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Prognostic Value of Optic Nerve Sheath Diameter in Patients after Extracorporeal Cardiopulmonary Resuscitation

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Objective

To determine whether optic nerve sheath diameter (ONSD) could be used to predict neurological outcomes in patients after extracorporeal cardiopulmonary resuscitation (ECPR).

Methods

This was a retrospective and observational study of adult unconscious patients who were evaluated by brain computed tomography (CT) scan within 48 hours after ECPR between May 2010 and December 2016. ONSDs were estimated on initial brain CT. The primary outcome was neurological status upon hospital discharge assessed with Cerebral Performance Categories (CPC) scale. CPC scores of 1 and 2 indicated good neurological outcome while CPC scores of 3, 4, and 5 indicated poor neurological outcome.

Results

Among 52 unconscious patients, survival to discharge was identified in 19 (36.5%) patients. Of these 19 survivors, 13 (25.0%) had good neurological outcome (CPC score of 1 or 2). ONSDs and their modification in the poor neurological outcome group were significantly greater than those in the good neurological outcome group (all $p \leq 0.003$). However, eyeball transverse diameter was not significantly different between the two groups ($p=0.770$). Analysis of the receiver operating characteristic curves for predicting poor neurological outcome showed that ONSDs had considerable predictive value (C-statistics: 0.735 to 0.812). In addition, ONSDs and their modification had similar performances for predicting poor neurological outcome.

Conclusion

ONSDs measured with CT may be used to predict neurological outcomes of ECPR survivors.

Keywords: Brain computed tomography; Optic nerve sheath diameter; ardiopulmonary resuscitation; Extracorporeal membrane oxygenation

INTRODUCTION

Recently, extracorporeal cardiopulmonary resuscitation (ECPR) has been increasingly utilized to supply oxygenated blood and hemodynamic support in the absence of spontaneous cardiac circulation[15]. Neurological outcome is an important issue in patients who have survived cardiac arrest. In these survivors, several predictors of neurological outcomes such as physical examination, several biomarkers, and electrophysiologic studies have been reported[19,25]. Similar to studies on conventional cardiopulmonary resuscitation (CPR), there have been several studies on neurological prognosis of patients receiving ECPR[11,12,18]. However, there are limited data on prognostic imaging markers of neurological outcomes after ECPR[15].

After cardiac arrest, primary and secondary brain injuries are associated with intracranial hypertension[21]. Therefore, early monitoring of intracranial hypertension is important as it may allow prediction of neurological outcomes in these patients. Optic nerve sheath diameter (ONSD) has been proposed as an alternative measure for the detection of intracranial hypertension[6,22]. In addition, ONSD on initial brain computed tomography (CT) may be correlated with neurologic outcomes in conventional CPR setting[6,9]. However, whether ONSD may facilitate systemic evaluation of neurological outcomes of survivors after ECPR has not been reported yet. Therefore, the objective of this study was to investigate if ONSD with some modifications could be used to predict neurological outcomes of patients who underwent ECPR.

METHODS

Study population

This was a retrospective and observational study of adult patients who underwent ECPR during hospitalization at Samsung Medical Center between May 2010 and December 2016. This study was approved by the Institutional Review Board of Samsung Medical Center (SMC 2017-11-088-002). The requirement for informed consent was waived due to its retrospective nature. Clinical and laboratory data were collected by a trained study coordinator using a standardized case report form. Patients who underwent ECPR during the study period were included. Those who were unconscious (a score of <9 on Glasgow Coma Scale)[16] on admission to the hospital after cardiac arrest and those who were given brain CT scan within 48 hours after ECPR were selected. Of these patients, we excluded patients who were under 18 years of age, those who had malignancy whose expected life span was less than one year, those who had insufficient medical records, and those who had a history of head trauma, neurosurgery, or chronic neurological abnormality on ICU admission.

Definitions and outcomes

In this study, ECPR was defined as both successful veno-arterial extracorporeal membrane oxygenation (ECMO) implantation and pump-on with cardiac massage during index procedure in patients with cardiac arrest. When a return of spontaneous circulation (ROSC) occurred during ECMO cannulation, practitioners typically did not remove the cannula or stop the ECMO pump-on process[2,13]. ECMO pump-on was defined by stopping chest compressions following successful ECMO implantation and activation. ECMO flow was then gradually increased until the patient was hemodynamically stable. Resuscitation was performed in the same way as described in our previous study[16,17]. Arrest to ECMO pump-on time was defined as the time from cardiac arrest to the time at which the ECMO pump was turned on. Targeted temperature management (TTM) was performed with surface cooling devices. A commercial temperature regulation system consisting of a hydrogel pad (Arctic Sun®; Medivance Corp, Louisville, CO, USA) or a cooling blanket was used. Surface cooling and the degree of targeted temperature were determined by each intensivist in the ICU according to the therapeutic hypothermia protocol[7]. The primary outcome was neurological status upon hospital discharge assessed with Glasgow-Pittsburgh Cerebral Performance Categories (CPC) scale (score of 1 to 5)[4]. CPC scores of 1 and 2 indicated good neurological outcome while CPC scores of 3, 4, and 5 indicated poor neurological outcome. Medical records were thoroughly reviewed. Patients were graded on the CPC scale by two independent neurologists.

All recorded brain CT scans were taken within 48 hours after ROSC in this study. After successful ECPR, for patients who had a rapid recovery of mentality and neurological deficits, brain CT scan was not performed. Otherwise, brain CT scan was performed to determine whether control was needed for increased intracranial pressure (ICP). Brain CT scan was also used to exclude intracranial hemorrhage before therapeutic hypothermia by an intensivist. For all CT studies, 64-channel scanners (Light Speed VCT; GE Healthcare, Milwaukee, WI, USA) with a 5-mm slice width were used. Brain CT images were reviewed by two independent neurologists. Investigators who were blinded to clinical information opened these CT scans for each patient using commercial image-viewing software (Centricity RA1000 PACS Viewer; GE Healthcare, Milwaukee, WI, USA). ONSD and eyeball transverse diameter (ETD) were measured using the same initial CT and subsequent scans. The ONSD was measured at a distance of 3 mm behind the eyeball, immediately below the

sclera in a perpendicular vector with reference to the linear axis of the nerve (Fig. 1A)[6,9,22]. Images were changed to the "chest/abdomen" window (window width 300 & window level 10) and magnified four-fold on the particular image slice that demonstrated the largest diameter of the optic nerve sheath[22]. The ONSD was measured from one side of the optic nerve sheath to the other as a section through the center of the optic nerve[9]. The transverse diameter of the eyeball was chosen because the ONSD was usually measured in the transverse plane[24]. ETD was defined as the maximal transverse diameter of the eyeball measured from one side of the retina to the other (in-to-in, Fig. 1B)[1,24]. $ONSD_{average}$ and the $ETD_{average}$ measured for the patient's left and right eyes were averaged to yield mean values[9]. $ONSD_{index}$ was defined as median ETD (23.0 mm) multiplied by the average value of bilateral ONSDs divided by the average value of bilateral ETDs ($23.0 \times ONSD_{average}/ETD_{average}$).

Resuscitation procedure

CPR was led by the hospital's CPR team. All data related to the CPR scene were recorded by a bedside nurse according to the Utstein-style guidelines[3]. The on-call ECMO team leader was called when CPR was performed for longer than 10 minutes or in the event of unstable vital signs or recurrent cardiac arrest. The ECMO team leader along with the CPR leader assessed the patient and decided whether to institute ECPR. ECPR was performed when a witnessed arrest was confirmed, the arrest persisted despite at least 10 minutes of conventional CPR, and the underlying cause of the arrest was considered reversible[15]. Cases in which ECPR was deferred included a short life expectancy (< 6 months), terminal malignancy, an unwitnessed collapse, limited physical activity, an unprotected airway, or CPR undertaken for longer than 60 minutes at the time of initial contact. Age alone did not constitute a contraindication of ECPR[15]. The ECMO team at our institution consisted of cardiologists, cardiovascular surgeons, intensivists, specialized nurses, and perfusionists. Either a Capiox Emergency Bypass System (Terumo, Tokyo, Japan) or a Prolonged Life Support System (Maquet Cardiopulmonary, Hirrlingen, Germany) was used in these cases. A crystalloid solution such as normal saline or balanced solution was used for priming. No patient in this study underwent blood-primed ECMO. A percutaneous vascular approach was tried initially in all cases using the Seldinger technique. If percutaneous cannulation failed, a surgical cutdown exposure was performed[15]. Femoral vessels were the most common sites of vascular access and 14 to 17 French arterial cannulas and 20 to 24 French venous cannulas were placed[13]. Cardiac compression was stopped once ECMO initiation was deemed successful. Anticoagulation was accomplished with a bolus injection of unfractionated heparin followed by a continuous intravenous heparin infusion to maintain an activated clotting time between 150 and 180 seconds. The initial number of revolutions per minute of the ECMO device was adjusted to achieve an ideal cardiac index greater than

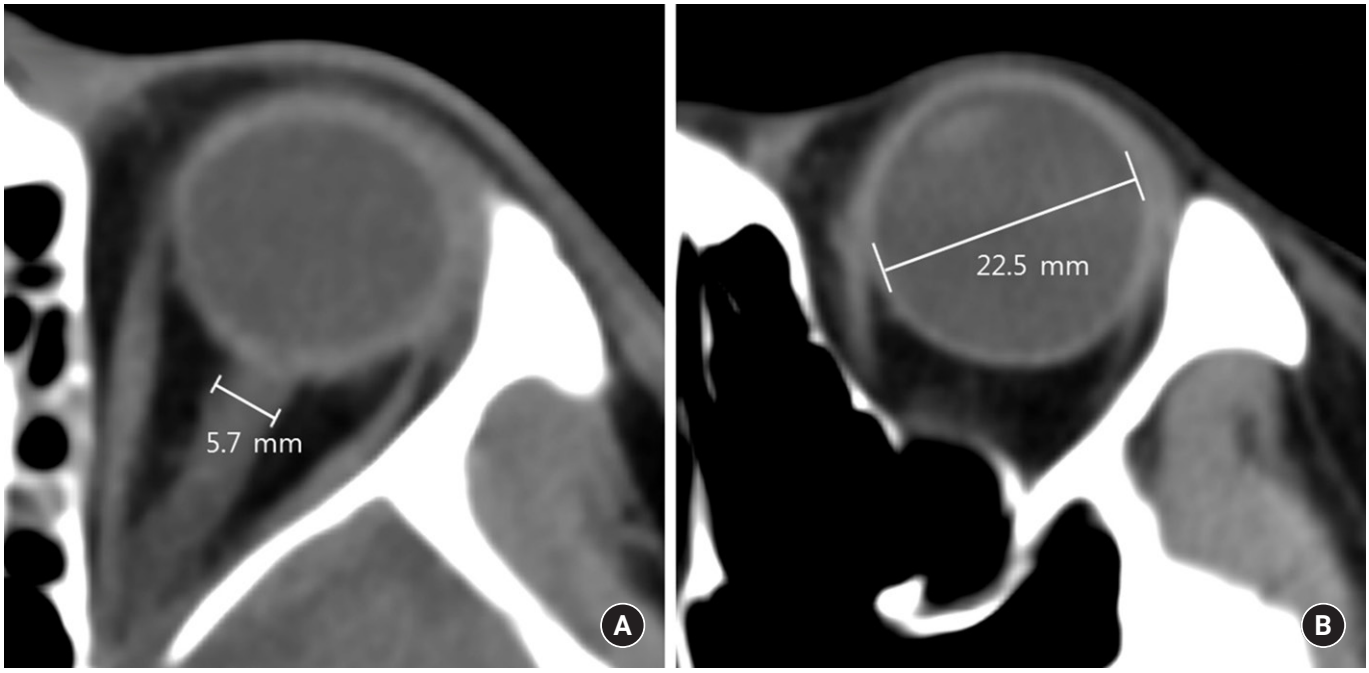

Fig. 1. A: Measurement of optic nerve sheath diameter. B: Eyeball transverse diameter on brain computed tomography scan.

2.2 L/min/m^2 of body surface area, a central mixed venous oxygen saturation above 70%, and a mean arterial pressure above 65 mmHg[13]. Blood pressure was monitored continuously through an arterial catheter and an artery in the right arm was used for arterial blood gas analysis to estimate cerebral oxygenation. After ECMO was established, necessary steps were taken to treat the underlying cause of cardiac arrest, including percutaneous coronary intervention, coronary artery bypass grafting, heart transplantation, and non-cardiopulmonary surgery[13].

Statistical analyses

All data are presented as medians and interquartile ranges (IQRs) for continuous variables and numbers (percentages) for categorical variables. Data were compared using Mann-Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. Predictive performances of ONSDs and their modification were assessed using area under the curve (AUC) of the receiver operating characteristic (ROC) curves for sensitivity vs. 1-specificity. AUCs were compared using the nonparametric approach published by DeLong et al.[5] for two correlated AUCs. Optimal cut-off values of ONSDs for predicting poor neurological outcome were obtained by ROC curve and Youden index[14,20]. All tests were two-sided and p-values <0.05 were considered statistically significant. Data were analyzed using IBM SPSS statistics version 20 (IBM, Armonk, NY, USA).

RESULTS

Baseline characteristics and clinical outcomes

A total of 52 patients with cardiac arrest who were rescued by veno-arterial ECMO were analyzed. Their median age was 53.0 years (IQR: 40.5–64.5 years). Of 52 patients, 39 (75.0%) were males. A cardiac cause of arrest was verified in 46 (88.5%) patients. Thirty-nine (75.0%) patients experienced cardiac arrest in the hospital while 13 (25.0%) patients had cardiac arrest in an out-of-hospital setting. The median time from arrest to ECMO pump-on was 43.0 minutes (IQR: 27.0–53.0 minutes). TTM was performed in 25 (48.1%) patients using surface cooling devices. Baseline characteristics of ECPR patients are presented in Table 1. Characteristics of cardiac arrest are shown in Table 2. There were no significant differences in baseline or arrest-related characteristics between the two neurological outcome groups except hemoglobin level before ECMO. Successful ECMO weaning was achieved in 29 (55.8%) patients. Survival to discharge was identified in 19 (36.5%) patients. Of these 19 survivors, 13 (25.0%) had good neurological outcomes (CPC score of 1 or 2).

Table 1. Baseline characteristics of patients

	Good neurological outcome (n=13)	Poor neurological outcome (n=39)	p-value
Age (yr) — median (IQR)	50.0 (34.0–54.0)	54.0 (46.0–64.5)	0.224
Gender, male — no. of patients (%)	11.0 (84.6)	28.0 (71.8)	0.579
Body mass index (kg/m2)	23.1 (21.3 – 25.7)	25.4 (23.4–28.4)	0.053
Medical history — no. of patients (%)			
Hypertension	3.0 (23.1)	15.0 (38.5)	0.501
Current smoker	5.0 (38.5)	12.0 (30.8)	0.864
Diabetes mellitus	2.0 (15.4)	8.0 (20.5)	0.999
Malignancy	1.0 (7.7)	9.0 (23.1)	0.416
Previous myocardial infarction	0.0 (0.0)	4.0 (10.3)	0.548
Target temperature management — no. of patients (%)			
Arctic Sun	6.0 (46.2)	13.0 (33.3)	0.531
Cooling pad	2.0 (15.4)	4.0 (10.3)	
Initial Glasgow Coma Scale — median (IQR)	3.0 (3.0–6.0)	3.0 (3.0–4.0)	0.834
Laboratory data on admission			
Initial lactate (mmol/L)	12.3 (8.8–14.5)	8.7 (6.2–12.8)	0.266
Hemoglobin before ECMO (g/dL)	15.5 (14.4–15.7)	12.8 (10.9–14.1)	0.016
Hemoglobin after ECMO (g/dL)	11.9 (10.5–12.8)	10.5 (8.8–12.9)	0.631
Total bilirubin (mg/dL)	0.8 (0.4–0.8)	0.8 (0.6–1.1)	0.270
Blood urea nitrogen (mg/dL)	15.6 (13.6–16.9)	15.5 (12.4–23.3)	0.695
Creatinine (mg/dL)	1.1 (0.9–1.4)	1.1 (1.0–1.5)	0.769
Bicarbonate (IU/L)	11.7 (10.3–17.9)	17.8 (13.0–20.7)	0.089

IQR: interquartile range; ECMO: extracorporeal membrane oxygenation.

Optic nerve sheath diameters and their modifications

In this study, ONSDs and ONSDindex in the poor neurological outcome group were significantly greater than those in the good neurological outcome group (Table 3). However, ETD was not significantly different between the two groups (p = 0.770). In ROC curve analysis for predicting poor neurological outcome (Fig. 2), the C-statistic of $ONSD_{average}$ was 0.856 (95% CI: 0.731 to 0.938). A cut-off > 5.79 mm had a sensitivity of 71.8% (95% CI: 55.1% to 85.0%) and a specificity of 92.3% (95% CI: 64.0% to 99.8%). The C-statistic of $ONSD_{max}$ was 0.778 (95% CI: 0.641 to 0.882). A cut-off > 6.24 mm had a sensitivity of 51.3% (95% CI: 34.8% to 67.6%) and a specificity of 100% (95% CI: 75.3% to 100%). The C-statistic of $ONSD_{index}$ was 0.860 (95% CI: 0.736 to 0.941). A cut-off > 5.91 had a sensitivity of 71.8% (95% CI: 55.1% to 85.0%) and a specificity of 100% (95% CI: 75.3% to 100%). However, ONSDs and their modification showed similar performances for predicting poor neurological outcome. The predictive performance of $ONSD_{index}$ for poor neurological outcome was not significantly different from that of $ONSD_{average}$ or $ONSD_{max}$ (p = 0.913 and p = 0.138, respectively).

DISCUSSION

In the present study, we evaluated whether ONSD with their modification could be used to predict neurological outcomes in patients after ECPR. Major findings of this study were as follows: 1) ONSDs and $ONSD_{index}$ in the poor neurological outcome group were significantly greater than those in the good neurological outcome group. These markers might predict neurological outcomes of patients after ECPR; 2) ETD was not significantly different between the two groups with different neurological outcomes; 3) Analysis of ROC curves for prediction of poor

Table 2. Characteristics of patients with cardiac arrest and procedures

	Good neurological outcome (n=13)	Poor neurological outcome (n=39)	p-value
Type of cardiac arrest — no. of patients (%)			0.999
Out of hospital cardiac arrest	3.0 (23.1)	10.0 (25.6)	
In hospital cardiac arrest	10.0 (76.9)	29.0 (74.4)	
Bystander witnessed cardiac arrest — no. of patients (%)	13.0 (100.0)	39.0 (100.0)	
Bystander performed CPR — no. of patients (%)	11.0 (84.6)	38.0 (97.4)	0.303
First monitored rhythm — no. of patients (%)			0.177
Asystole	1.0 (9.1)	11.0 (29.7)	
Pulseless electrical activity	4.0 (36.4)	16.0 (43.2)	
Shockable rhythm (VT or VF)	6.0 (54.5)	10.0 (27.0)	
Defibrillation — no. of patients (%)	7.0 (58.3)	17.0 (45.9)	0.679
Arrest to ECMO pump-on time — median (IQR)	43.0 (17.0–51.0)	42.5 (30.0–53.0)	0.502
Location of ECMO insertion — no. of patients (%)			0.718
Emergency room	7.0 (53.8)	18.0 (46.2)	
Intensive care unit	3.0 (23.1)	11.0 (28.2)	
Cath room	3.0 (23.1)	7.0 (17.9)	
Other	0.0 (0.0)	3.0 (7.7)	
Cardiac cause of arrest — no. of patients (%)			0.516
Ischemic	3.0 (25.0)	14.0 (41.2)	
Non-ischemic	9.0 (75.0)	20.0 (58.8)	

CPR: cardiopulmonary resuscitation; VT: ventricular tachycardia; VF: ventricular fibrillation; ECMO: extracorporeal membrane oxygenation; IQR: interquartile range.

Table 3. Optic nerve sheath diameters and their modifications according to neurological outcomes

	Good neurological outcome (n=13)	Poor neurological outcome (n=39)	p-value
ONSDaverage	5.43 (5.20–5.70)	6.14 (5.80–6.65)	<0.001
ONSDmax	5.68 (5.39–6.10)	6.41 (5.85–6.83)	0.003
ETDaverage	22.50 (21.80–24.00)	23.10 (22.1–23.40)	0.770
ONSDindex	5.62 (5.34–5.87)	6.29 (5.86–6.54)	<0.001

ONSD: optic nerve sheath diameter; ETD: eyeball transverse diameter.

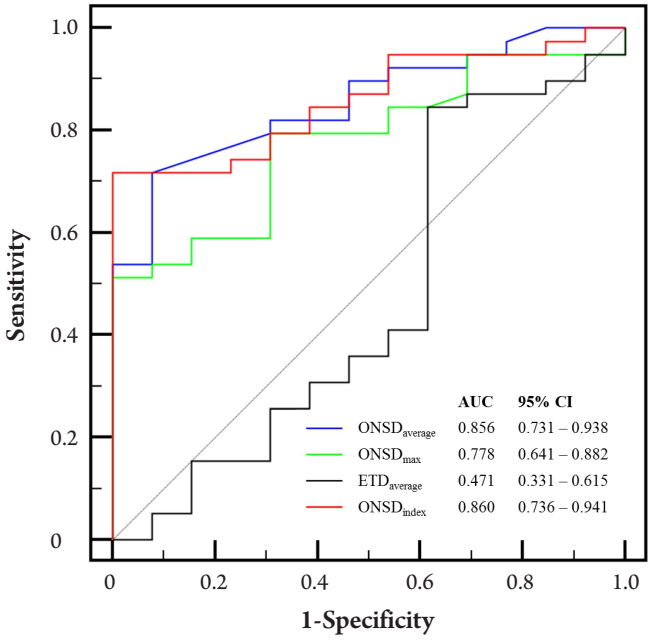

Fig. 2. Receiver operating characteristic curves for prediction of poor outcomes using optic nerve sheath diameters and their modifications. $ONSD_{index}$ was defined as median ETD (23.0 mm) multiplied by the average value of bilateral ONSDs divided by the average value of bilateral ETDs ($23.0 \times ONSD_{average}/ETD_{average}$). AUC: area under the curve; CI: confidence interval; ONSD: optic nerve sheath diameter; ETD: eyeball transverse diameter.

neurological outcome showed that ONSDs and $ONSD_{index}$ had considerable predictive values and similar predictive performances for poor neurological outcome.

Primary cerebral injury is caused by immediate cessation of cerebral blood flow following cardiac arrest that results in neuron ischemia and brain cell death[21]. In addition, secondary cerebral injury can occur and cause additive cerebral injury characterized by an imbalance in post-resuscitation cerebral oxygen delivery and use, ultimately culminating in neuronal death[21]. This injury begins immediately after ROSC, including reperfusion injury, microcirculatory dysfunction, impaired cerebral autoregulation, refractory intracranial hypertension, hypoxemia, hyperoxia, hyperthermia, fluctuations in arterial carbon dioxide, and concomitant anemia[21]. Several pathophysiologic mechanisms involved in the increased risk of intracranial hypertension after cardiac arrest has been suggested. Blood brain barrier alterations have been demonstrated after global ischemia[6]. Impaired autoregulation and post-ischemic hyperperfusion associated with global ischemia may also increase the risk of ICP elevation[6]. Eventually, primary and secondary injuries are associated with intracranial hypertension.

ONSD has been proposed as an alternative parameter for detection of increased ICP[6]. The optic nerve is surrounded by cerebrospinal fluid because it is a part of the central nervous system. Therefore, increased ICP is transmitted through the subarachnoid space surrounding the optic nerve within the nerve sheath, especially the retrobulbar segment, unless circulation of cerebrospinal fluid is not blocked[6]. ONSD measured during the initial brain CT may be correlated with neurologic outcomes after traumatic brain injury[22,23]. Simultaneous measurement of ONSD with initial CT and ICP are correlated and ONSD is indicative of intracranial hypertension in patients with severe traumatic brain injury[22,23].

Although ONSD is considered an indirect marker for ICP, its optimal cut-off for an abnormal ONSD indicating elevated ICP and its associated factors have been unclear[8]. In addition, there are limited studies reporting the role of ONSD modifications or indices in detecting intracranial hypertension compared with absolute ONSD[1,24]. ONSD correlates strongly with ETD in healthy people. ONSD/ETD ratio may provide highly reliable data than absolute ONSD as a marker of ICP[8]. However, in this study, there were no significant differences between ONSD/ETD ratio and absolute ONSD for predicting poor neurological outcomes. Therefore, future studies with larger cohorts are needed to confirm these findings.

This study has several limitations. First, the CPC scale was retrospectively determined based on medical records. Second, the nonrandomized nature of the registry data might have resulted in selection bias. Although brain CT scans were performed within 48 hours following ECPR, a major limitation of this study might be that CT scans were performed at different time settings. Third, ONSD measurement requires high image resolution and specific CT settings such as optimal slice thickness and slice angle with the skull base. The heterogeneity of CT scan protocols might have led to the relatively weak correlation between ONSD and ICP in this study[10]. Fourth, a limited number of patients received targeted temperature management. Methods used were decided by each intensivist. They varied according to conditions and situations. Finally, our study had limited statistical power due to its small sample size. Although it still provides valuable insight, prospective large-scale studies are needed to evaluate the usefulness of ONSD based on brain CT for predicting neurological outcomes of patients after ECPR to obtain evidence-based conclusions.

CONCLUSION

In this study, ONSDs measured with CT may be used to predict neurological outcomes of ECPR survivors.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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