor neurological outcome groups were 0.006 (0.003–0.009) vs. 0.011 (0.007–0.018); 0.007 (0.004–0.009) vs. 0.027 (0.015–0.131); 0.007 (0.004–0.009) vs. 0.032 (0.017–0.151); and 0.006 (0.004–0.010) vs. 0.044 (0.017–0.226) (Fig. 2).

Serial comparison of the degree of BBB disruption and neurological outcome

Fig. 3 shows that the proportion of poor neurological outcomes was higher than that of good neurological outcomes, when there was a moderate or severe BBB disruption at all time point. Of the 68 patients, moderate and severe BBB disruption was determined for 22 (32.4%) patients on day 1, 37 (54.4%) on day 2, 37 (54.4%) on day 3, and 39 (57.3%) on day 4, with the highest number of patients on day 4. The distributions of poor neurological outcome at six months in the moderate and severe BBB disruption group and other groups were 19/22 (80%) vs. 18/46 (50%) on day 1, 31/37 (79%) vs. 6/31 (32%) on day 2, 32/37 (81%) vs. 5/31 (30%) on day 3, and 32/39 (85%) vs. 5/29 (30%) on day 4, respectively, with $P < 0.001$.

Q_A and 6-month neurological outcome

Using ROC analyses, optimal cutoff values of Q_A levels for prediction of poor neurological outcomes at six months were determined as: day 1, > 0.009 (sensitivity 56.8%, specificity 87.1%; $P < 0.001$); day 2, > 0.012 (sensitivity 81.1%, specificity 87.1%; $P < 0.001$); day 3, > 0.013 (sensitivity 83.8%, specificity 87.1%; $P < 0.001$); day 4, > 0.013 (sensitivity 86.5%, specificity 87.1%; $P < 0.001$); sum of all time points, > 0.039 (sensitivity 89.5%, specificity 79.4%; $P < 0.001$); and scoring system, > 9 (sensitivity 91.9%, specificity 87.1%; $P < 0.001$) (Fig. 4). Comparison of ROC curves revealed that predictive value of Q_A on day 1 was significantly lower compared with that on other days, sum of all time points, and scoring system (Table 2). Numerically, the largest area under the curve was of the scoring system, followed by sum of all time points and day 4 (Fig. 4).

Table 2
Comparison of ROC curves for day-specific Q_A prediction of poor neurological outcome at 6-month.

ROC	Difference AUC	95% Confidence interval	*P*
Day 1 – Day 2	0.118	0.007– 0.228	0.037
Day 1 – Day 3	0.122	0.004– 0.240	0.043
Day 1 – Day 4	0.142	0.033 – 0.250	0.011
Day 1 – Sum,	0.156	0.068– 0.244	<0.001
Day 1 – Score	0.168	0.075 – 0.260	<0.001
Day 2 – Day 3	0.004	-0.069– 0.078	0.907
Day 2 – Day 4	0.024	-0.041– 0.089	0.467
Day 2 – Sum	0.038	-0.023– 0.098	0.219
Day 2 – Score	0.050	-0.004 – 0.104	0.070
Day 3 – Day 4	0.020	-0.039 – 0.079	0.514
Day 3 – Sum	0.034	-0.021 – 0.089	0.232
Day 3 – Score	0.046	-0.007– 0.098	0.087
Day 4 – Sum	0.014	-0.035– 0.062	0.572
Day 4 – Score	0.026	-0.013– 0.065	0.188
Sum – Score	0.012	-0.011 – 0.036	0.303.
ROC, receiver operating characteristic; Q_A, albumin quotient			

Specific Q_A levels associated with poor neurological outcomes on the different days of measurement: Q_A level > 0.061 on day 1 with 100% specificity and 5.4% sensitivity; Q_A level > 0.056 on day 2 with 100% specificity and 34.2% sensitivity; Q_A level > 0.167 on day 3 with 100% specificity and 24.3% sensitivity; and Q_A level > 0.062 on day 4 with 100% specificity and 40.5% sensitivity. The sum of all time points Q_A level > 0.26 was associated with poor neurological outcomes with 100% specificity and 44.7% sensitivity; and scoring system > 27 points was associated with poor neurological outcomes with 100% specificity and 48.7% sensitivity.

Discussion

In this study, we determined that the degrees of BBB disruption measured during the 72 h after ROSC in OHCA survivors significantly associated with the 6-month poor neurological outcomes. However, the major result of our study was that the association of BBB disruption with neurological outcomes

significantly differed depending on the degree and day of measurement. Moderate and severe BBB disruption (Q_A > 0.01) was associated with poor neurological outcomes, and 72 h after ROSC had the highest predictive prognostic performance.

Several clinical studies have reported that BBB disruption occurs in people with severe traumatic brain injury and contributes to poor neurological outcomes [10, 11]. However, the relationship between BBB disruption and neurological outcomes in post-CA has primarily been reported in animal studies, except our previous study [12, 13]. Li et al. [12] reported that post-CA global cerebral ischemia resulted in BBB disruption at 24 h after ROSC in a swine model, and attenuation of the BBB disruption was achieved through mild hypothermia (33°C). Miclescu et al. [13] reported that the BBB disruption and neurologic injury increased 30 min after ROSC, the early stage in reperfusion after CA in a piglet model study, and that methylene blue could attenuate the BBB disruption.

In our previous study [6], we reported that the Q_A levels measured 24 h after ROSC would have poor prognosis if severe BBB disruption was observed; however, we did not provide an accurate cutoff value and time to predict the poor neurological outcomes. In this study, we determined the degree of BBB disruption, cutoff value, and time associated with poor neurological outcomes. The distributions of poor neurological outcome at six months in the moderate and severe BBB disruption group and other groups were 80% vs. 50% on day 1, 79% vs. 32% on day 2, 81% vs. 30% on day 3, and 85% vs. 30% on day 4. The moderate and severe BBB disruption group exhibited poorer neurological prognosis than the normal and mild BBB disruption group with the greatest difference on day 4. Although the Q_A levels on all individual days of measurement predicted six months poor neurological outcomes, our results indicated that association with outcomes varied depending on the Q_A measurement time. The Q_A levels measured on day 1 offered significantly weaker association compared with the other days, sum of all time points, and scoring system. Numerically, the largest area under the curve was of the scoring system, followed by sum of all time points. Unfortunately, the prediction of poor neurological outcomes using BBB disruption displayed low sensitivity at 100% specificity; thus, it could be used as part of the multimodal approach than as a single prognostic prediction tool.

It is important to determine the timing of BBB disruption in OHCA survivors for timely treatment and better prognosis [14]. International guidelines for the treatment of OHCA survivors do not recommend any special medication, except for TTM to reduce ICP [15]. From a clinical perspective, hyperosmolar therapy is performed to reduce ICP occurring in brain edema; it reduces edema by draining fluid from the brain. When the BBB is disrupted, osmotic active particles can accumulate in the brain and potentiate edema [16]. However, the use of hyperosmolar therapy in treating cerebral edema due to CA requires further investigations. Heradstveit et al. [17] conducted a comparative study of 19 CA survivors using 7.2% hypertonic saline with 6% poly starch solution (HH) therapy or standard fluid therapy (Ringer's acetate and normal saline) for 24 h after ROSC. The authors reported that the effects of both forms of fluid therapy on brain edema were similar, as magnetic resonance imaging (MRI) showed no differentiation between the two therapies. However, of the 10 patients who underwent MRI in their study, nine were scanned immediately at ROSC. The authors reported that MRI did not reveal vasogenic cerebral edema,

such as BBB disruption, in any of these patients. They explained that this absence of vasogenic edema may have been due to CA, that the arrests were witnessed, and the short time before CPR initiation. However, in our study, the number of patients with BBB disruption was 41/68 (60%) on day 1, 49/68 (72%) on day 2, 44/68 (65%) on day 3, and 46/68 (68%) on day 4. We assume that the study by Heradstveit et al. involved CA survivors without BBB disruption, and that there was selection bias in their comparison of cerebral edema deterioration between HH and standard fluid therapies. However, although some animal studies have shown that hyperosmolar therapy had an anti-edema effect [18, 19], Kaufmann and Cardoso [20] reported that repeated mannitol infusion of cold-induced cerebral edema in cat models worsened the vasogenic cerebral edema, possibly due to the accumulation of osmotic active particles in the interstitial space due to BBB disruption. Therefore, we consider that hyperosmolar therapy to reduce cerebral edema for OHCA survivors remains an under-researched area, and that determining whether BBB disruption has occurred in such patients is important.

This study had several limitations. First, this was a retrospective and single-centered study; however, it comprised the largest number of patients with BBB disruption among patients with OHCA, published to date. Future studies with larger sample sizes and prospective multicenter designs are warranted. Second, of the 81 patients who had undergone TTM during the study, 13 (16%) were excluded because their lumbar drainage had not been undertaken. This might have caused selection bias and could limit the generalizability of our findings. Third, lumbar drainage is rare in clinical practice and is very complex to apply; hence, the general use of this procedure is unlikely.

Conclusions

Our results suggest that the degree of BBB disruption is a useful tool for predicting 6-month neurological outcome in OHCA survivors treated with TTM. The highest associations of BBB disruption with poor neurological outcomes were observed on scoring system, followed by sum of all time points and on day 4 after ROSC. However, the prediction of poor neurological outcomes using BBB disruption displayed low sensitivity at 100% specificity; thus, it could be used as part of a multimodal approach than as a single prognostic prediction tool.

List Of Abbreviations

BBB, blood-brain barrier; CA, cardiac arrest; ICP, intracranial pressure; OHCA, out-of hospital cardiac arrest; TTM, target temperature management; ROSC, return of spontaneous circulation; LP, lumbar puncture; CPR, cardiopulmonary resuscitation; SOFA, sequential organ failure assessment; CPC, cerebral performance category; Q_A, albumin quotient; ROC, receiver operating characteristic; AUC, areas under the curve; HH, 7.2% hypertonic saline with 6% poly starch solution; MRI, magnetic resonance imaging

Declarations

Ethics approval and consent to participate

The study design and plan were approved by the institutional review boards (IRB) of Chungnam National University Hospital (Approval No. CNUH-2020-04-103). Written informed consent was waived by the IRB.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

JS Park and BK Lee contributed to study conception and design. YC Choi, W Jeong, C Kang, I Yoo, and JH Min contributed to data acquisition. GR Jeon, HJ Ahn and JS Park contributed to data analysis and interpretation. Y You and HJ Ahn contributed to statistical analysis and revision. Y You contributed to acquisition of funding. HR Jeon, I Yoo, HJ Ahn, BK Lee and JS Park contributed to the drafting of the manuscript and its critical revision for important intellectual content. All authors have read and approved the final version of the manuscript.

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Figures

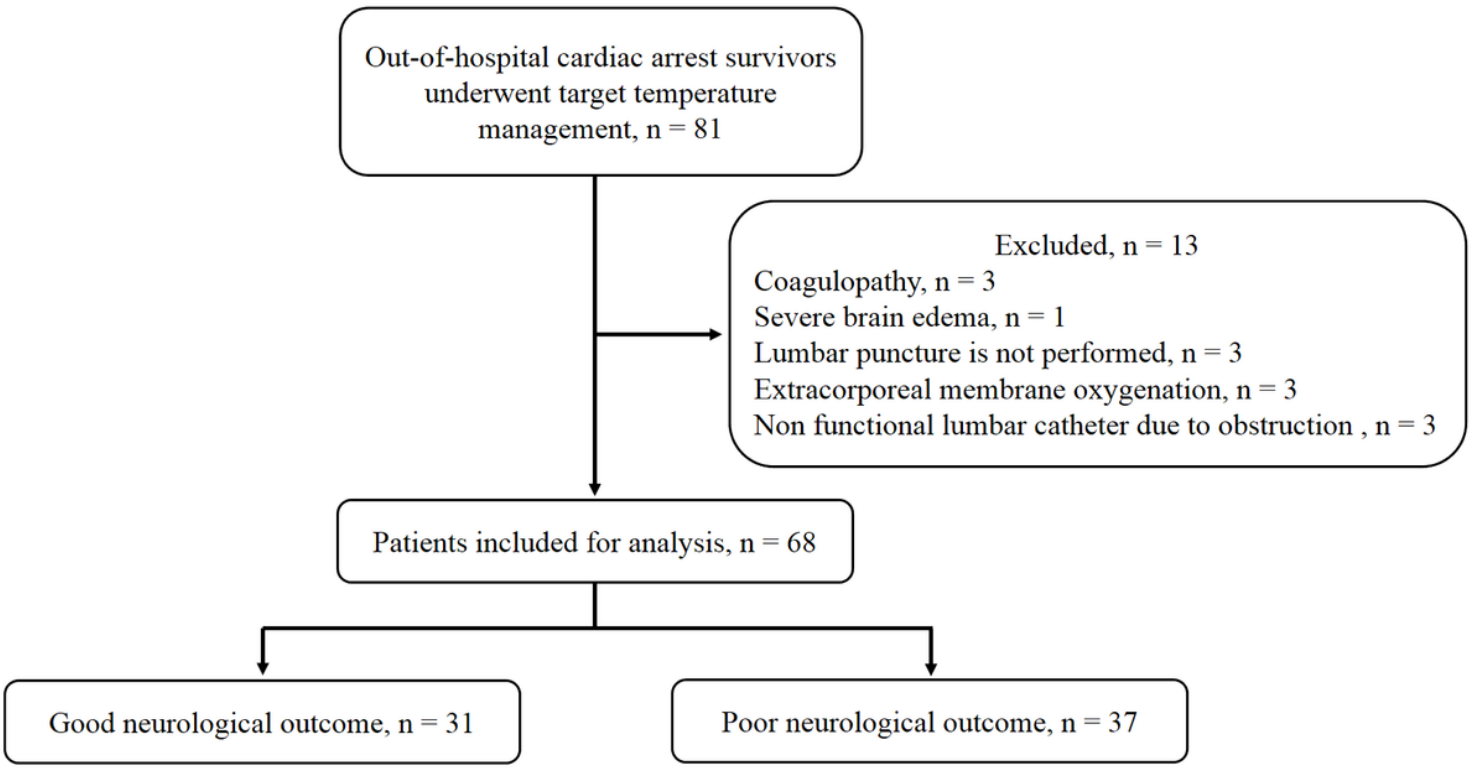

Figure 1

Flow diagram for patient inclusion

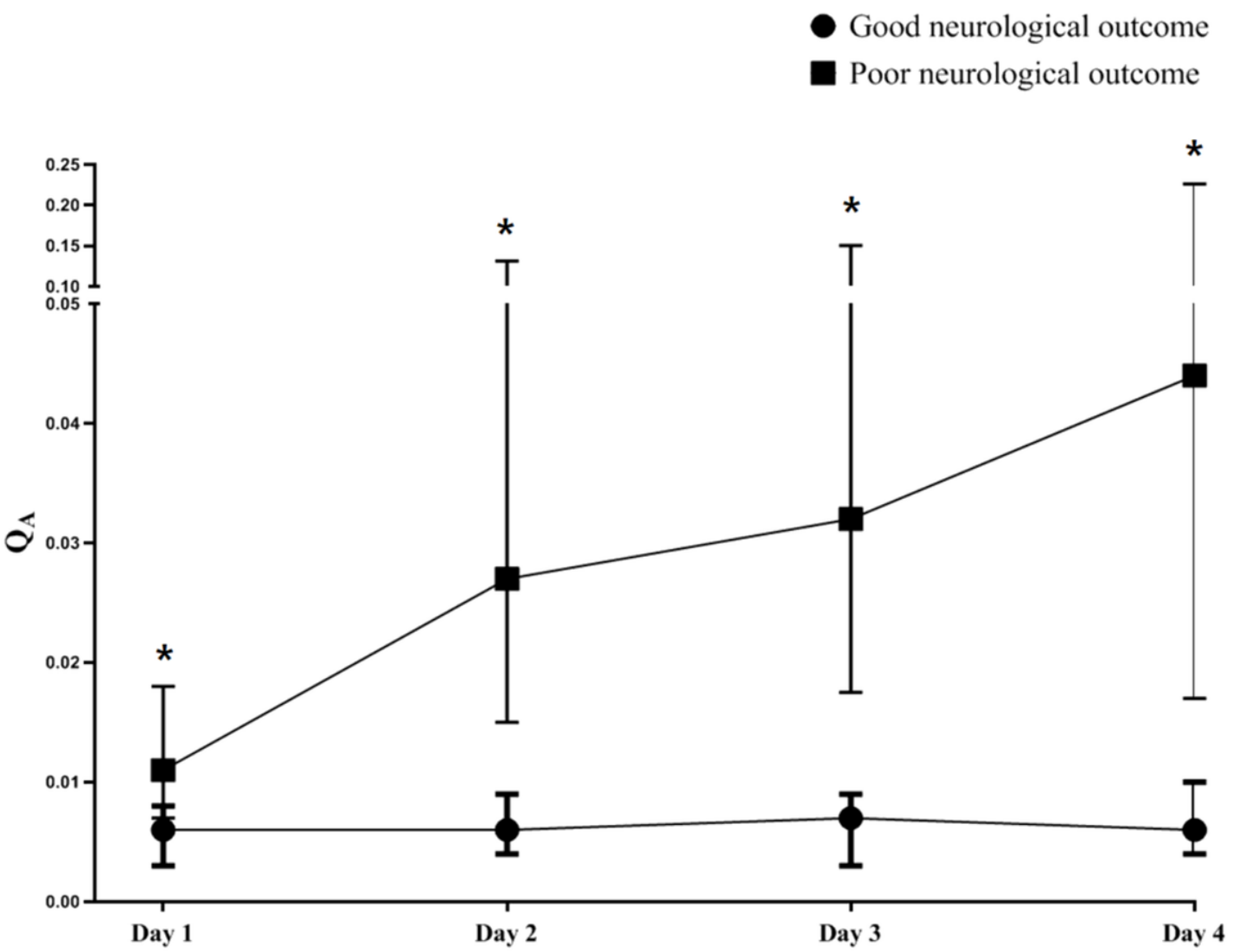

Figure 2

Comparison of the albumin quotient levels (QA) for different neurological outcomes at each time point. Poor neurological outcome group had significantly higher QA levels (median with interquartile range) than good neurological outcome group at all time point. *P < 0.001

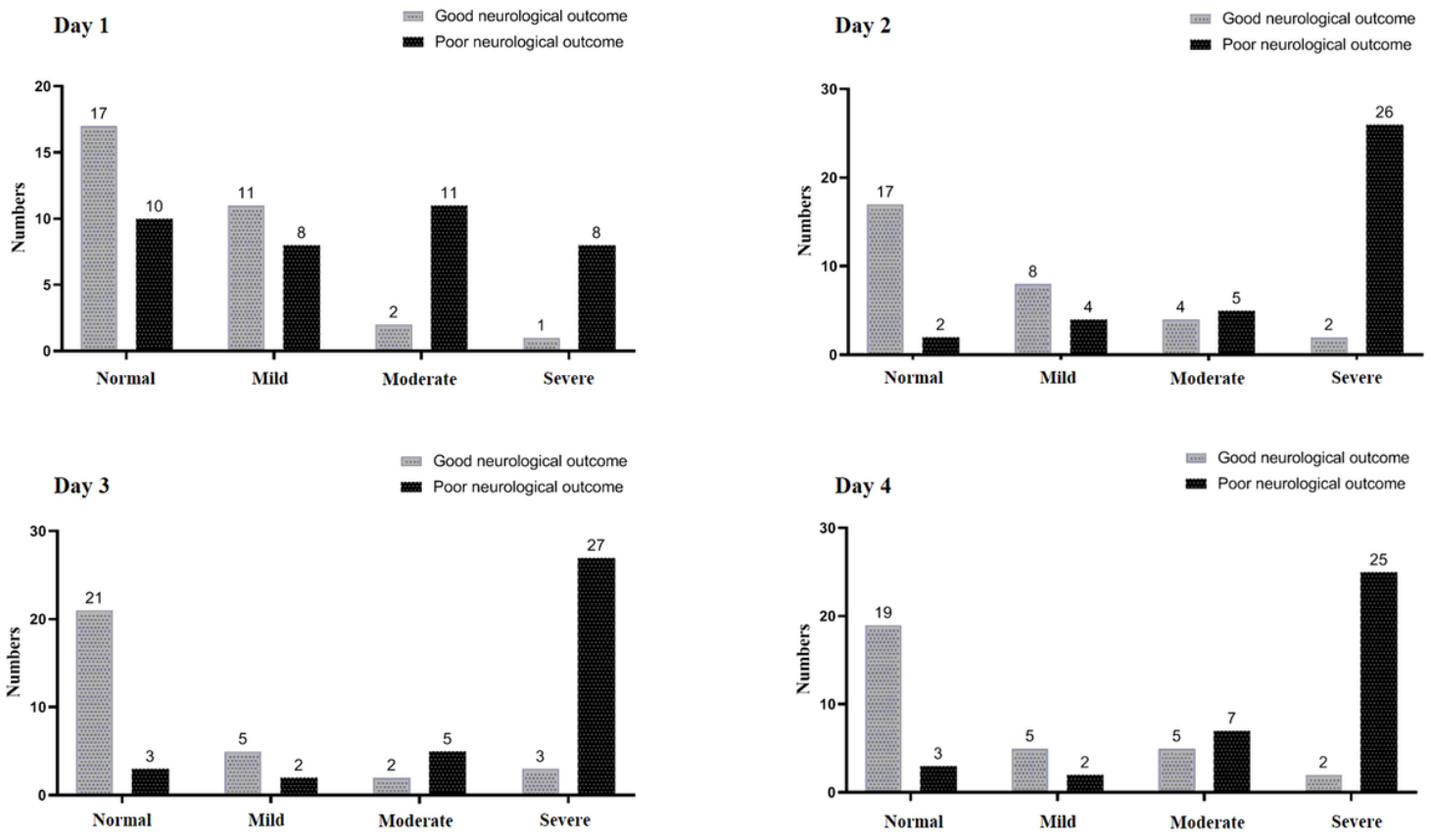

Figure 3

Comparison of neurological outcomes after six months of return of spontaneous circulation according to the degree of blood–brain barrier disruption at each time point. In the moderate and severe blood–brain barrier disruption group, the distribution of poor neurological outcome was significantly higher than hat in the normal and moderate blood–brain barrier disruption groups ($P < 0.001$)

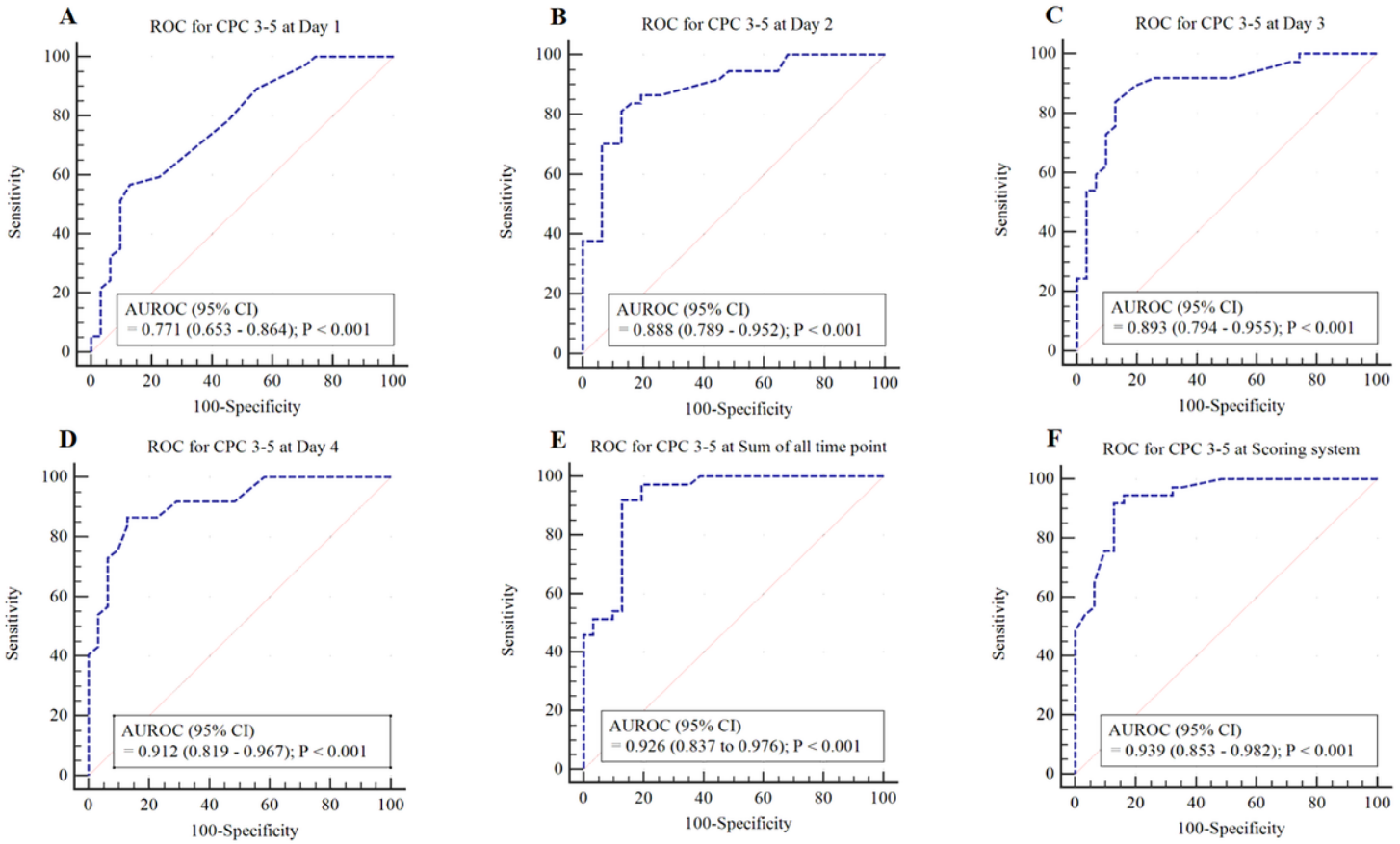

Figure 4

Association of albumin quotient (QA) with poor neurological outcomes. (A) Receiver operating characteristic (ROC) curve for QA levels on day 1. (B) ROC curve for QA levels on day 2. (C) ROC curve for QA levels on day 3. (D) ROC curve for QA levels on day 4. E ROC curve for QA levels at sum of all time points. (F) ROC curve for QA levels at scoring system