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Clinical paper

The usefulness of neuron-specific enolase in cerebrospinal fluid to predict neurological prognosis in cardiac arrest survivors who underwent target temperature management: A prospective observational study

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Abstract

Aim: Cerebrospinal fluid (CSF) neuron-specific enolase (NSE) levels increase ahead of serum NSE levels in patients with severe brain injury. We examined the prognostic performance between CSF NSE and serum NSE levels in out-of-cardiac arrest (OHCA) survivors who had undergone target temperature management (TTM).

Methods: This single-centre prospective observational study included OHCA patients who had undergone TTM. NSE levels were assessed in blood and CSF samples obtained immediately (Day 0), and at 24 h (Day 1), 48 h (Day 2), and 72 h (Day 3) after return of spontaneous circulation (ROSC). The primary outcome was the 6-month neurological outcome.

Results: We enrolled 34 patients (males, 24; 70.6%), and 16 (47.1%) had a poor neurologic outcome. CSF NSE and serum NSE values were significantly higher in the poor outcome group compared to the good outcome group at each time point, except for serum Day 0. CSF NSE and serum NSE had an area under curve (AUC) of 0.819–0.972 and 0.648–0.920, respectively. CSF NSE prognostic performances were significantly higher than serum NSE levels at Day 1 and showed excellent AUC values (0.969; 95% confidence interval [CI] 0.844–0.999) and high sensitivity (93.8%; 95% CI 69.8–99.8) at 100% specificity.

Conclusion: We found CSF NSE values were highly predictive and sensitive markers of 6-month poor neurological outcome in OHCA survivors treated with TTM at Day 1 after ROSC. Therefore, CSF NSE levels at day 1 after ROSC can be a useful early prognosticator in OHCA survivors.

Keywords: Cardiac arrest, Prognosis, Neuron-specific enolase, Cerebrospinal fluid

Abbreviations: AUC, areas under the curve; BBB, blood–brain barrier; CA, cardiac arrest; CI, confidence interval; CNUH, Chungnam National University Hospital; CPC, cerebral performance category; CSF, cerebrospinal fluid; IQR, interquartile range; OHCA, out-of-hospital cardiac arrest; CT, computed tomography; LP, lumbar puncture; NSE, neuron-specific enolase; ROC, receiver operating characteristic; ROSC, return of spontaneous circulation; TTM, time temperature management; WLST, withdrawal of life-sustaining therapy.

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Introduction

Despite advances in post-cardiac arrest (CA) care, 50%–89% of OHCA patients die in hospital after the return of spontaneous circulation (ROSC), and 18% of survivors have been reported to have moderate to severe functional impairment at hospital discharge.[1–3] The most common cause of death in OHCA patients with ROSC in hospitals has been reported to be withdrawal of life-sustaining therapy (WLST) for patients with perceived poor neurological prognosis, of whom 26% might have survived if life-sustaining therapy had not been interrupted and, of these, 64% might have had a functionally favourable survival.[2,4] The current international guidelines recommend that WLST be determined at least 72 h post-ROSC[5–7] as, prior to 72 h, it is difficult to accurately distinguish patients with recoverable or irreversible injuries. Despite this recommendation, for reasons such as medical, economic, and social opportunity costs in relation to intensive care unit admission and the possibility of survival with severe brain injury, WLST prior to 72 h has been reported to be common.[8,9] Therefore, it is necessary to develop a tool that can accurately predict neurological outcomes earlier concerning comatose OHCA survivors.

To date, among available predictive tools, biomarkers such as neuron-specific enolase (NSE) have been widely used for patients after OHCA because there is no inter-observer variability and the results are easy to interpret.[10–16]

The Target Temperature Management after Cardiac Arrest (TTM) trial showed that serial NSE values were strong predictors of poor outcome after OHCA.[13] The TTM trial also suggested that the best time point for serum NSE determination was 48 h or 72 h, and that the 24 h time point was too early to predict reliable outcomes.[13] However, a number of previously published studies[17–21] have reported that NSE is released from damaged neuron cells into the cerebrospinal fluid (CSF), and then released into the systemic circulation due to blood–brain barrier (BBB) disruption.[18–20] In our previous study, we reported that the BBB began to be disrupted in the first 24 h after ROSC in patients with poor neurologic outcome.[22,23] Therefore, the CSF NSE level can be useful to predict neurologic outcome in cardiac arrest survivors even in the early hours before BBB disruption.[24]

We hypothesised that the NSE levels measured in the CSF would change earlier with higher sensitivity than NSE levels measured in the serum. Therefore, we aimed to investigate the prognostic performance between serum NSE and CSF NSE for 6-month neurologic outcome in OHCA survivors who had undergone TTM.

Methods

Study design and population

This was a prospective single-centre observational cohort study of adult comatose OHCA survivors treated with TTM at Chungnam National University Hospital, a 1365-bed tertiary care referral centre, in Daejeon, Korea, from December 2017 to November 2018. This study was approved by the Institutional Review Board of Chungnam National University Hospital (CNUH-2017-10-027). The inclusion criteria comprised OHCA patients >18 years old who had been treated using TTM. The exclusion criteria for this study comprised the following: patients who had experienced a traumatic CA; patients ineligible for lumbar puncture (LP) (i.e., brain computed tomography [CT] showed severe cerebral oedema, obliteration of the basal cisterns, or an occult intracranial mass lesion); patients receiving extracorporeal membrane oxygenation; responsible relatives from the patient's family unable to consent to an LP, and; the provision of further patient treatment declined by the next of kin.

TTM protocol

Comatose OHCA survivors were treated according to our previously published TTM protocols,[25] which were implemented as soon as possible after a patient's arrival to the emergency department or after ROSC.

TTM was applied using cooling devices (Arctic Sun® Energy Transfer Pads TM, Bard Medical, Louisville, CO, USA). A target temperature of 33 °C or 36 °C was maintained for 24 h, with rewarming to 37 °C at a rate of 0.25 °C/h, and monitored using a bladder temperature probe. Sedatives and a neuromuscular blocking agent were used during TTM. We used ADMS™ (Anaesthetic Depth Monitor for Sedation, Unimedics CO., LTD., Seoul, Korea) to monitor anaesthesia depth. All other aspects of patient management involved standard intensive care in accordance with our institutional intensive care unit protocol. Patients with intracranial haemorrhage, active bleeding, known terminal illness, or a poor pre-arrest neurologic status (cerebral performance category [CPC] scale ≥4) were not eligible for TTM.

Data collection and the primary outcome

The following data were recorded: age, sex, first monitored rhythm, aetiology of CA, presence of a witness on collapse, bystander cardiopulmonary resuscitation (CPR), time from collapse to CPR (no-flow time), time from CPR to ROSC (low-flow time), time from ROSC to LP (LP time), serum and CSF NSE levels immediately (Day 0), and at 24 h (Day 1), 48 h (Day 2), and Day Max, and neurologic outcome at 6 months after ROSC. The highest NSE level among four NSE levels in each patients was defined as Day Max. WLST during TTM can be performed only for patients who are pronounced brain dead, according to legal requirements. We measured neurological outcomes 6 months after ROSC using the Glasgow Pittsburgh CPC scale, either through face-to-face interviews or structured telephone interviews (Supplemental Fig. S1).[26] Phone interviews were undertaken by an emergency physician who was fully informed of the protocol and blinded to the patient's prognosis and NSE levels. The CPC score classifies patients into 5 categories: CPC 1 (good performance), CPC 2 (moderate disability), CPC 3 (severe disability), CPC 4 (vegetative state), or CPC 5 (brain death or death). The primary outcome was a poor neurological outcome, defined as from CPC 3 to CPC 5.

The patients' neurologic status was obtained by assessing the hospital records or directly calling the patient's caregiver.

Obtaining CSF and serum samples

A CSF sample was obtained via lumbar catheter drainage. Lumbar catheter insertion was performed with hips and knees flexed, with the patient lying in the lateral decubitus position using the Hermetic™ lumbar catheter accessory kit (Integra Neurosciences, Plainsboro, NJ, USA). A serum blood sample was obtained via venepuncture. CSF and serum samples were taken from patients immediately (Day 0), then at Day 1, Day 2, and Day 3 (72 h) after ROSC.

NSE analysis

All samples were analysed by Green Cross Laboratories (GC Labs) (Yongin, Geonggi-do, Korea) at the same laboratory, and aliquots grossly contaminated with blood or haemolysed were discarded. NSE levels were determined using an electro-chemi-luminescence immunoassay kit (COBAS® e801, Roche Diagnostics, Rotkreuz, Switzerland). The measurement range was from 0.1 to 300 ng/ml (normal values, <16.3 ng/ml). At GC Labs, the between-run precision at concentrations of 12.39 and 96.16 ng/ml was 1.74% and 1.66%, respectively.

Sample size

Based on previous studies[21] that have reported CSF NSE levels of 17 ± 6.7 ng/ml in patients with good outcomes and 147 ± 171 ng/ml in patients with poor outcomes, 32 patients were required to achieve a power of 0.80 at a significance level of 0.05 (two-sided test). The sample size was calculated using MedCalc version 15.2.2 (MedCalc Software, Mariakerke, Belgium).

Statistical analysis

Categorical variables were presented as frequencies and percentages. Continuous variables were presented as median with interquartile range (IQR) values. We used the Mann–Whitney test to compare NSE levels between neurological outcome groups. At each time point, receiver operating characteristic (ROC) curves were plotted and corresponding areas under the curve (AUC) were determined to evaluate the predictive performance of CSF and serum NSE levels on poor neurological outcome (CPC 3–5). The cut-off value for predicting poor neurological outcomes after 6 months post–OHCA was determined using the Youden index. Subsequently, to determine differences in prognostic performance between Day 0, Day 1, Day 2, and Day 3 and poor neurological outcome, we used the Delong test. Data were analysed using SPSS for Windows, version 21 (IBM Corp., NY, NY, USA). The ROC curves were calculated using MedCalc version 15.2.2 (MedCalc Software, Mariakerke, Belgium). Results were considered significant at $p < 0.05$.

Results

Patient characteristics

A total of 41 adult comatose OHCA survivors were treated with TTM during the study period. Of these, 34 patients were enrolled in the present study, as shown in Fig. 1. At 6 months after ROSC, 18 (52.9%) patients were assessed as being in the good outcome group and 16 (47.1%) were assessed as being in the poor outcome group. The demographic and CA characteristics, stratified according to neurological outcome at 6 months, are shown in Table 1. Patients with good neurological outcome had a higher incidence of bystander CPR, were more likely to have a shockable rhythm and a cardiac aetiology, and had a shorter no- and low-flow time.

Serial comparison of CSF and serum NSE levels between good and poor outcome groups

The CSF NSE values between good and poor neurologic outcome groups were 19.9 ng/ml (11.4–37.4) versus 49.0 ng/ml (24.1–105.1 ng/ml) ($p = 0.001$); 23.0 ng/ml (12.4–60.1 ng/ml) versus 300.0 ng/ml (258.0–300.0 ng/ml) ($p < 0.001$); 21.5 ng/ml (11.2–44.7 ng/ml) versus 300.0 ng/ml (300.0–300.0 ng/ml) ($p < 0.001$); 18.7 ng/ml (12.0–44.7 ng/ml) versus 300.0 ng/ml (300.0–300.0 ng/ml) ($p < 0.001$), and; 26.7 ng/ml (17.3–103.5 ng/ml) versus 300.0 ng/ml (300.0–300.0 ng/ml) ($p < 0.001$) at Day 0, Day 1, Day 2, Day 3, and Day Max, respectively.

Serum NSE values between good and poor neurologic outcome groups were 25.8 ng/ml (20.5–34.9) versus 33.1 ng/ml (23.0–60.2 ng/ml) ($p = 0.15$); 25.7 ng/ml (20.0–34.2 ng/ml) versus 87.7 ng/ml (26.9–300.0 ng/ml) ($p = 0.008$); 22.2 ng/ml (16.3–24.6 ng/ml) versus 152.5 ng/ml (56.0–300.0 ng/ml) ($p < 0.001$); 18.3 ng/ml (13.9–20.7 ng/ml) versus 212.0 ng/ml (37.3–294.5 ng/ml) ($p < 0.001$), and; 29.8 ng/ml (23.1–48.4 ng/ml) versus 213.5 ng/ml (78.0–300.0 ng/ml) ($p < 0.001$) at Day 0, Day 1, Day 2, Day 3, and Day-Max, respectively.

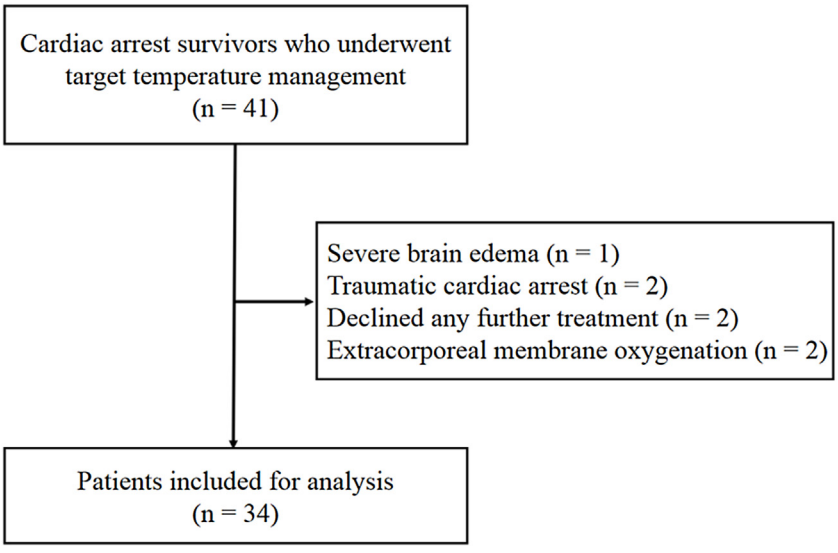

Fig. 1 – Schematic diagram showing the number of patients included in the study.

Table 1 – Baseline demographics and clinical characteristics.

	Cohort, (N = 34)	Good outcome, (N = 18)	Poor outcome, (N = 16)	p
Demographics				
Age, years	46.5 (36.8–58.3)	45.5 (36.8–63.8)	51.5 (37.3–57.8)	0.66
Sex, male, N (%)	24 (70.6)	15 (83.3)	7 (43.8)	0.13
Charlson Comorbidity Index score, median (IQR)	1.0 (0.0–3.0)	0.5 (0.0–4.0)	1.0 (0.0–2.5)	0.95
Witness arrest, N (%)	23 (67.6)	14 (77.8)	9 (56.3)	0.27
Bystander CPR, N (%)	26 (76.5)	17 (94.4)	9 (56.3)	0.01
Shockable rhythm, N (%)	12 (35.3)	11 (61.1)	1 (6.3)	0.001
Cardiac aetiology, N (%)	11 (32.4)	9 (50.0)	3 (12.5)	0.03
No flow time, min (IQR)	1.5 (0.0–12.3)	0.5 (0.0–5.0)	5.0 (0.3–20.8)	0.06
Low flow time, min (IQR)	16.5 (8.0–30.0)	8.5 (4.8–20.0)	27.0 (15.0–41.3)	0.001
LP time, min (IQR)	270.0 (235.8–372.6)	245.5 (200.0–446.8)	285.0 (252.0–328.3)	0.42

IQR, Interquartile range; CPR, Cardiopulmonary resuscitation; LP, Lumbar puncture.

CSF NSE and serum NSE values were significantly higher in the poor outcome group compared to the good outcome group at each time point, except for serum Day 0 (Fig. 2).

Prognostic performance using CSF NSE versus serum NSE

The capacity of NSE to predict poor neurological outcome (CPC 3–5) at 6 months was determined using ROC analysis. Fig. 3 shows the comparisons of the AUC between serum and CSF NSE at each time point. The AUC of CSF NSE at Day 0 (p = 0.08) and Day 1 (p = 0.02) were significantly higher than those of serum NSE (Fig. 3).

CSF NSE showed similarly high AUC values from Day 1 to Day 3. During this time, the specificity for poor outcome was equally 100% (95% CI 81.5–100.0), with 93.8% sensitivity (95% CI 69.8–99.8). The cut-off values were 99.9 ng/ml, 136.0 ng/ml, and 84.2 ng/ml, respectively (Table 2, Fig. 3).

Discussion

In this prospective observational study, NSE levels in both CSF and serum were significantly higher in the poor outcome group than the good outcome group at each time point, except serum NSE at Day 0. CSF NSE prognostic performances were significantly higher than serum NSE at Day 1 and showed excellent AUC values and high sensitivity at 100% specificity.

The international guidelines for post-OHCA care suggest various methods to predict the prognosis for OHCA survivors.[27] These methods include clinical examinations such as light reflex testing; neuroimaging such as brain CT, magnetic resonance imaging, or electroencephalography; or biomarkers such as NSE. These guidelines suggest using a multimodal prognostication rather than a single modality for poor neurologic outcome prediction because single modalities have a low sensitivity with a false positive rate of 0 and the narrowest confidence interval. In addition, biomarkers such as NSE have many limitations in predicting prognosis. The main reasons for the observed variability in NSE thresholds include the use of heterogenous measurement techniques,[28–30] the presence of extra-neuronal sources of biomarkers such as haemolysis and neuro-endocrine tumors,[24,31] and incomplete knowledge of the kinetics of blood concentrations in the first few days after ROSC.[31] However, recent studies[12,13] have shown that the prognostic performance of NSE has improved considerably compared to earlier studies.[32–34]

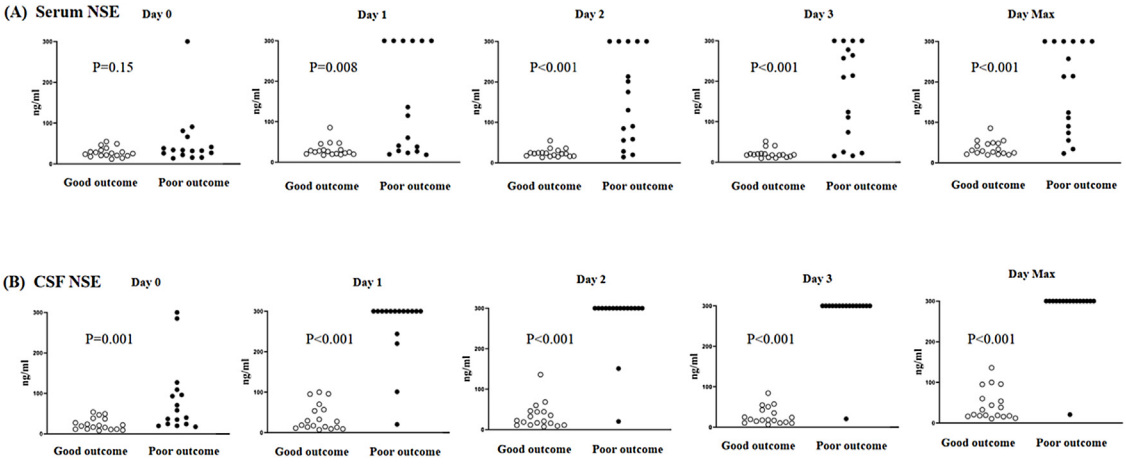

Fig. 2 – Neuron-specific enolase (NSE) levels measured on individual days. (A) Serum NSE values on individual days are shown on panel (B) CSF NSE values on individual days are shown on panel. The NSE levels were significantly higher in the poor outcome group compared to the good outcome group at each day point, except for serum day 0. CSF, cerebrospinal fluid.

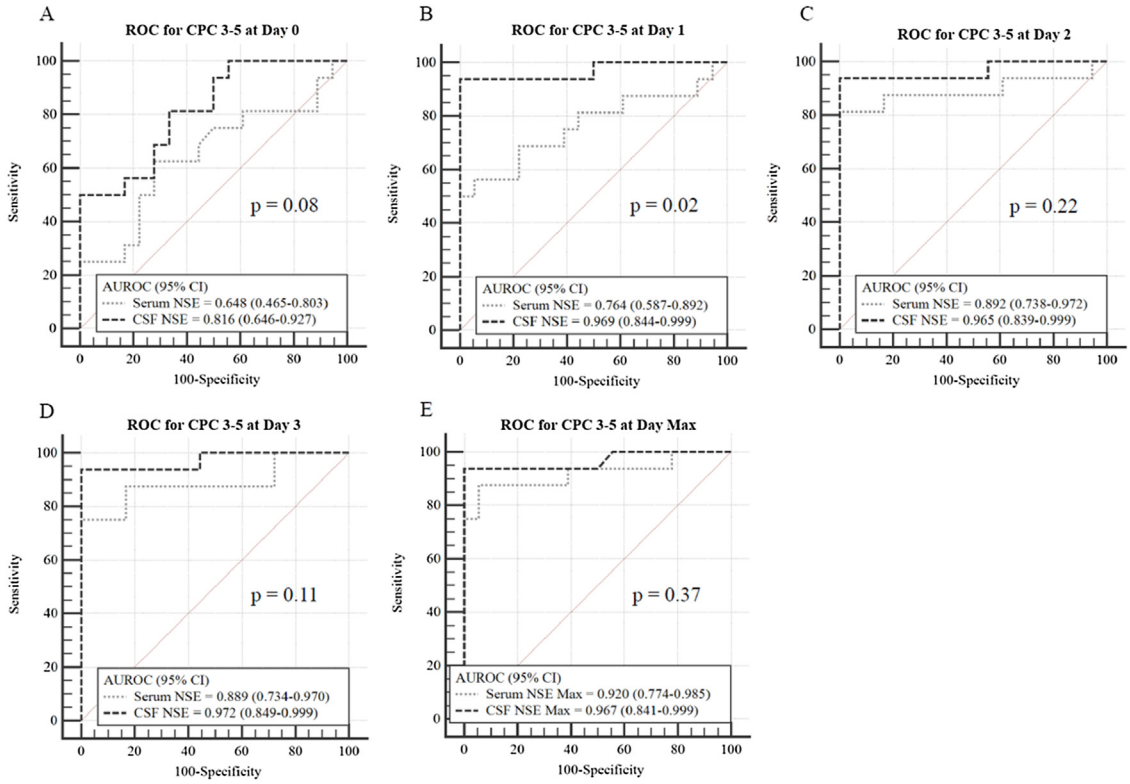

Fig. 3 – Area under the curves (AUC) for predicting poor neurological outcome at 6 months post-OHCA between CSF NSE and serum NSE. (A) ROC curve for NSE values at Day 0 is shown on panel. (B) ROC curve for NSE values at Day 1 is shown on panel (C) ROC curve for NSE values at Day 2 is shown on panel (D) ROC curve for NSE values at Day 3 is shown on panel (E) ROC curve for NSE values at Day Max is shown on panel.
CSF, cerebrospinal fluid; OHCA, out-of-hospital cardiac arrest; NSE, neuron-specific enolase; ROC, receiver operating characteristic.

Table 2 – Association of neuron-specific enolase with poor neurological outcome.

	Time	AUROC (95% CI)	p Value	Cut-off	Sensitivity (95% CI)	Specificity (95%CI)	PPV/NPV
Serum	Day 0	0.648 (0.465–0.803)	0.14	29.5	62.5 (35.4–84.8)	72.2 (46.5–90.3)	66.7/68.4
	Day 1	0.764 (0.587–0.892)	0.003	48.1	56.3 (29.9–80.2)	94.4 (72.7–99.9)	90.0/70.8
	Day 2	0.892 (0.738–0.972)	<0.001	54.6	81.3 (54.4–96.0)	100.0 (81.5–100.0)	100.0/85.7
	Day 3	0.889 (0.734–0.970)	<0.001	51.6	75.0 (47.6–92.7)	100.0 (81.5–100.0)	100.0/81.8
	Max	0.920 (0.774–0.985)	<0.001	54.8	87.5 (61.7–98.4)	94.4 (72.7–99.9)	93.3/89.5
CSF	Day 0	0.816 (0.646–0.927)	<0.001	53.7	50.0 (24.7–75.3)	100.0 (81.5–100.0)	100.0/69.2
	Day 1	0.969 (0.844–0.999)	<0.001	99.9	93.8 (69.8–99.8)	100.0 (81.5-100.0)	100.0/94.7
	Day 2	0.965 (0.839–0.999)	<0.001	136	93.8 (69.8–99.8)	100.0 (81.5–100.0)	100.0/94.7
	Day 3	0.972 (0.849–0.999)	<0.001	84.2	93.8 (69.8–99.8)	100.0 (81.5–100.0)	100.0/94.7
	Max	0.967 (0.841–0.999)	<0.001	136	93.8 (69.8–99.8)	100.0 (81.5–100.0)	100.0/94.7

AUROC, Area under the receiver-operating characteristic curve; CI, Confidence interval; PPV, positive predictive value; NPV, Negative predictive value; CSF, Cerebrospinal fluid.

The TTM trial involved the largest cohort and used serial NSE measurement for the analysis.[13] The authors found that the median serum NSE at three time points, namely, 24 h, 48 h, and 72 h after ROSC, was significantly higher in the poor outcome group than in the good outcome group, which is consistent with our results using the same methods of NSE measurement. However, in our study, the CSF NSE values were significantly higher in the poor outcome group than in the good outcome group even immediately after ROSC compared to serum NSE values. Stammet et al.[13] reported that the AUC for prognosis prediction of serum NSE at 24 h, 48 h, and 72 h after ROSC was 0.74, 0.83, and 0.86, respectively, in the 33 °C TTM trial. At 24 h, sensitivity was found to be too low to be of clinical interest compared to 48 h and 72 h. Sensitivity at 24 h, 48 h, and 72 h was 11% (95% CI, 6–16), 25% (95% CI, 18–32), and 54% (45–62), respectively, at 100% specificity. The authors suggested that serum NSE should not be considered when assessing WLST using this single test alone because the sensitivity is low, even when looking for cut-off points with a false positive rate of 0. In this study, the AUC and sensitivity for prognosis prediction of CSF NSE immediately, and at 24 h, 48 h, and 72 h after ROSC were higher than those reported in

Stammet et al.'s study. The AUC and sensitivity of CSF NSE at 24 h after ROSC were 0.969 (95% CI, 0.844–0.999) and 93.8% (95% CI, 69.8–99.8), respectively, with 100% specificity and a cut-off value at 99.9 ng/ml. Moseby-Knappe et al.[35] recently showed that, when comparing neurofilament light chain (NFL) test results with the serum biomarkers NSE, S100, and tau, the NFL level was the only marker that predicted poor outcome with high performance at 24 h after ROSC, and the NFL level remained superior to the other biomarkers at 48 h and 72 h. The AUC and sensitivity of serum NFL for 24 h after ROSC were 0.94 (95% CI, 0.92–0.96) and 0.53 (95% CI, 41–64), respectively, with 100% specificity. However, our results indicated that CSF NSE is superior to serum NFL. It appears that CSF NSE may provide the quickest predictive performance with the highest sensitivity compared to other serum biomarkers. There are several possible reasons for this apparently superior performance. First, the CSF NSE level is less sensitive to haemolysis than serum NSE. Second, NSE is confined solely to neurons under normal conditions, and present only in negligible amounts in peripheral blood.[36] However, when the BBB is disrupted, NSE leaks from the CSF into the systemic circulation.[18–20,36] Our previous study found that severe BBB disruption with Qa >0.02 occurred in a poor outcome group treated with TTM at 24 h after ROSC.[22] Third, the molecular weight of NSE is 78 kDa, which is larger than albumin 67 kDa. Therefore, the serum NSE level obtained early before BBB disruption is not useful for predicting poor outcomes for OHCA survivors. However, the CSF NSE value was useful regardless of BBB disruption, and was able to provide a pure value because it was measurable before mixing with peripheral blood.

This study had several limitations. First, this was a single-centre prospective study with a small number of patients; therefore, a multicentre study is required to enhance the generalisability of the findings. However, compared to other similar investigations, no studies with larger patient numbers were found.

Second, in this study, the possibility of bias for predicting a poor outcome could not be excluded because the results of the NSE values were available to the treating physicians. However, WLST is not permitted unless the patient is pronounced brain-dead in Korea. In this study, none of the patients underwent WLST during the TTM; however, after completion of the TTM, 6 patients were diagnosed with brain death, and their organs were donated. Third, of 48 patients achieving ROSC during the study, 7 (14.6%) were excluded because TTM had not been undertaken. This might have caused selection bias and could limit the generalisability of our findings. Fourth, before analysing samples, we did not assess the objective haemolytic index, such as the Roche haemolysis index. However, we mitigated the risk for haemolysis through immediate sample processing, and aliquots grossly contaminated with blood or haemolysed were discarded. Moreover, CSF is less likely to haemolyse than serum, so the haemolysis effect was likely to be limited. However, we cannot exclude the possibility that the NSE levels were affected through haemolysis. Fifth, the maximum measurement range was 300 ng/ml. Samples with values above the measurement range were not diluted and analysed. Therefore, the CSF NSE of the poor outcome group showed a maximum value from Day 1, so a precisely accurate trend from Day 1 to Day 3 could not be predicted. However, the maximum value of the CSF NSE in the good outcome group was 136 ng/ml on Day 2, which was not difficult to differentiate from the poor outcome group. Last, at the 6-month evaluation, we only measured the CPC score rather than perform an analysis of health-related quality of life.

Conclusion

CSF NSE values were shown to have early, high predictive, and high sensitivity values for predicting poor neurological outcome in comatose OHCA survivors treated with TTM. These values showed better performance that other serum biochemical markers such as NSE. A large sample, multi-centre study is warranted to identify the exact association between CSF NSE values and neurological outcomes.

Conflicts of interest statement

All authors declare no conflicts of interest.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.09.027.

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