의학박사 학위논문

심정지 환자에게 체외막형 산화기를 이용한 심폐소생술 이후의 신경학적 예후: 예측 인자와 예측 시점에 관하여

Neuron-specific enolase as a predictor of the neurologic outcome in extracorporeal cardiopulmonary resuscitation patients

울 산 대 학 교 대 학 원

의 학 과

정 용 호

체외막형 산화기 적용 환자의 신경학적 예후: 예측 인자와 예측 시점에 관하여

지 도 교 수　　김 형 렬

이 논문을 의학박사학위 논문으로 제출함

2022 년　7 월

울 산 대 학 교 대 학 원

의　　학　　과

정 용 호

정용호의 의학박사학위 논문을 인준함

심사위원 홍 상 범 인

심사위원 김 형 렬 인

심사위원 김 혁 인

심사위원 이 근 동 인

심사위원 최 창 민 인

울 산 대 학 교 대 학 원

2022 년 7 월

ABSTRACT

Background

Venoarterial extracorporeal life support is a viable option in critically ill patients with cardiac arrest. Neuronal injury is a common complication in patients undergoing extracorporeal cardiopulmonary resuscitation (ECPR). Neuron-specific enolase (NSE) is frequently used to predict neurological outcomes in patients undergoing ECPR. This study aimed to evaluate the predictive value of NSE in ECPR patients with poor neurological outcomes.

Methods

We studied 47 adult patients who underwent ECPR from January 2018 to December 2021 at our institution. NSE levels were measured 24, 48, and 72 h after ECPR. Patients were divided into two groups according to their neurological status, based on the best c-score during hospitalization and 30-day mortality.

Results

A poor neurological outcome with a Cerebral Performance Category score of 3–5 was observed in 46.8% of the patients. The 30-day all-cause mortality was 42.6%. The NSE level at 72 h after ECPR was the best prognostic factor for neurological outcome during hospitalization (area under the receiver operator characteristic (ROC) curve of 0.791 with a cut-off value of 61.9 μg/L) and 30-day mortality (area under the ROC curve of 0.838 with a cut-off value of 62.1 μg/L).

Conclusion

In adult ECPR patients, NSE can be used to predict neurological outcomes and mortality. Importantly, NSE measurement at 72 h after ECPR has the most accurate predictive value for short-term poor neurological outcomes and 30-day mortality.

Keywords: extracorporeal life support, extracorporeal cardiopulmonary resuscitation, neuron-specific enolase, neurological outcome, mortality

Contents

Figure and Table legends

INTRODUCTION

Extracorporeal life support (ECLS) is a therapeutic option that is proven to be an effective treatment for patients undergoing cardiopulmonary resuscitation (CPR)[1]. Several studies have shown that the survival rate of patients undergoing extracorporeal cardiopulmonary resuscitation (ECPR) ranges between 25.5–41.6% [2,3]. Although the survival rate has increased after the introduction of ECLS, neurologic complications still occur in 8–39% of patients receiving ECPR, including brain death, stroke, intracranial hemorrhage, and seizure[4,5]. The Utstein guidelines recommend using the cerebral performance category (CPC) score or modified Rankin scale (mRS) to evaluate neurological function in patients who survived cardiac arrest[6]. The CPC score is a five-point scale measuring neurological status ranging from good performance to brain death (Table 1).

Early detection of the neurological status of patients receiving ECPR is important to decide whether to continue life-supporting treatment. However, it is difficult to diagnose neurological complications in the early stages of ECLS treatment. Recently, the role of biomarkers in the early prediction of neurological outcomes has been reported. Neuron-specific enolase (NSE) is a known biomarker for predicting the neurological outcome of ECPR patients[7–9]. NSE is a protein abundant in the white matter of the brain; therefore, increased levels in the bloodstream are related to possible brain injury[10]. NSE has been studied in neuroendocrine tumors[11,12] and

neuroblastoma[13,14] since the early 1980s. In 1989, Risto et al. reported on the neurological outcomes of 75 out-of-hospital cardiac arrest (OHCA) patients by measuring NSE levels in cerebrospinal fluid and suggested that NSE levels >24 ng/mL at 24 h of arrest resulted in unconsciousness[15]. Studies have reported that increased serum NSE levels lead to poor neurological outcomes[16–18].

Studies have reported that increased NSE levels are correlated with poor neurological outcomes in ECPR patients; however, no specific guidelines are available to obtain an NSE sample according to the ECLS insertion time, and no clear cut-off NSE level is provided that could assume a good neurological outcome. In this study, we aimed to provide the most accurate period of ECLS that could predict a poor neurological outcome with a corresponding cut-off NSE serum level.

Table 1. Cerebral Performance Category (CPC) score[19]

Score	Definition
1	Good cerebral performance: conscious, alert, able to work, may have a mild neurologic or psychologic deficit.
2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in a sheltered environment.
3	Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
4	Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with the environment; may have spontaneous eye-opening and sleep/wake cycles. Cerebral unresponsiveness.
5	Brain death: apnea, areflexia, electroencephalography silence, etc.

MATERIALS and METHODS

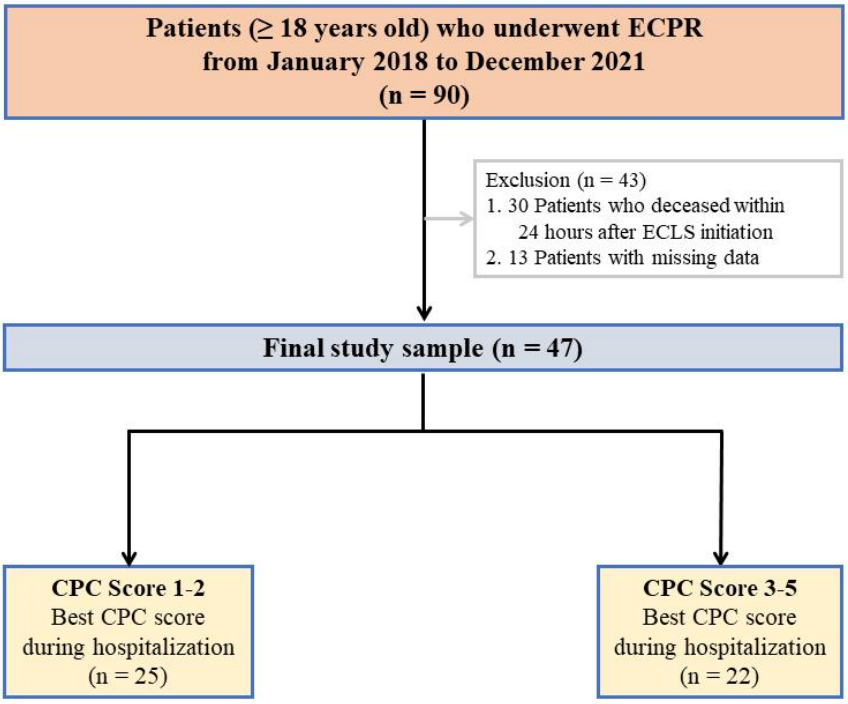
Study patients

This single-center prospective study was conducted between January 2018 and December 2021 on ECPR patients in the intensive care unit (ICU) of Hanyang University Seoul Hospital. All adult patients (aged ≥18 years) with cardiogenic shock or cardiac arrest requiring CPR were included. The following were the exclusion criteria: 1) patients deceasing within 24 h of ECLS initiation and 2) patients with missing data. A total of 47 adult ECPR patients were enrolled during the study period (Figure 1). Patients were divided into two groups according to their neurological status, using the best CPC score during hospitalization and 30-day mortality.

Patients were also divided into two groups according to their location when the cardiac arrest occurred: in-hospital cardiac arrest (IHCA) and OHCA groups. Patients with OHCA were selected according to the guidelines shown in Figure 2. We attempted to apply the same guidelines for patients with IHCA; however, exceptions were applied when the department admitting the patient strongly insisted that the patient had a high chance of recovery.

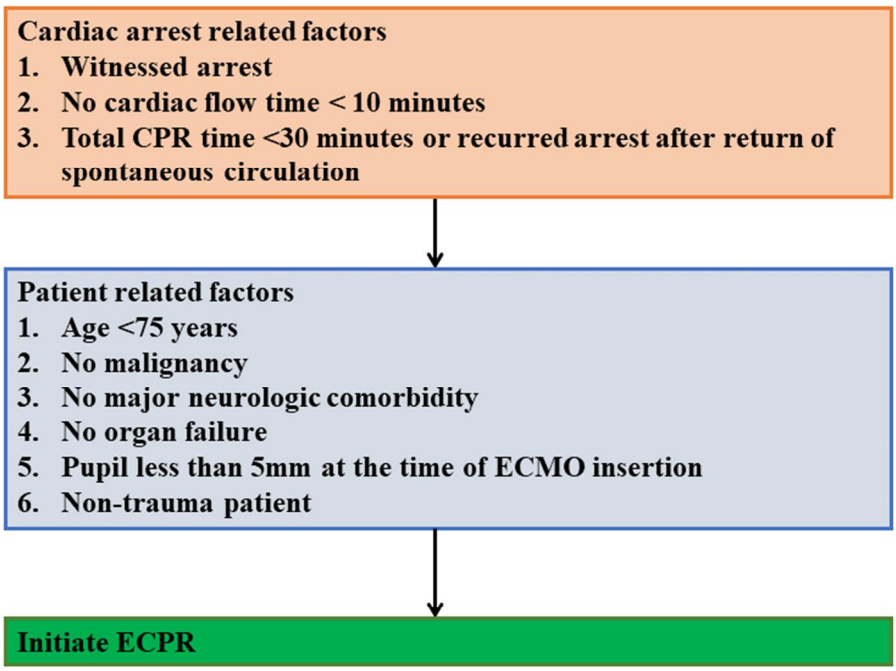
This study was approved by the Institutional Review Board of Hanyang University Hospital (Seoul, Republic of Korea) after obtaining informed consent (2022-05-004-002).

Figure 1. Flow diagram of enrolled patients



ECPR, extracorporeal cardiopulmonary resuscitation; CPC, Cerebral Performance Category; ECLS, extracorporeal life support

Figure 2. Patients with out-of-hospital cardiac arrest guidelines for ECPR enrollment



ECPR, extracorporeal cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation

Treatment for ECPR patients

Patients with OHCA were treated using a routine protocol. When the patient was enrolled for ECPR, the ECLS team gathered in the resuscitation room of the emergency department. Cardiologists were notified to prepare for emergency coronary angiography (CAG) and possible percutaneous coronary intervention (PCI) before ECLS activation.

When inserting the vein and arterial catheters into the femoral vein and artery, left-side vessels were preferred for several reasons. First, cardiologists usually use the right femoral artery because it is more comfortable and ergonomic during the intervention. Second, the ultrasound position allows easier access to the left-side vessels. In our clinic, all ECLS catheterizations are performed with sonography guidance. Ultrasound is usually performed on the right side of the patient, making left-side catheterization more ergonomic, leading to more successful access to the vessels. If catheterization fails, the right-sided vessels are immediately accessed. ECLS was performed following cannulation of both catheters. Distal perfusion catheterization is routinely performed after a stable flow of extracorporeal membrane oxygenation (ECMO) is achieved.

The cardiologists were contacted after stable ECLS flow was checked. Emergency CAG was performed. PCI was performed in patients with myocardial infarction (MI). When multi-vessel disease was diagnosed, culprit-vessel PCI was performed, and staged PCI was planned.

After the coronary intervention, if the patient's vital status was stable, computed tomography (CT) of the brain, chest, and abdomen was performed for initial

evaluation. After transferring the patient to the ICU, target temperature management (TTM) was consulted with the emergency department.

During the ECLS treatment, the mean pressure was maintained between 60 and 80 mmHg. Inotropes were initiated if the blood pressure was lower than the target blood pressure. Cardiac pulse pressure was maintained at least 10 mmHg above the mean arterial pressure if the arterial pulse was still present to open the aortic valve.

Electroencephalography (EEG) was not routinely performed. It was performed when the patient did not show mental recovery after withdrawing sedatives or when the patient showed symptoms of seizures.

NSE level measurement

Blood samples were obtained for NSE measurements 24, 48, and 72 h after ECLS initiation. To prevent hemolysis, the sample was drawn from the arterial line with minimal negative pressure applied and transferred to vacutainers using large 16-gauge needles. If hemolysis occurred, the samples were redrawn. NSE analysis was performed directly after the blood was drawn on weekdays and refrigerated during weekends before sending for analysis early on Monday morning.

Study outcomes

Follow-up was performed by retrospectively reviewing patient medical files. The primary endpoint was the best neurological outcome during the entire hospitalization period. A good neurological outcome was defined as a CPC score of 1 (good cerebral performance) or 2 (moderate cerebral disability), and a poor neurological outcome was defined as a CPC score of 3 (severe cerebral disability) to 5 (brain death)[20]. The secondary endpoint was the 30-day all-cause mortality.

Statistical analysis

Continuous variables were described as means and standard deviations for normally distributed variables and medians (Q1, Q3) for non-normally distributed variables. Independent t-tests were used to compare normally distributed variables, and Wilcoxon rank-sum test was used to compare non-normally distributed variables. Chi-square and Fisher's exact tests were used to compare categorical variables. Statistical significance was set at $P < 0.05$. For every 24 h up to 72 h after ECLS initiation, receiver operating curve (ROC) analysis using the NSE level was performed to predict poor neurological outcomes and 30-day mortality. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patients

The baseline characteristics of the patients are shown in Table 2. The mean age of the patients was 57.9 ± 15.2 years, and 35 (74.5%) were male. Acute MI was the most common cause, accounting for 59.6% of the patients. The mean total CPR time was 30.0 ± 20.4 min. The prehospital CPR time was recorded only for patients with OHCA, and the median time was 19.5 min. The initial arterial pH, lactate, creatinine, and troponin I levels were obtained at the time of CPR (Table 2). Median ICU stay was 9.0 (5.0–14.0) days, and median duration of hospitalization was 13.0 (5.0–25.0) days.

There were 27 and 20 patients with IHCA and OHCA, respectively (Table 3). The two groups showed significant differences in age, CPR time, and arterial pH at the time of ECLS insertion. The OHCA group had patients with younger age (52.1 ± 14.6 vs. 62.1 ± 14.4 years, $p = 0.023$), longer total CPR time (44.85 ± 17.49 vs. 19.04 ± 14.75 min, $p < 0.001$), and lower arterial pH (7.04 ± 0.21 vs. 7.17 ± 0.15, $p = 0.016$).

Brain CT was performed in 40 patients. Normal brain CT findings were observed in 25 (53.2%) patients. The following were the abnormal brain CT results: mild edema, 3 (6.4%); severe edema, 5 (10.6%); cerebral infarction, 4 (8.5%); brain hemorrhage, 2 (4.2%); and others, 2 (4.2%). The neurological outcomes and mortality rates according to the brain CT images are shown in Table 4.

EEG was performed on 12 patients. Owing to the examination being performed in unconscious patients in the protocol, all 12 cases showed diffuse cerebral dysfunction.

Table 2. Baseline characteristics of the patients

	All patients n=47	CPC scores 1–2 n=25	CPC scores 3–5 n=22	*p*-value	Alive n=27	Expired n=20	*p*-value
Age (mean ± SD) (years)	57.9 ± 15.2	55.4 ± 13.8	60.7 ± 16.5	0.231	57.6 ± 15.1	58.3 ± 15.8	0.870
Sex				1.000			0.737
Male	35 (74.5)	19 (76.0)	16 (72.7)		21 (77.78)	14 (70.0)	
Cause of cardiogenic shock				0.565			0.436
Acute MI	28 (59.6)	13 (52.0)	15 (68.18)		15 (55.6)	13 (65.0)	
ICMP	3 (6.4)	3 (12.0)	0 (0)		3 (11.1)	0 (0)	
DCMP	2 (4.3)	1 (4.0)	1 (4.6)		0 (0)	2 (10.0)	
Acute myocarditis	4 (8.5)	3 (12.0)	1 (4.6)		3 (11.1)	1 (5.0)	
PTE	2 (4.3)	1 (4.0)	1 (4.6)		1 (3.7)	1 (5.0)	
Infective endocarditis	1 (2.1)	0 (0)	1 (4.6)		0 (0)	1 (5.0)	
SCMP	2 (4.3)	1 (4.0)	1 (4.6)		1 (3.7)	1 (5.0)	
Fatal arrhythmia	2 (4.3)	2 (8.0)	0 (0)		2 (7.4)	0 (0)	
Others	3 (6.4)	1 (4.0)	2 (9.1)		2 (7.4)	1 (5.0)	

CPR time (minutes)							
Total (mean ± SD)	30.0 ± 20.4	29.2 ± 32.0	30.9 ± 25.0	0.783	30.5 ± 21.7	29.4 ± 19.1	0.848
Pre-hospital, median (Q1–Q3)	19.5 (9.5–29.0)	18.0 (9.0–30.0)	26.0 (9.5–28.0)	0.054	19.5 (10.0–29.0)	18.0 (9.0–27.0)	0.109
In-hospital (mean ± SD)	21.6 ± 15.2	20.1 ± 17.3	23.3 ± 12.4	0.471	20.0 ± 17.0	23.8 ± 12.4	0.408
pH (mean ± SD)							
ECMO insertion time	7.12 ± 0.19	7.17 ± 0.18	7.06 ± 0.19	0.069	7.17 ± 0.18	7.05 ± 0.18	0.023
POD#1	7.37 ± 0.13	7.39 ± 0.12	7.36 ± 0.15	0.440	7.40 ± 0.12	7.34 ± 0.14	0.122
Lactate (mean ± SD) (mmol/L)							
ECMO insertion time	8.17 ± 4.48	6.82 ± 4.26	9.64 ± 4.35	0.032	7.04 ± 4.50	9.63 ± 4.12	0.051
POD#1	6.58 ± 4.70	5.64 ± 5.25	7.52 ± 3.99	0.199	5.68 ± 5.03	7.9 ± 3.96	0.135
Creatinine, median (Q1–Q3) (mg/dL)							
ECMO insertion time	1.19 (0.91–1.69)	1.15 (0.88–1.61)	1.25 (1.07–1.71)	0.190	1.12 (0.86–1.61)	1.36 (1.14–2.16)	0.048
POD#1	1.08 (0.87–1.78)	1.01 (0.86–1.37)	1.22 (0.94–1.88)	0.147	0.98 (0.86–1.37)	1.41 (0.98–2.00)	0.083
eGFR (mean ± SD)							
ECMO insertion time	60.38 ± 30.62	67.0 ± 31.4	52.9 ± 28.6	0.115	67.7 ± 31.6	50.5 ± 27.0	0.056
POD#1	65.96 ± 33.14	74.5 ± 35.9	56.2 ± 27.3	0.058	74.2 ± 35.8	54.9 ± 26.1	0.047

Trop I, median (Q1–Q3) (ng/mL)							
ECMO insertion time	0.23 (0.06–0.95)	0.25 (0.06–1.68)	0.09 (0.05–0.82)	0.668	0.29 (0.05–2.25)	0.15 (0.06–0.68)	0.629
POD#1	46.03 (1.78–50.0)	46.03 (2.23–50.00)	43.49 (1.78–50.00)	0.930	46.03 (0.77–50.0)	43.49 (2.24–50.0)	0.833
ICU stay (days), median (Q1–Q3)	9.0 (5.0–14.0)	12.0 (8.0–14.0)	6.0 (4.0–14.0)	0.016	12.0 (7.0–17.0)	7.0 (4–12.5)	0.026
Hospital stay (days), median (Q1–Q3)	13.0 (5.0–25.0)	20.0 (8.0–29.0)	7.0 (4.0–14.0)	0.001	20.0 (8.0–30.0)	7.0 (4.0–12.5)	0.001

Baseline characteristics of patients with cardiogenic arrest treated with ECMO. Mean ± standard deviation (SD) is presented for normally distributed variables, and median (Q1, Q3) for non-normally distributed variables. N (%) is presented for categorical variables. MI, myocardial infarction; ICMP, ischemic cardiomyopathy; DCMP, dilated cardiomyopathy; PTE, pulmonary thromboembolism; SCMP, stress-induced cardiomyopathy; eGFR, estimated glomerular filtration rate; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; CPC, Cerebral Performance Category

Table 3. Characteristics according to the place where the cardiac arrest occurred

	IHCA n=27	OHCA n=20	*p*-value
Age (years)	62.1 ± 14.4	52.1 ± 14.6	0.023
Sex			0.737
Male	21 (77.8)	14 (70.0)	
Cause of cardiogenic shock			0.120
Acute MI	18 (66.7)	10 (50.0)	
ICMP	0 (0)	3 (15.0)	
DCMP	2 (7.4)	0 (0)	
Acute myocarditis	2 (7.4)	2 (10.0)	
PTE	1 (3.7)	1 (5.0)	
Infective endocarditis	0 (0)	1 (5.0)	
SCMP	2 (7.4)	0 (0)	
Fatal arrhythmia	0 (0)	2 (10.0)	
Others	2 (7.4)	1 (5.0)	
CPC score			0.556
CPC scores 1–2	13 (48.2)	12 (60.0)	
CPC scores 3–5	14 (51.9)	8 (40.0)	
30-day mortality			0.152
Alive	13 (48.2)	14 (70.0)	
Death	14 (51.9)	6 (30.0)	
CPR time (minute)			
Total (mean ± SD)	19.0 ± 14.85	44.9 ± 17.5	<.0001
Pre-hospital, median (Q1–Q3)	-	19.5 (9.5–29.0)	
In-hospital (mean ± SD)	19.0 ± 14.8	25.1 ± 15.4	0.182
pH (mean ± SD)			
ECMO insertion time	7.17 ± 0.15	7.04 ± 0.21	0.016
POD#1	7.40 ± 0.11	7.35 ± 0.15	0.215
Lactate (mean ± SD) (mmol/L)			
ECMO insertion time	7.04 ± 3.77	9.63 ± 4.99	0.051
POD#1	6.81 ± 5.59	6.33 ± 3.62	0.744
Creatinine, median (Q1–Q3) (mg/dL)			
ECMO insertion time	1.24 (0.95–1.69)	1.18 (0.91–1.66)	0.863
POD#1	1.08 (0.94–1.67)	1.0 (0.81–2.29)	0.739
eGFR (mean ± SD)			

ECMO insertion time	59.89 ± 28.47	61.05 ± 34.06	0.899
POD#1	63.22 ± 23.21	69.65 ± 43.55	0.554
Trop I, median (Q1–Q3) (ng/mL)			
ECMO insertion time	0.19 (0.06–3.31)	0.32 (0.06–0.78)	0.849
POD#1	50.0 (1.78–50.0)	6.12 (1.50–50.0)	0.358
ICU stay, median (Q1–Q3) (day)	11.0 (7.0–17.0)	8.5 (4.5–12.0)	0.185
Hospital stay, median (Q1–Q3) (day)	13.0 (7.0–25.0)	11.5 (4.5–23.5)	0.419

Baseline characteristics of patients with cardiogenic arrest treated with ECMO according to the location of the arrest. Mean ± standard deviation (SD) is presented for normally distributed variables, and median (Q1, Q3) for non-normally distributed variables. N (%) is presented for categorical variables. MI, myocardial infarction; ICMP, ischemic cardiomyopathy; DCMP, dilated cardiomyopathy; PTE, pulmonary thromboembolism; SCMP, stress-induced cardiomyopathy; eGFR, estimated glomerular filtration rate; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation

Table 4. Brain CT results of ECLS patients

Brain CT findings	CPC score		Mortality	
	CPC scores 1–2	CPC scores 3–5	Alive	Expired
Normal	18 (38.3%)	7 (14.9%)	16 (34.0%)	9 (19.1%)
Mild edema	1 (2.1%)	2 (4.2%)	1 (2.1%)	2 (4.2%)
Severe edema	0	5 (10.6%)	0	5 (10.6%)
Cerebral infarction	2 (4.2%)	2 (4.2%)	2 (4.2%)	2 (4.2%)
Brain hemorrhage	0	1 (2.1%)	1 (2.1%)	0
Others	0	2 (4.2%)	0	2 (4.2%)

CPC, Cerebral Performance Category; CT, computed tomography; ECLS, extracorporeal life support

Clinical outcomes

Of the 47 ECPR patients, 25 (53.2%) showed good neurological outcomes with CPC scores of 1–2 during the hospitalization period. The other 22 patients (46.8%) showed poor neurological outcomes, with CPC scores of 3–5 during the hospitalization period. Thirty-day all-cause mortality occurred in 20 (42.6%) patients (Table 2).

The initial lactate level (p = 0.032) was significantly higher in patients with poor neurological outcomes. Initial arterial blood pH (p = 0.023), initial creatinine level (p = 0.048), and estimated glomerular filtration rate 24 h after ECLS initiation (p = 0.047) showed a significant difference in the 30-day mortality (Table 2).

The poor neurological outcome rate tended to be higher in patients with IHCA (51.9%) than that in patients with OHCA (40.0%) (p = 0.556). The 30-day mortality rate also tended to be higher in patients with IHCA (51.9%) than that in patients with OHCA (30.0%) (p = 0.152; Table 3).

TTM was performed on 13 patients. Poor neurological outcomes occurred in six patients and showed no significance (p = 0.957) on the neurological outcome. Mortality occurred in seven patients and showed no significance (p = 0.685).

Univariate and multivariate analyses were performed to identify the prognostic factors for predicting poor neurological outcomes and mortality (Table 5). A CPR time longer than 30 min, an arterial pH lower than 7.35, a lactate level higher than 1.6 mmol/L, a creatinine level higher than 0.95 mg/dL, and an eGFR value lower than 60 were analyzed as predictive factors. An NSE level over 60 ug/L at 72 h was the only significant prognostic factor for poor neurological outcomes in both univariate and multivariate analyses (p = 0.005 and 0.008, respectively). An NSE level over 60 ug/L at 72 h was significant only in the

univariate analysis ($p = 0.001$) for predicting mortality.

Table 5. Univariate and multivariate analyses of poor neurological outcomes and mortality

	Poor neurological outcome				Mortality			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
CPR time								
Total	0.639 (0.201–2.032)	0.448	0.122 (0.013–1.114)	0.062	0.431 (0.131–1.419)	0.166	<0.001 (<0.001–>999.99)	0.942
pH								
ECMO insertion	0.525 (0.086–3.190)	0.484	3.407 (0.277–41.848)	0.338	0.232 (0.025–2.160)	0.199	6.775 (0.169–271–746)	0.310
lactate								
ECMO insertion	4.706 (0.878–25.223)	0.071	13.728 (0.704–267.669)	0.084	1.143 (0.276–4.740)	0.854	0.547 (0.023–13.158)	0.710
creatinine								
POD#1	2.095 (0.615–7.142)	0.237	0.298 (0.019–4.765)	0.392	3.714 (0.982–14.051)	0.053	1.097 (0.047–25.680)	0.954
eGFR								
POD#1	0.556 (0.174–1.771)	0.320	0.315 (0.021–4.666)	0.401	0.392 (0.120–1.286)	0.122	0.483 (0.016–14.137)	0.673
NSE								
POD#3	8.800 (1.920–40.336)	0.005	19.48 (2.150–176.46)	0.008	24.000 (4.133–139.38)	0.001	>999.99 (<0.001–>999.99)	0.935

A CPR time longer than 30 min, an arterial pH lower than 7.35, a lactate level higher than 1.6 mmol/L, a creatinine level higher than 0.95 mg/dL, an EGFR value lower than 60, and an NSE level at 72 h over 60 ug/L are analyzed as predictive factors.

CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; NSE, neuron-specific enolase; eGFR, estimated glomerular filtration rate

NSE levels and study endpoints

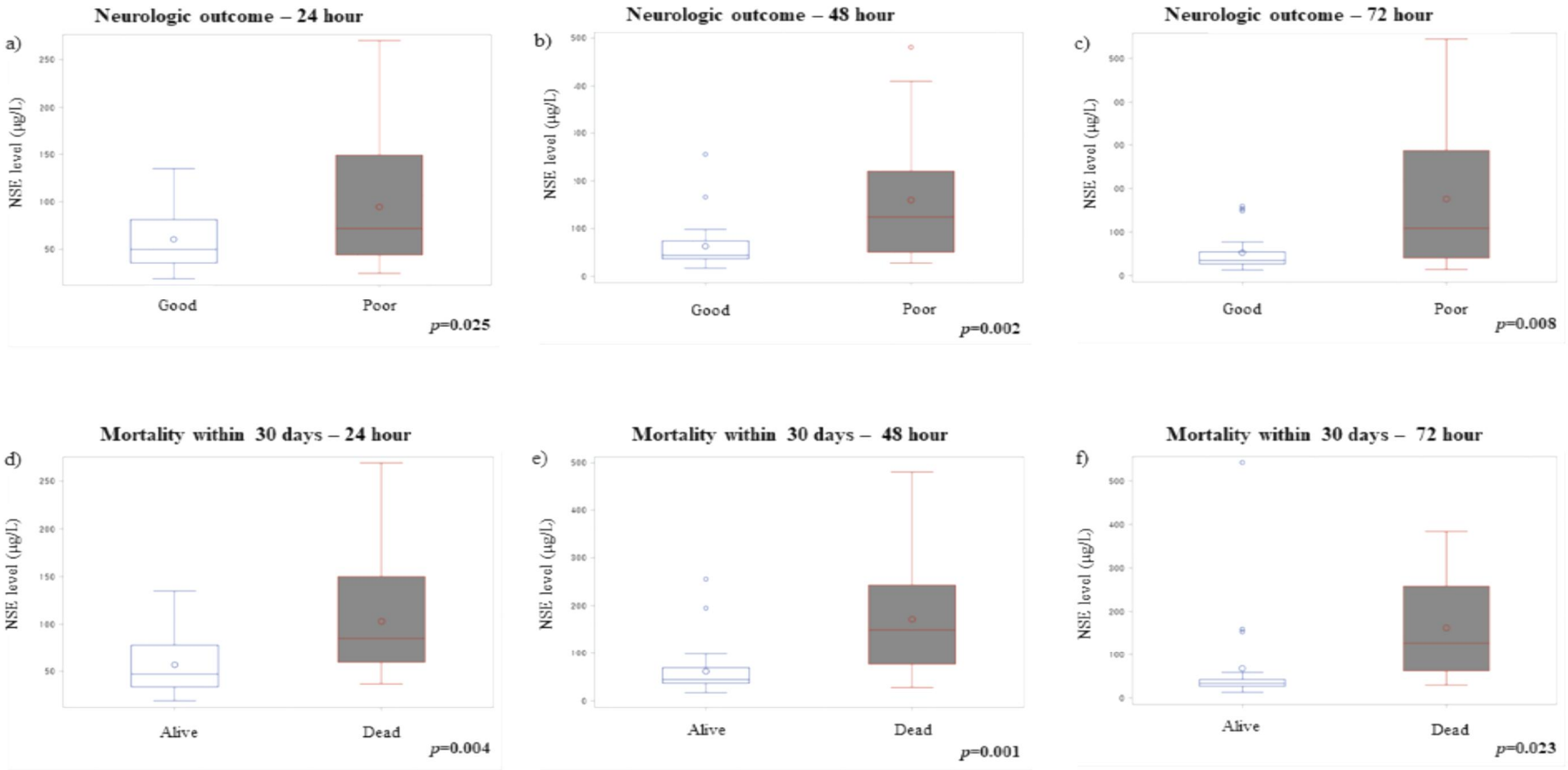
The median NSE serum levels at 24, 48, and 72 h after ECPR were 63.0 (19.1–270.0), 64.8 (16.8–481.0), and 41.4 (12.9–544.0) μg/L, respectively.

The NSE levels at 24, 48, and 72 h after ECPR according to neurological outcomes and 30-day mortality are shown in Figure 3. NSE levels showed a significant difference in both the poor neurological outcomes and 30-day mortality groups at any time.

The diagnostic accuracy of NSE serum levels for predicting poor neurological outcomes during hospitalization and 30-day mortality is shown in Table 6. An NSE threshold >25 ug/L at 72 h after ECPR had a sensitivity of 73.3% and 80.0% for the prediction of poor neurological outcomes and 30-day mortality, respectively. An NSE threshold >75 ug/L at 72 h after ECPR had a specificity of 100% for both the prediction of poor neurological outcomes and 30-day mortality.

The ROC curve was used to derive NSE cut-off values for poor neurological outcomes and 30-day mortality, and the results are shown in Figure 4. The area under the curve (AUC) values derived for 24-, 48-, and 72-h NSE levels predicting poor neurological outcomes were 0.664, 0.783, and 0.791, respectively, with cut-off NSE levels of 100.7, 115.7, and 61.9 μg/L, respectively. The AUC values derived for 24-, 48-, and 72-h NSE levels predicting 30-day mortality were 0.768, 0.832, and 0.838, respectively, with cut-off NSE levels of 48.4, 83.0, and 62.1 μg/L, respectively. The AUC values of both ROC curves for poor neurological outcomes and 30-day mortality were highest at 72 h after ECLS initiation, with values of 0.791 and 0.838, respectively.

Figure 3. NSE levels at 24, 48, and 72 h after ECLS initiation according to neurological outcomes and 30-day mortality



Neuron-specific enolase (NSE) levels at 24, 48, and 72 h after extracorporeal life support (ECLS) application are shown according to neurological outcomes (a), (b), (c), and mortality within 30 days (d), (e), and (f). The p-values for each category are presented in the corresponding graphs.

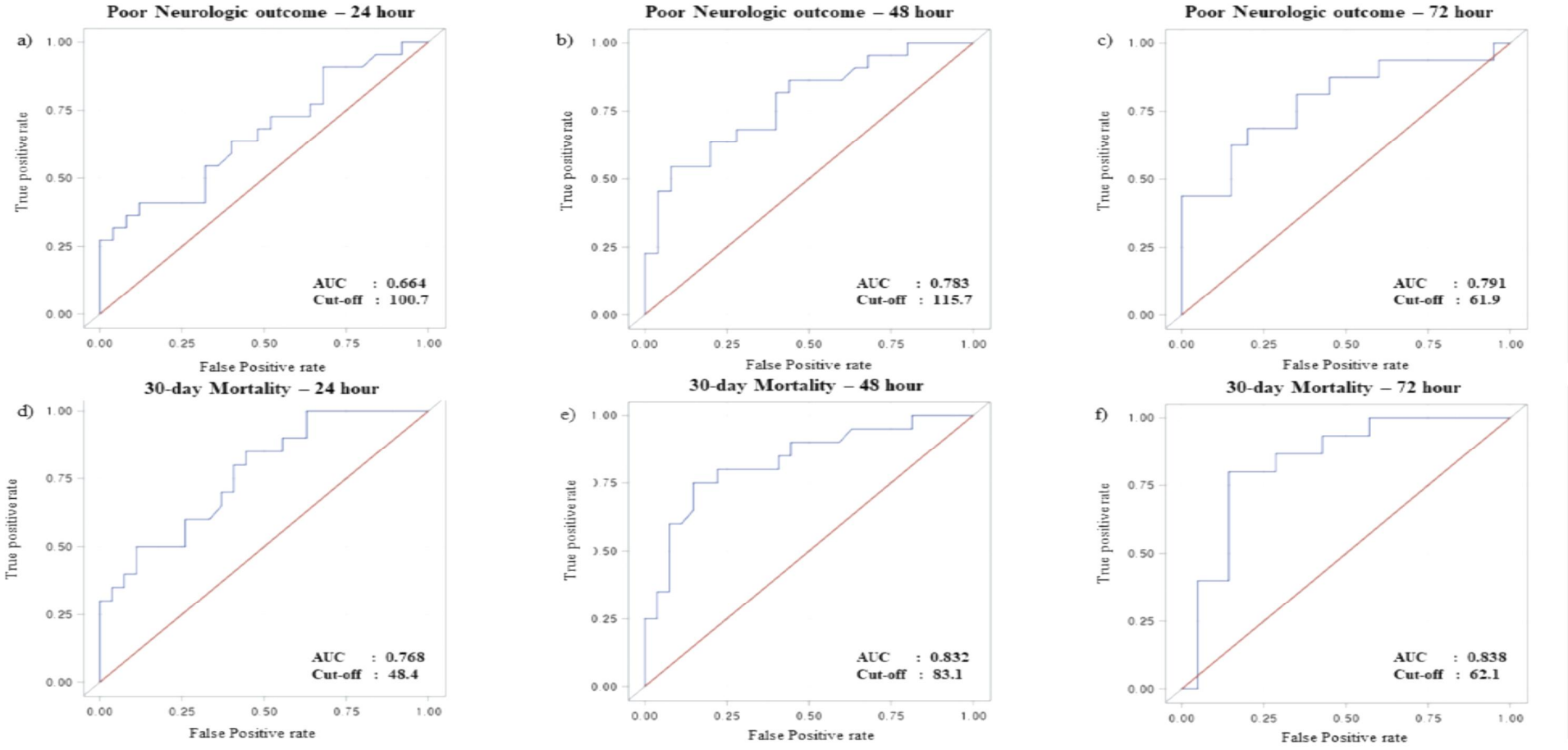
Table 6. Diagnostic accuracy of NSE level predicting poor neurological outcomes (CPC scores 3–5) during hospitalization and 30-day mortality

CPC scores 3–5 during hospitalization			30-day mortality		
Variable	Sensitivity (95% CI)	Specificity (95% CI)	Variable	Sensitivity (95% CI)	Specificity (95% CI)
NSE level at 24 h after ECPR			NSE level at 24 h after ECPR		
NSE > 25	48.9 (28.0–69.8)	87.0 (73.8–100.0)	NSE > 25	50.0 (28.1–71.9)	87.5 (75.0–100.0)
NSE > 50	40.0 (19.5–60.5)	100.0 (100–100)	NSE > 50	37.5 (16.3–58.7)	100 (100–100)
NSE > 75	60.0 (39.5–80.5)	100.0 (100–100)	NSE > 75	54.6 (32.7–76.4)	100 (100–100)
NSE level at 48 h after ECPR			NSE level at 48 h after ECPR		
NSE > 25	54.5 (33.7–75.4)	90.0 (78.2–101.8)	NSE > 25	75.0 (56.0–94.0)	81.8 (67.3–96.4)
NSE > 50	66.7 (47.0–86.4)	80.0 (64.3–95.7)	NSE > 50	70.6 (50.6–90.6)	81.8 (67.3–96.4)
NSE > 75	71.4 (52.5–90.3)	83.3 (68.7–98.0)	NSE > 75	80.0 (62.5–97.5)	60.0 (41.5–78.5)
NSE level at 72 h after ECPR			NSE level at 72 h after ECPR		
NSE > 25	73.3 (54.9–91.8)	75.0 (58.0–92.0)	NSE > 25	80.0 (62.5–97.5)	81.3 (66.5–96.0)

NSE > 50	63.6 (43.5–83.7)	100 (100–100)	NSE > 50	100 (100–100)	40.0 (21.5–58.5)
NSE > 75	70.0 (50.9–89.2)	100 (100–100)	NSE > 75	45.5 (23.6–67.3)	100 (100–100)

Diagnostic accuracy of NSE levels at 24, 48, and 72 h according to different threshold concentrations for predicting CPC scores of 3–5 during hospitalization and 30-day mortality. NSE, neuron-specific enolase; ECPR, extracorporeal life support; CI, confidence interval

Figure 4. Receiver operating characteristic curves for predicting neurological outcomes and 30-day mortality at 24, 48, and 72 h after ECLS initiation



Receiver operating characteristic curves (ROCs) are used to predict neurological outcomes using neuron-specific enolase (NSE) levels at 24, 48, and 72 h after extracorporeal life support (ECLS) application (a), (b), (c), and mortality within 30-days at 24, 48, and 72 h after ECLS application (d), (e), and (f). The area under the curve (AUC) and NSE cut-off values are presented below each corresponding graph.

DISCUSSION

This study showed that the NSE level at 72 h after ECLS initiation had the highest AUC value for both poor neurological outcomes and 30-day mortality. This suggests that the NSE level at 72 h after ECLS initiation could predict poor neurological outcomes and 30-day mortality more precisely. This study suggests that using the NSE level cut-off value at 72 h after ECLS initiation to predict a poor neurological outcome is 61.9 μg/L. Furthermore, an NSE cut-off value of 62.1 μg/L at 72 h after ECPR for predicting 30-day mortality is suggested.

We performed both univariate and multivariate analyses for possible prognostic factors for poor neurological outcomes and mortality (Table 5), and only NSE levels >60 μg/L at 72 h after ECMO insertion showed significance in both univariate and multivariate analyses for predicting poor neurological outcomes. An NSE level >60 μg/L at 72 h after ECMO insertion was also the only significant prognostic factor in the univariate analysis.

Cell-specific glycolytic isoenzymes have the following three different expression types: ubiquitous enolase α, muscle-specific enolase β, and neuron-specific enolase γ (defined as NSE)[21]. Because NSE is highly expressed in neurons and neuroendocrine cells, it serves as a biomarker for neurological diseases, such as neuroendorince tumor[22,23]. The role of NSE as a tumor marker is increasing owing to its increased serum levels in several cancers at the time of diagnosis. NSE is recognized as a reliable tumor marker for small cell lung cancer[24,25]. Huang et al. conducted a meta-analysis on the clinical value of NSE in diagnosing small cell

lung cacner and suggested a sensitivity of 0.688 and specificity of 0.921[26]. NSE also serves as a biomarker for gastric adenocarcinoma[27], prostate cancer[28], and metastatic melanoma[29]. Owing to the diverse applications of NSE as a biomarker, several clinics have acquired NSE measurement equipment, and laboratory results can be easily obtained.

Apart from the convenient examination, NSE was chosen as a candidate for predicting neurologic prognosis in ECPR patients according to prior studies on patients with cardiac arrest[15–17]. Roine et al. published a study suggesting that an increased NSE level higher than 24 ng/mL at 24 h after cardiac arrest led to unconsciousness and death[15]. Wihersaari et al. reported that NSE at 48 h after cardiac arrest is a prognostic factor for 12-month survival[16]. Ostlund et al. suggested that NSE levels of >101 μg/L at 48 h and >80 μg/L at 72 h predict poor neurological outcomes[17]. Only a few studies have focused on NSE levels and neurological outcomes in ECLS patients[7–9].

The results of this study are similar to those of previous studies. Schrage et al. suggested a cut-off NSE serum level of 70 μg/L at 48 h after ECPR for predicting poor neurological outcomes[9]. This study defined poor neurological outcome as a score of 4–5, and a CPC score of 3 could improve after rehabilitation. Reuter et al. claimed that day 3 NSE levels >25 μg/L were associated with 28-day mortality and poor 90-day neurological outcomes, and an NSE threshold larger than 80 μg/L at day 3 predicted both poor neurological outcomes and mortality with 100% specificity [7]. This study defined a poor neurological outcome as an mRS score of 4–6. Our study suggests a lower cut-off value for NSE level of 61.9 μg/L at 72 h for poor neurological prediction and a threshold of over 75 μg/L at 72 h with 100% specificity for poor neurological outcomes. This study suggests a lower NSE value compared with other studies. This may be a result of the different

definitions of poor prognosis. We defined good neurological outcome as CPC scores of 1 and 2 and defined poor neurological outcome as CPC scores of 3–5. A CPC score of 3 was defined as a poor neurological outcome because patients are dependent on others for their daily activities; this definition was approved to show substantial inter-rater agreement in a previous study[20].

The 30-day mortality rate in this study was 42.6%. This result is similar to the survival to discharge reported in other studies, which ranged from 38% to 52%[30–32]. Poor neurological outcomes were found in 46.8% of the patients in this study and were slightly higher than those in other studies, which ranged between 30.7% and 38%[8,9]. The inferior results may have resulted from the placement of CPC score 3, which was marked as poor prognosis in this study and as good neurological outcome in the other study[9]. The use of the CPC score instead of brain CT images for neurological outcomes[8] may be another contributing factor. In this study, 7 of 25 patients with normal brain CT showed poor neurological outcomes (Table 4), showing a higher possibility of poor neurological outcomes being derived in our study.

The mortality and poor neurological outcome rates were higher in the IHCA group in this study. This result may be due to the following factors: 1) patients who died within 24 h of ECLS insertion were excluded. 2) Baseline patient characteristics were different in significantly younger patients having IHCA. At Hanyang University Seoul Hospital, ECLS insertion for cardiogenic arrest is limited to patients under the age of 75, with a CPR time of <30 min, no irreversible medical conditions, and witnessed cardiac arrests. Conversely, IHCA is inserted into more chronic patients and tends to be inserted into older adult patients. This difference in selection criteria seems to be the main factor for better OHCA ECLS results.

Therefore, we suggest providing ECLS support to patients with cardiac arrest when the criteria are met with less concern for negative results. The impact of excluding mortality within 24 h will be investigated in future studies. Another factor contributing to good ECPR results is the presence of a communication system between the emergency medical services and the emergency department. Emergency medical technicians inform the clinic about the patient and their history with a timeline of arrival. After receiving such notice, the emergency department alerts the ECLS team, and the team stands by with all the required equipment until the patient arrives. This chain of communication allows for minimal time loss and leads to improved survival.

Other neurological examinations could also help predict the neurological outcomes. Brain imaging techniques, such as CT, can be used. Florechinger et al. reported by studying 131 patients with cardiac arrest undergoing ECLS treatment that an increase in the 48-h NSE value was associated with a higher probability of brain damage in brain CT[33]. Most of the patients in this study had an initial brain CT done due to the protocol of examining the brain, chest, and abdomen after insertion of ECLS if the patient's vital signs were stable. Our data showed that 62.5% of the brain CT scans were normal (Table 4), which was higher than the proportion of good neurological outcomes (53.2%). This may be due to brain CT being performed usually within 6 h after the arrest, and this period seems to be too short for the damage to reach the brain. This finding is correlated with other studies suggesting that a brain CT scan in the emergency department does not affect the management of the patients[34,35].

Transcranial Doppler (TCD) ultrasonography can be used to evaluate brain damage. TCD sonography is a rapid, noninvasive diagnostic tool that can be applied at the bedside of the patient[36]. This easy accessibility is a major advantage over CT imaging for patients with ECLS who do not have to move for the examination. TCD is frequently used in diagnosing

traumatic brain injury[37,38], evaluation during treatement[39,40], and even in diagnosing brain death[41,42]. Change et al. presented a meta-analysis on the accuracy of TCD in confirming brain death and showed a sensitivity and specificity of 0.90 (95% confidence interval [CI], 0.87–0.92) and 0.98 (95% CI, 0.96–0.99), respectively. However, TCD was not available for adult patients in our clinic; therefore, no results were obtained. In the future, TCD results should be obtained after consulting with the radiology department during the ECLS period for proper evaluation and diagnosis of brain death.

Other biomarkers, such as S100 calcium-binding protein β (S-100 β) are emerging as new possible biomarkers for predicting neurological outcomes[43]. S-100 β is mainly released by glial cells after brain injury and, therefore, increases after cardiac arrest[44]. Elevated S-100 β levels (>0.5 μg/L) could predict poor outcomes even after 24 h of cardiac arrest[45,46]. S-100 β has limitations in that it is more frequently examined (as a tumor marker) and has a short half-life of 2 h[47]. Therefore, combined examinations with other neurological examinations could provide more precise results.

TTM was applied in 13 cases in this study, of which only seven showed good neurological outcomes, and six survived. Certain guidelines recommend 24 h of cooling in patients with OHCA[48], and several studies have suggested better neurological outcomes after applying TTM[49,50]. Bernard et al. compared post-cardiac arrest comatose patients, which consisted of 43 patients receiving hypothermia therapy and 34 patients receiving normothermic treatment, and suggested that hypothermia provided a better neurological outcome[51]. Using surface cooling devices is recommended in TTM[48,52]. The neurological outcomes of this study could have improved if TTM was applied more frequently.

This study showed that elevated lactate levels at the time of ECLS insertion were

significantly higher in the poor neurological outcome group. A significantly lower arterial pH and elevated creatinine levels at the time of ECLS insertion were observed in the mortality group. Several studies have suggested that elevated lactate levels are associated with mortality[33,53]; however, no study seems to relate elevated lactate levels with poor neurological outcomes in ECLS patients. Some studies have suggested that elevated lactate levels in the cerebrospinal fluid are related to delayed cerebral ischemia in patients with intracranial hemorrhage, which could cause poor neurological outcomes[54,55]. If a similar mechanism could be applied to ECLS patients, elevated lactate levels could predict poor neurological outcomes for lactate that can pass through the blood–brain barrier[56]. Acidosis is a known prognostic factor of mortality[57–59]. Acidosis represents poor tissue perfusion, which could lead to multiple organ injuries[57] and result in a higher risk of mortality.

Limitations

This study had several limitations. First, this was a retrospective single-center study with a small number of patients. Multicenter research with a larger number of patients is needed to support the results of this study. Second, NSE is known to be present in other non-brain organs, and it is impossible to identify whether NSE level elevation is due to brain damage or hemolysis that could occur due to ECLS. Therefore, the patient was carefully managed to prevent hemolysis, and meticulous methods were used when drawing samples to minimize hemolysis; however, these preventive measures may not have been efficient in decreasing hemolysis.

CONCLUSION

In adult ECPR patients, NSE can be used to predict neurological outcomes and mortality. Importantly, NSE measurement at 72 h (poor neurological outcome during hospitalization: 61.9 μg/L; 30-day mortality: 62.1 μg/L) after ECPR had the most accurate predictive value for short-term poor neurological outcomes and 30-day mortality.

REFERENCES

1. Stub D, Bernard S, Pellegrino V, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). *Resuscitation*. 2015;86:88-94. doi:10.1016/j.resuscitation.2014.09.010

2. Schmidt M, Burrell A, Roberts L, et al. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. *Eur Heart J*. 2015;36(33):2246-2256. doi:10.1093/eurheartj/ehv194

3. Marinacci LX, Mihatov N, D'Alessandro DA, et al. Extracorporeal cardiopulmonary resuscitation (ECPR) survival: A quaternary center analysis. *J Card Surg*. 2021;36(7):2300-2307. doi:10.1111/jocs.15550

4. Lorusso R, Barili F, Mauro MD, et al. In-Hospital Neurologic Complications in Adult Patients Undergoing Venoarterial Extracorporeal Membrane Oxygenation: Results From the Extracorporeal Life Support Organization Registry. *Crit Care Med*. 2016;44(10):e964-e972. doi:10.1097/CCM.0000000000001865

5. Xie A, Lo P, Yan TD, Forrest P. Neurologic Complications of Extracorporeal Membrane Oxygenation: A Review. *J Cardiothorac Vasc Anesth*. 2017;31(5):1836-1846. doi:10.1053/j.jvca.2017.03.001

6. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: A Statement for Healthcare Professionals From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Resuscitation*. 2015;96:328-340. doi:10.1016/j.resuscitation.2014.11.002

7. Reuter J, Peoc'h K, Bouadma L, et al. Neuron-Specific Enolase Levels in Adults Under Venoarterial Extracorporeal Membrane Oxygenation. *Crit Care Explor*. 2020;2(10):e0239. doi:10.1097/CCE.0000000000000239

8. Floerchinger B, Philipp A, Foltan M, et al. Neuron-specific enolase serum levels predict severe neuronal injury after extracorporeal life support in resuscitation†. *Eur J Cardiothorac Surg*. 2014;45(3):496-501. doi:10.1093/ejcts/ezt370

9. Schrage B, Rübsamen N, Becher PM, et al. Neuron-specific-enolase as a predictor of the neurologic outcome after cardiopulmonary resuscitation in patients on ECMO. *Resuscitation*. 2019;136:14-20. doi:10.1016/j.resuscitation.2019.01.011

10. Reiber H. Proteins in cerebrospinal fluid and blood: barriers, CSF flow rate and source-

related dynamics. *Restor Neurol Neurosci*. 2003;21(3-4):79-96.

11. Tapia FJ, Polak JM, Barbosa AJ, et al. Neuron-specific enolase is produced by neuroendocrine tumours. *Lancet Lond Engl*. 1981;1(8224):808-811. doi:10.1016/s0140-6736(81)92682-9

12. Vinores SA, Marangos PJ, Parma AM, Guroff G. Increased levels of neuron-specific enolase in PC12 pheochromocytoma cells as a result of nerve growth factor treatment. *J Neurochem*. 1981;37(3):597-600. doi:10.1111/j.1471-4159.1982.tb12528.x

13. Påhlman S, Odelstad L, Larsson E, Grotte G, Nilsson K. Phenotypic changes of human neuroblastoma cells in culture induced by 12-O-tetradecanoyl-phorbol-13-acetate. *Int J Cancer*. 1981;28(5):583-589. doi:10.1002/ijc.2910280509

14. Odelstad L, Påhlman S, Nilsson K, et al. Neuron-specific enolase in relation to differentiation in human neuroblastoma. *Brain Res*. 1981;224(1):69-82. doi:10.1016/0006-8993(81)91117-3

15. Roine RO, Somer H, Kaste M, Viinikka L, Karonen SL. Neurological Outcome After Out-of-Hospital Cardiac Arrest: Prediction by Cerebrospinal Fluid Enzyme Analysis. *Arch Neurol*. 1989;46(7):753-756. doi:10.1001/archneur.1989.00520430047015

16. Wihersaari L, Tiainen M, Skrifvars MB, et al. Usefulness of neuron specific enolase in prognostication after cardiac arrest: Impact of age and time to ROSC. *Resuscitation*. 2019;139:214-221. doi:10.1016/j.resuscitation.2019.04.021

17. Lissner Östlund E, Levin H, Nielsen N, Frigyesi A, Lybeck A. Neuron-specific enolase and long-term neurological outcome after OHCA - A validation study. *Resuscitation*. 2021;168:206-213. doi:10.1016/j.resuscitation.2021.09.001

18. C D, C Q, S A, et al. Serum neuron-specific enolase as predictor of outcome in comatose cardiac-arrest survivors: a prospective cohort study. *BMC Cardiovasc Disord*. 2011;11. doi:10.1186/1471-2261-11-48

19. Safar P. *Brain Failure and Resuscitation. New York: Churchill Livingstone; 1981; p. 155–84.*; 1981.

20. Grossestreuer AV, Abella BS, Sheak KR, et al. Inter-rater reliability of post-arrest cerebral performance category (CPC) scores. *Resuscitation*. 2016;109:21-24. doi:10.1016/j.resuscitation.2016.09.006

21. Isgrò MA, Bottoni P, Scatena R. Neuron-Specific Enolase as a Biomarker: Biochemical and Clinical Aspects. *Adv Exp Med Biol*. 2015;867:125-143. doi:10.1007/978-94-017-7215-0_9

22. Mjønes P, Sagatun L, Nordrum IS, Waldum HL. Neuron-Specific Enolase as an Immunohistochemical Marker Is Better Than Its Reputation. *J Histochem Cytochem Off J Histochem Soc*. 2017;65(12):687-703. doi:10.1369/0022155417733676

23. Braga F, Ferraro S, Mozzi R, Dolci A, Panteghini M. Biological variation of

neuroendocrine tumor markers chromogranin A and neuron-specific enolase. *Clin Biochem*. 2013;46(1-2):148-151. doi:10.1016/j.clinbiochem.2012.09.005

24. Fujita K, Haimoto H, Imaizumi M, Abe T, Kato K. Evaluation of gamma-enolase as a tumor marker for lung cancer. *Cancer*. 1987;60(3):362-369. doi:10.1002/1097-0142(19870801)60:3<362::aid-cncr2820600313>3.0.co;2-u

25. Huang Z, Xu D, Zhang F, Ying Y, Song L. Pro-gastrin-releasing peptide and neuron-specific enolase: useful predictors of response to chemotherapy and survival in patients with small cell lung cancer. *Clin Transl Oncol Off Publ Fed Span Oncol Soc Natl Cancer Inst Mex*. 2016;18(10):1019-1025. doi:10.1007/s12094-015-1479-4

26. Huang L, Zhou JG, Yao WX, et al. Systematic review and meta-analysis of the efficacy of serum neuron-specific enolase for early small cell lung cancer screening. *Oncotarget*. 2017;8(38):64358-64372. doi:10.18632/oncotarget.17825

27. Luo H, Shen K, Sun H, Li R, Wang Z, Xie Z. Clinical significance of serum neuron-specific enolase in gastric adenocarcinoma. *Medicine (Baltimore)*. 2020;99(16):e19829. doi:10.1097/MD.0000000000019829

28. Muoio B, Pascale M, Roggero E. The role of serum neuron-specific enolase in patients with prostate cancer: a systematic review of the recent literature. *Int J Biol Markers*. 2018;33(1):10-21. doi:10.5301/ijbm.5000286

29. Sato S, Kato J, Sawada M, et al. Usefulness of neuron-specific enolase as a serum marker of metastatic melanoma. *J Dermatol*. 2020;47(10):1141-1148. doi:10.1111/1346-8138.15502

30. Takayama H, Truby L, Koekort M, et al. Clinical outcome of mechanical circulatory support for refractory cardiogenic shock in the current era. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant*. 2013;32(1):106-111. doi:10.1016/j.healun.2012.10.005

31. Schurr JW, Noubani M, Santore LA, et al. Survival and Outcomes After Cardiac Arrest With VA-ECMO Rescue Therapy. *Shock Augusta Ga*. 2021;56(6):939-947. doi:10.1097/SHK.0000000000001809

32. Dalia AA, Ortoleva J, Fiedler A, Villavicencio M, Shelton K, Cudemus GD. Extracorporeal Membrane Oxygenation Is a Team Sport: Institutional Survival Benefits of a Formalized ECMO Team. *J Cardiothorac Vasc Anesth*. 2019;33(4):902-907. doi:10.1053/j.jvca.2018.06.003

33. Orban JC, Novain M, Cattet F, et al. Association of serum lactate with outcome after out-of-hospital cardiac arrest treated with therapeutic hypothermia. *PloS One*. 2017;12(3):e0173239. doi:10.1371/journal.pone.0173239

34. Çankaya Gökdere D, Emektar E, Çorbacıoğlu ŞK, Yüzbaşıoğlu Y, Öztürk C, Çevik Y. The Role of Brain CT in Patients with Out-of-Hospital Cardiac Arrest with Return of Spontaneous Circulation. *Am J Emerg Med*. 2022;52:143-147. doi:10.1016/j.ajem.2021.12.008

35. Fuller ZL, Faro JW, Callaway CW, Coppler PJ, Elmer J, University of Pittsburgh Post-Cardiac Arrest Service. Recovery among post-arrest patients with mild-to-moderate cerebral edema. *Resuscitation*. 2021;162:149-153. doi:10.1016/j.resuscitation.2021.02.033

36. Blanco P, Blaivas M. Applications of Transcranial Color-Coded Sonography in the Emergency Department. *J Ultrasound Med*. 2017;36(6):1251-1266. doi:10.7863/ultra.16.04050

37. Bouzat P, Oddo M, Payen JF. Transcranial Doppler after traumatic brain injury: is there a role? *Curr Opin Crit Care*. 2014;20(2):153-160. doi:10.1097/MCC.0000000000000071

38. Gomez A, Batson C, Froese L, Sainbhi AS, Zeiler FA. Utility of Transcranial Doppler in Moderate and Severe Traumatic Brain Injury: A Narrative Review of Cerebral Physiologic Metrics. *J Neurotrauma*. 2021;38(16):2206-2220. doi:10.1089/neu.2020.7523

39. Dearden NM. Mechanisms and prevention of secondary brain damage during intensive care. *Clin Neuropathol*. 1998;17(4):221-228.

40. Rincon F. Bedside transcranial sonography: a promising tool for the neurointensivist. *Crit Care Med*. 2012;40(6):1969-1970. doi:10.1097/CCM.0b013e31824e1b80

41. Chang JJ, Tsivgoulis G, Katsanos AH, Malkoff MD, Alexandrov AV. Diagnostic Accuracy of Transcranial Doppler for Brain Death Confirmation: Systematic Review and Meta-Analysis. *AJNR Am J Neuroradiol*. 2016;37(3):408-414. doi:10.3174/ajnr.A4548

42. Hashemian SM, Delavarkasmaei H, Najafizadeh K, et al. Role of Transcranial Doppler Sonography in Diagnosis of Brain Death: A Single Center Study. *Tanaffos*. 2016;15(4):213-217.

43. Kang C, Jeong W, Park JS, et al. Comparison of Prognostic Performance between Neuron-Specific Enolase and S100 Calcium-Binding Protein B Obtained from the Cerebrospinal Fluid of Out-of-Hospital Cardiac Arrest Survivors Who Underwent Targeted Temperature Management. *J Clin Med*. 2021;10(7):1531. doi:10.3390/jcm10071531

44. Rossetti AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome in patients in coma after cardiac arrest. *Lancet Neurol*. 2016;15(6):597-609. doi:10.1016/S1474-4422(16)00015-6

45. Rundgren M, Karlsson T, Nielsen N, Cronberg T, Johnsson P, Friberg H. Neuron specific enolase and S-100B as predictors of outcome after cardiac arrest and induced hypothermia. *Resuscitation*. 2009;80(7):784-789. doi:10.1016/j.resuscitation.2009.03.025

46. Calderon LM, Guyette FX, Doshi AA, Callaway CW, Rittenberger JC. Combining NSE and S100B with clinical examination findings to predict survival after resuscitation from cardiac arrest. *Resuscitation*. 2014;85(8):1025-1029. doi:10.1016/j.resuscitation.2014.04.020

47. Moseby-Knappe M, Cronberg T. Blood biomarkers of brain injury after cardiac arrest – A dynamic field. *Resuscitation*. 2020;156:273-276. doi:10.1016/j.resuscitation.2020.09.004

48. Madden LK, Hill M, May TL, et al. The Implementation of Targeted Temperature Management: An Evidence-Based Guideline from the Neurocritical Care Society. *Neurocrit Care*. 2017;27(3):468-487. doi:10.1007/s12028-017-0469-5

49. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation*. 2007;73(1):29-39. doi:10.1016/j.resuscitation.2006.08.016

50. Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest. *N Engl J Med*. 2002;346(8):549-556. doi:10.1056/NEJMoa012689

51. Geocadin RG, Koenig MA, Jia X, Stevens RD, Peberdy MA. Management of brain injury after resuscitation from cardiac arrest. *Neurol Clin*. 2008;26(2):487-506, ix. doi:10.1016/j.ncl.2008.03.015

52. Elmer J, Polderman KH. Emergency Neurological Life Support: Resuscitation Following Cardiac Arrest. *Neurocrit Care*. 2017;27(1):134-143. doi:10.1007/s12028-017-0457-9

53. Fux T, Holm M, Corbascio M, van der Linden J. Cardiac Arrest Prior to Venoarterial Extracorporeal Membrane Oxygenation: Risk Factors for Mortality. *Crit Care Med*. 2019;47(7):926-933. doi:10.1097/CCM.0000000000003772

54. van Donkelaar CE, Dijkland SA, van den Bergh WM, et al. Early Circulating Lactate and Glucose Levels After Aneurysmal Subarachnoid Hemorrhage Correlate With Poor Outcome and Delayed Cerebral Ischemia: A Two-Center Cohort Study. *Crit Care Med*. 2016;44(5):966-972. doi:10.1097/CCM.0000000000001569

55. Anan M, Nagai Y, Fudaba H, Fujiki M. Lactate and Lactate Dehydrogenase in Cistern as Biomarkers of Early Brain Injury and Delayed Cerebral Ischemia of Subarachnoid Hemorrhage. *J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc*. 2020;29(5):104765. doi:10.1016/j.jstrokecerebrovasdis.2020.104765

56. El Hayek L, Khalifeh M, Zibara V, et al. Lactate Mediates the Effects of Exercise on Learning and Memory through SIRT1-Dependent Activation of Hippocampal Brain-Derived Neurotrophic Factor (BDNF). *J Neurosci Off J Soc Neurosci*. 2019;39(13):2369-2382. doi:10.1523/JNEUROSCI.1661-18.2019

57. Guru PK, Seelhammer TG, Singh TD, et al. Outcomes of adult patients supported by extracorporeal membrane oxygenation (ECMO) following cardiopulmonary arrest. The Mayo Clinic experience. *J Card Surg*. 2021;36(10):3528-3539. doi:10.1111/jocs.15804

58. Haneya A, Philipp A, Diez C, et al. A 5-year experience with cardiopulmonary resuscitation using extracorporeal life support in non-postcardiotomy patients with cardiac arrest. *Resuscitation*. 2012;83(11):1331-1337. doi:10.1016/j.resuscitation.2012.07.009

59. Sakamoto S, Taniguchi N, Nakajima S, Takahashi A. Extracorporeal life support for cardiogenic shock or cardiac arrest due to acute coronary syndrome. *Ann Thorac Surg*. 2012;94(1):1-7. doi:10.1016/j.athoracsur.2012.01.032

국문 요약

체외막형 산화기는 심정지와 같은 치명적인 상태에 처한 환자들이 사망하지 않고 생존할 수 있게 해주는 치료 수단으로 이를 사용하는 심폐소생술이 증가하고 있다. 체외막형 산화기를 사용한 환자들 중에 신경학적 합병증이 발생하는 비율이 높은 편이다. Neuron specific enolase (NSE)는 체외막형 산화기 치료를 받는 환자들의 신경학적 예후를 예측하는 인자로 사용되어져 왔다. 이 연구는 신경학적 예후를 정확하게 예측할 수 있는 NSE 의 측정 시기와 절사값을 구하고자 한다.

본 연구는 2018 년 1 월부터 2021 년 12 월까지 체외막형 산화기를 사용한 심폐소생술을 시행한 47 명의 환자를 대상으로 이루어졌다. 체외막형 산화기를 삽입하고 24, 48, 72 시간 후에 NSE 의 농도를 측정하였다. 입원기간 동안 시행한 Cerebral Performance Category(CPC) 점수에 따라 신경학적 예후가 좋은 군(CPC 1-2 점)과 예후가 좋지 않은 군(CPC3-5)으로 나누어 분석하였다. 또한 30 일 이내 사망 여부를 확인하여 생존군, 사망군으로도 환자를 분류하였다.

환자들의 평균 연령은 57.9 세이고 남성이 74.5%를 차지하였다. 신경학적 예후가 좋지 않은 환자군은 46.8%였고 30 일 이내 사망한 환자군은 45.6%였다. 신경학적 예후를 가장 잘 예측하는 NSE 의 측정 시점은 체외막형 산화기 삽입후 72 시간이었고 절사점은 61.9 μg/L 였다. 30 일 이내 사망 여부를 가장 잘 예측하는 NSE 의 측정 시점 또한 체외막형 산화기 삽입후 72 시간이었고 절사점은 62.1 μg/L 였다.

체외막형 산화기의 삽입후 신경학적 합병증은 약 40%까지 발생한다는 연구가 있다. 이러한 합병증을 미리 예측할 수 있는 인자로 NSE 가 사용될 수 있고 체외막형 산화기 치료 72 시간 시점에 시행한 검사값을 통해 불량한 신경학적 예후와 사망률을 예측할 수 있다고 여겨진다.