Neuron-specific enolase concentrations for the prediction of poor prognosis of comatose patients after out-of-hospital cardiac arrest: an observational cohort study

Robert Ryczek[1], Przemysław J Kwasiborski[2], Jolanta Dymus[3], Agata Galas[1], Anna Kaźmierczak-Dziuk[1],
Anna M Karasek[1], Marta Mielniczuk[1], Małgorzata Buksińska-Lisik[2], Paweł Krzesiński[1]

[1]Department of Cardiology and Internal Diseases, Military Institute of Medicine, Warszawa, Poland
[2]3rd Department of Internal Diseases and Cardiology, Second Faculty of Medicine, Medical University of Warsaw, Warszawa, Poland
[3]Department of Laboratory Diagnostics, Military Institute of Medicine, Warszawa, Poland

Correspondence to:
Robert Ryczek, MD, PhD,
Department of Cardiology
and Internal Diseases,
Military Institute
of Medicine,
Szaserów 128, 01–141
Warszawa, Poland
phone: +48 261 816 372,
+48 691 380 560,
email: rryczek@wim.mil.pl

ABSTRACT

Background: Neuron-specific enolase (NSE) is a biomarker for neurological outcomes after cardiac arrest with the most evidence collected thus far; however, recommended prognostic cutoff values are lacking owing to the discrepancies in the published data.

Aims: The aim of the study was to establish NSE cutoff values for prognostication in the environment of a cardiac intensive care unit following out-of-hospital cardiac arrest (OHCA).

Methods: A consecutive series of 82 patients admitted after OHCA were enrolled. Blood samples for the measurement of NSE levels were collected at admission and after 1 hour, 3, 12, 24, 48, and 72 hours. Neurological outcomes were quantified using the cerebral performance category (CPC) index. Each patient was classified into either the good (CPC ≤2) or poor prognosis (CPC ≥3) group.

Results: Median NSE concentrations were higher in the poor prognosis group, and the difference reached statistical significance at 48 and 74 hours (84.4 ng/ml vs 22.9 ng/ml at 48 hours and 152.1 ng/ml vs 18.7 ng/ml at 72 hours; P <0.001, respectively). Moreover, in the poor prognosis group, NSE increased significantly between 24 and 72 hours (P <0.001). NSE cutoffs for the prediction of poor prognosis after OHCA were 39.8 ng/ml, 78.7 ng/ml, and 46.2 ng/ml for 24, 48, and 72 hours, respectively. The areas under the curve were significant at each time point, with the highest values at 48 and 72 hours after admission (0.849 and 0.964, respectively).

Conclusions: Elevated NSE concentrations with a rise in levels in serial measurements may be utilized in the prognostication algorithm after OHCA.

Key words: biomarkers of brain injury, hypoxic brain injury, ischemic encephalopathy, neurologic prognostication, neuron-specific enolase

INTRODUCTION

Cardiac arrest is one of the leading causes of death in high-income countries. Only one-third of out-of-hospital cardiac arrest (OHCA) patients, who have reached emergency medical services, survive until hospital admission [1]. Mortality rates for those admitted comatose to hospitals after (OHCA) remain high depending on the mechanism of cardiac arrest and quality of care and usually exceed 50% [2, 3]. Most deaths are caused by ischemic brain injury [4], and therefore, adequate neurological prognostication is an important part of the therapeutic process. Establishing a poor prognosis allows medical personnel to avoid inappropriate treatment, justify the withdrawal of life-sustaining therapy, and provide important information to the patients' families. Clinical examination and brain computed tomography (CT) are commonly used for this purpose; however, both lack appropriate diagnostic accuracy, especially at an early stage of hospitalization. Given that the gravity of decisions in this medical context is extremely high and to minimize the possibility of false-positive results (FPR), it is a commonly accepted strategy to use a multimodal prognostic

WHAT'S NEW?

Determining the concentrations of neuron-specific enolase (NSE) in patients admitted to the hospital following cardiac arrest is a method to assess the neurological prognosis of such patients. Since 2015, the European Resuscitation Council has recommended the use of NSE levels as a component in a multimodal prognostication algorithm for this group of patients. The main limitation of NSE levels, as reported by several authors, is the discrepancies in the cutoff thresholds for a poor prognosis. Therefore, the European Resuscitation Council recommends that such thresholds be set by local laboratories. To our knowledge, this study is the first to assess the use of NSE concentrations for the prognosis of patients following cardiac arrest at a Polish hospital. Setting cutoff values for poor prognosis of cardiac arrest patients may promote the application of this prognostic tool in Polish intensive care units, especially in centers cooperating with laboratories that can assess NSE levels.

algorithm for that purpose. Such algorithm includes the results of the neurological assessment and brain CT, but also short-latency somatosensory evoked potentials, electroencephalography, and biomarkers for brain injury [5].

Next to the glial S-100B protein, neuron-specific enolase (NSE) is the biomarker in ischemic brain injury that is most supported by the clinical evidence collected so far. NSE is an intracellular glycolytic enzyme that is mostly present in neurons, tissues of neuroectodermal origin, and erythrocytes. Following cardiac arrest, NSE is released from ischemic brain tissue, and its serum concentrations correlate with the extent of neurological injury. Many authors have proven that high NSE concentrations after cardiac arrest and its rise in serial measurements may predict poor neurologic outcomes. However, NSE concentration cutoff thresholds vary between studies, ranging from 33 ng/ml to 85 ng/ml for different time points, with the most discriminative being from 48 hours to 72 hours post-OHCA [5, 6].

The European Resuscitation Council (ERC) recommends incorporating NSE levels into a multimodal prognostication strategy algorithm, but at the same time, they advise that each laboratory establish its own values and cutoff levels for poor prognoses based on the assay used [7].

We intended to address these recommendations and for this purpose, we conduct the current study. Our aim was to define NSE cutoff values, at a few time points within the first 72 hours after admission, that have a high specificity for a poor prognosis prediction after cardiac arrest in settings specific to our center.

METHODS

Patient recruitment took place in the Cardiac Intensive Care Unit of the Military Institute of Medicine, Warsaw, Poland, between September 2016 and July 2019. The study had an observational, prospective design in the cohort of consecutive patients admitted after OHCA who remained unconscious at first presentation with a Glasgow Coma Scale score ≤8. In addition to standard care, blood samples for evaluation of NSE levels were collected at the time of admission and then after 1 hour, 3, 6, 24, 48, and 72 hours.

This study was approved by the Ethics Committee of the Military Institute of Medicine (no. 39/WIM/2013). Informed consent was obtained from relatives and all participants who regained consciousness.

Blood samples for the measurement of NSE levels were analyzed in a local laboratory using the Cobas e601 system and an electrochemiluminescence immunoassay (ECLIA) kit (Roche Diagnostics, Mannheim, Germany; reference number 12133113 122). The normal value for NSE concentration was <17 ng/ml, functional sensitivity was 0.25 ng/ml, and the range of measurements was 0.05–370 ng/ml.

A neurologist evaluated all patients 72 hours (standard deviation 24 h) after admission and at discharge. Each participant was classified using the cerebral performance category (CPC) scale: CPC 1, good cerebral performance; CPC 2, minor neurological deficit; CPC 3, severe neurological impairment and dependence for everyday activities; CPC 4, coma; and CPC 5, brain death [8]. Clinical outcomes were evaluated at discharge using the CPC classification. CPC 1–2 were considered as good clinical outcomes, and CPC 3–5, including death, were considered as poor clinical outcomes.

Statistical analysis

Data distributions were analyzed for each continuous variable. Non-Gaussian variables were presented as medians with an interquartile range. Comparison of the patients' clinical characteristics was conducted using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. Changes in NSE concentrations over time and between CPC groups were tested for significance using the Friedman rank test, nonparametric variant of ANOVA test with post hoc analysis. Bonferroni correction was applied to address the multiple comparisons issue. At each time point, a receiver operating characteristic curve was plotted, and the area under the curve was determined to evaluate the predictive power of NSE concentrations on CPC. Cutoff values were determined by maximizing the Youden index and using values providing 95% specificity. Sensitivity and specificity values were corrected using bootstrap internal validation. When possible, a normal approximation was used to obtain confidence intervals. Survival analyses and Kaplan–Meier curves were calculated for the four 4-quartiles of NSE concentrations and generalized log-rank test was used to compare the

Table 1. Basic demographic and selected clinical data for the cerebral performance category 1–2 and cerebral performance category 3–5 patient groups admitted after out-of-hospital cardiac arrest

	CPC 1–2 (n = 22)	CPC 3–5 (n = 60)	*P* value
Male	15 (68.2)	41 (68.3)	0.98
Age, years, median (IQR)	60 (45–70)	67 (62–76.5)	0.008
Time to CPR, min, median (IQR)	0 (0–0)	5 (0–10)	<0.001
Time to ROSC, min, median (IQR)	15 (10–25)	28 (19–45)	<0.001
Bystander CPR	20 (90.9)	31 (51.7)	0.002
Shockable rhythm	20 (90.9)	34 (56.7)	0.004
Lactate, mmol/l, median (IQR)	3.3 (2.8–5.1)	7.6 (4.6–12.25)	<0.001
Time to ROSC, min, median (IQR)	4.5 (3–6)	3 (3–3)	<0.001
SOFA, median (IQR)	8 (6–10)	12 (9–14)	<0.001
APACHE II, median (IQR)	19.5 (18–24)	29 (25–38)	<0.001
Hospitalization time, days, median (IQR)	16 (12–22)	9 (2–26)	0.09
Targeted temperature management	14 (63.6)	35 (58.3)	0.8

Data are presented as number (percentage) of patients unless otherwise indicated.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; GCS, Glasgow Coma Scale; IQR, interquartile range; ROSC, return of spontaneous circulation; SOFA, Sequential Organ Failure Assessment Score

proportion of survival with good clinical outcome in analyzed groups. A *P* value <0.05 was considered significant for all tests performed. All statistical analyses were performed using Statistica 13.0 (StatSoft, Tulsa, OK, USA).

RESULTS
Eighty-two consecutively admitted adult OHCA patients were enrolled in this study. Overall, 450 serum samples were analyzed. The patients' basic clinical and demographic characteristics are shown in Table 1. Of the 82 patients, 22 were classified into the CPC 1–2 group and 60 were placed in the CPC 3–5 group. Except for sex, hospitalization time, and frequency of targeted temperature management (TTM) utilization, most parameters differed significantly between the groups.

The median (IQR) plasma NSE concentrations for the CPC 1–2 groups vs the CPC 3–5 groups, respectively, were as follows: at admission, 22.8 ng/ml (19.7–34.4) vs 37.65 ng/ml (29.4–51.0); *P* = 0.7; at 1 hour, 28.7 ng/ml (22.6–45.7) vs 38 ng/ml (29.5–60.5); *P* = 0.9; at 3 hours, 29.2 ng/ml (21.7–37.6) vs 44.55 ng/ml (31.4–87.6); *P* = 0.6; at 12 hours, 25.4 ng/ml (21.0–32.8) vs 46.55 ng/ml (30.9–87.7); *P* = 0.1; at 24 hours, 23 ng/ml (18.7–34.5) vs 55.9 ng/ml (34.1–134.1); *P* = 0.1; at 48 hours, 22.9 ng/ml (15.1–33.5) vs 84.4 ng/ml (42.0–192.0); *P* <0.001; and at 72 hours, 18.7 ng/ml (14.1–29.0) vs 152.1 ng/ml (62.3–264.4); *P* < 0.001. In the poor prognosis group, NSE levels increased significantly between 24 and 72 hours (*P* <0.001). In the good prognosis group, the NSE levels were constant within the first 72 hours (*P* = 0.3). Both groups tended to differ significantly in terms of NSE levels starting from 48 hours after the OHCA (*P* <0.001), and at 72 hours, the difference increased (Figure 1).

Receiver operating characteristic analyses were carried out for NSE levels at each time point to predict CPC at discharge (Figure 2). The area under the curves for NSE levels in the CPC prediction were all significant, with the highest area under the curve value at 72 hours after OHCA (detailed data are shown in Supplementary material, *Table S1*). The cutoff values for NSE that maximized the Youden index, as well as those with FPR of 5% at each time point, are shown in Table 2. In the analyzed cohort the cutoff values for the concentrations of NSE calculated for a specificity of 95% (FPR <5%) at the time points during the first 24 hours had low sensitivity (14%–37%). The sensitivity of these cutoffs calculated to maximize the Youden index at the same time points was more eligible (71%–81%). The range of those cutoffs was from 27.2 ng/ml at admission to 39.8 ng/ml at 24 hours. The NSE concentration thresholds calculated for a 5% of FPR at subsequent time points had acceptable sensitivity exceeding 53%; these cutoff points were 78.7 ng/ml at 48 hours and 46.2 ng/ml at 72 hours.

The survival analysis indicated that the higher the NSE levels, the higher the probability of a poor neurological outcome. Kaplan–Meier curves (Figure 3) show that high NSE levels early after OHCA significantly increase the probability of a poor prognosis. The probability of a good prognosis would be >60% for the first NSE quartile at admission, in contrast to patients with higher NSE levels, where the probability of a good prognosis would be approximately 20% (Figure 3).

DISCUSSION
To our knowledge, this study presents the first attempt to test NSE levels as a predictor of poor clinical outcomes in comatose patients admitted to the hospital after OHCA in a Polish population. We identified the NSE cutoffs highly specific to ischemic brain damage. We also confirmed the negative prognostic value of the rise of NSE concentrations in serial measurements within the first 3 days after OHCA.

The prognostic usefulness of NSE concentrations as a neurologic outcome predictor after OHCA has been confirmed in diverse populations in the past [5] and in the era of TTM treatment [9]. Thus, based on the strongest evidence, NSE has been incorporated as a biomarker in
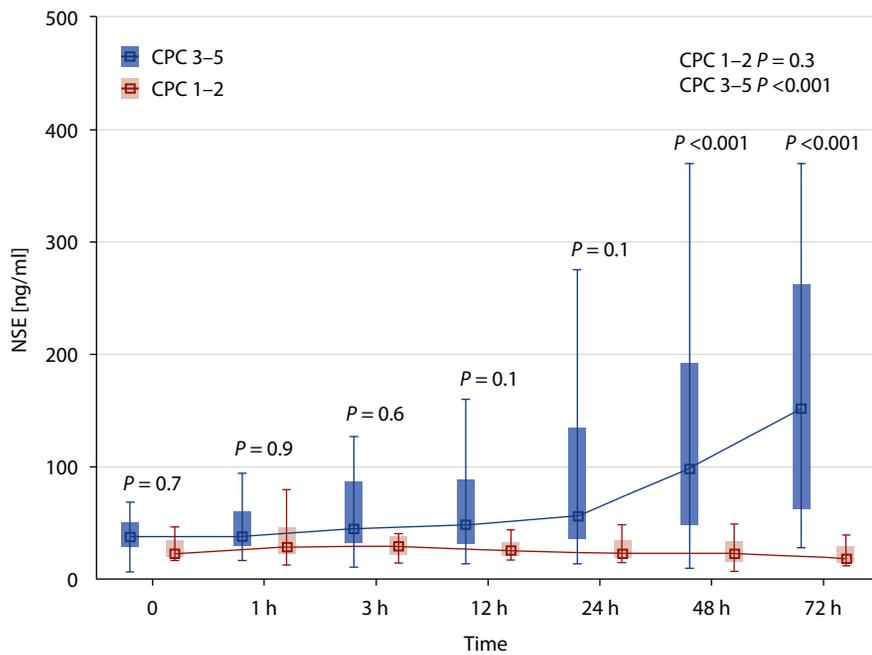
Figure 1. Neuron-specific enolase (NSE) concentrations at admission and 1, 3, 12, 24, 48, and 72 hours after admission in both groups.
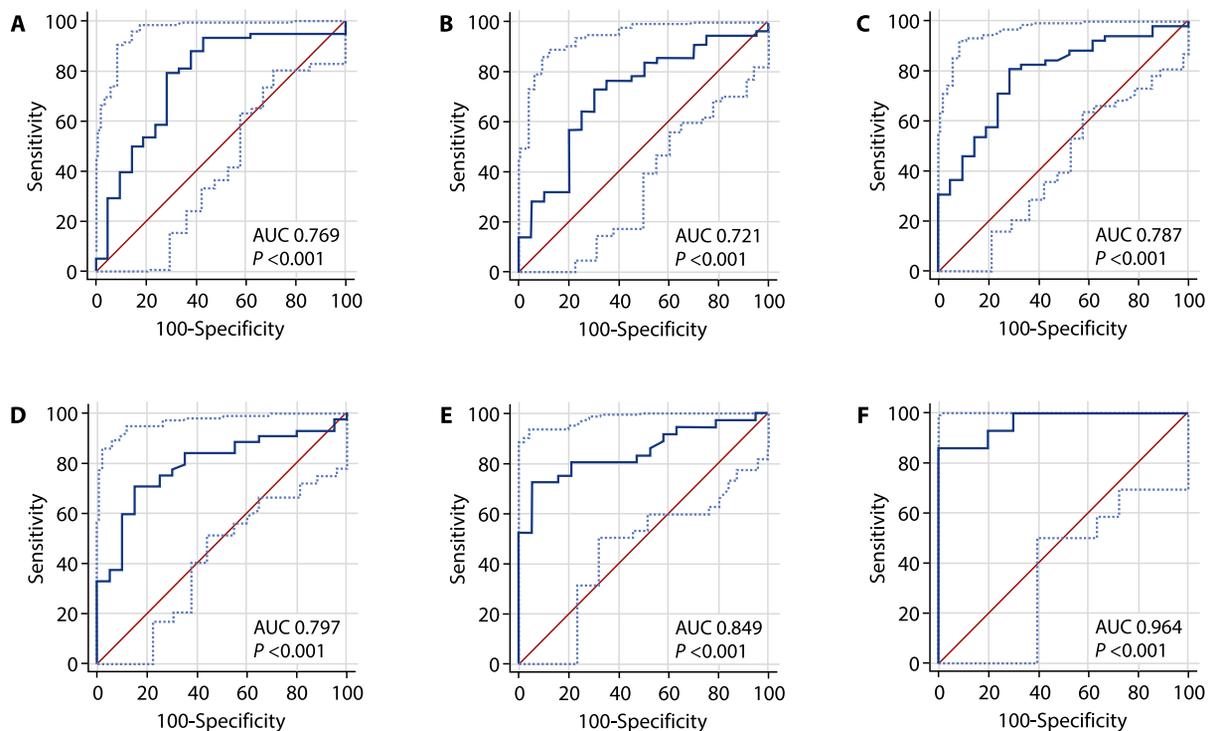Abbreviations: see Table 1

Figure 2. Receiver operating characteristic curves for the capacity of neuron-specific enolase at each time point to predict cerebral performance category at discharge. **A.** At admission; **B.** After 3 hours; **C.** After 12 hours; **D.** After 24 hours; **E.** After 48 hours; **F.** After 72 hours

brain injury and an important element of a multimodal prognostic algorithm for comatose patients admitted to the hospital after OHCA [7]. The advantages of NSE are that it is a simple and widely available laboratory measurement as it is utilized for monitoring the treatment of tumors of the neuroectodermal origin or small cell lung cancer. Further, the results of the measurements are quantitative and independent of the sedative and neuromuscular blockade effects that may influence the outcomes of a neurological examination. However, the continuous nature of the

Table 2. Neuron-specific enolase (NSE) concentration cutoff values for poor neurological prediction at each time point. Cutoff values are calculated to maximize the Youden index and at a fixed false-positive rate level of 5%

NSE, hours	Cutoff, ng/ml	Sensitivity, %	95% CI	Specificity, %	95% CI
0					
Youden	27.2	79	67–89	71	48–89
FPR <5	46.6	29	2–59	95	95–100
1					
Youden	28.9	77	64–87	57	34–78
FPR <5	79.7	16	4–37	95	95–100
3					
Youden	31.8	73	60–84	70	46–88
FPR <5	106.1	14	2–27	95	95–100
12					
Youden	28.2	81	68–90	71	48–89
FPR <5	62.5	37	21–62	95	95–100
24					
Youden	39.8	71	56–84	85	62–97
FPR <5	81.8	33	16–56	95	95–100
48					
Youden	48.9	72	55–86	95	74–100
FPR <5	78.7	53	28–69	95	95–100
72					
Youden	52.9	86	57–98	100	69–100
FPR <5	46.2	86	57–100	95	95–100

Abbreviations: CI, confidence interval; FPR, false-positive rate

numerical results implies the need to determine a cutoff value for a poor prognosis with the lowest risk of an FPR. The main reason why the evaluation of NSE levels cannot be implemented in routine clinical practice is that the reported threshold values differ among studies. In a recently published meta-analysis [10], the proposed cutoff values for predicting a poor neurological outcome varied from 13.3 ng/ml [11] to 47.6 ng/ml [12] for early periods of up to 24 hours of observation and from 22.4 ng/ml [13] to 97 ng/ml [14] for 48 hours to 72 hours after admission. Thus, the ERC, in its latest Guidelines for Post-Resuscitation Care has advised that ideally "every hospital laboratory assessing NSE should create its own normal values and cutoff levels based on the test kit used" [7]. It has also been emphasized that those thresholds should optimally minimize the risk of an FPR below 5%.

In the analyzed cohort, the cutoffs for the concentrations of NSE calculated for a specificity of 95% (FPR <5%) at the time points during the first 24 hours had an unacceptably low sensitivity. Therefore, in case of intention to predict bad outcome basing on the measurements done at first 24 hours we propose to use cutoffs that compromise sensitivity and specificity (calculated to maximize the Youden index). The range of those cutoffs was 27.2–39.8 ng/ml. So, to avoid FPR we propose to use the most conservative value — 39.8 ng/ml as a predictor of a poor outcome in the first 24 hours of observation.

The tools for evaluating the neurological prognoses of OHCA patients during the first 24 hours after admission are very scarce. Only the lack of pupillary or corneal reflexes [15] and the absence of somatosensory evoked potentials [16, 17] allow the prediction of poor outcomes with a high likelihood. However, both tests have low sensitivity as the observation of reflexes is highly subjective and the assessment of somatosensory evoked potentials requires expertise and is vulnerable to artifacts [18]. The possibility of utilizing the patient's NSE level, an observer-independent marker, in the prognostication process, seems a very valuable addition for this period of treatment, even if prognostic accuracy does not meet the assumed accuracy criteria.

On subsequent days of hospitalization, the sensitivity of NSE concentration thresholds calculated for a 5% FPR exceeded 53%; thus, we suggest using the following cutoff points calculated for 95% specificity: 78.7 ng/ml at 48 hours and 46.2 ng/ml at 72 hours.

It is interesting to compare our results with those obtained by the Target Temperature Management After Cardiac Arrest (TTM) Trial investigators [6], as they have been using the same test to determine NSE levels. The subpopulation of the TTM Trial with NSE concentration testing is the largest cohort analyzed so far (686 participants) that has dealt with the problem of establishing the role of NSE levels as a neurological outcome predictor after OHCA. Our cutoff points were higher than those obtained by the TTM Trial investigators: 39.8 ng/ml vs 27 ng/ml for a maximized Youden index 24 hours after admission, 78.7 ng/ml vs 42 ng/ml for 48 hours, and 46.2 ng/ml vs 33 ng/ml for 72 hours, with an FPR of 5%, respectively. These discrepancies can be explained by differences in the study population. Patients with unwitnessed cardiac arrest with asystole as the initial rhythm were excluded from the TTM Trial but not from our study. This may explain why we noted a higher percentage of non-shockable rhythms in our population than in the TTM Trial (34% vs 19%). The TTM Trial included only patients with a presumed cardiac cause of OHCA, while in our cohort, 18% of cases were defined as noncardiac or of unknown origin. In our population, 60% of the patients had TTM implemented, as compared
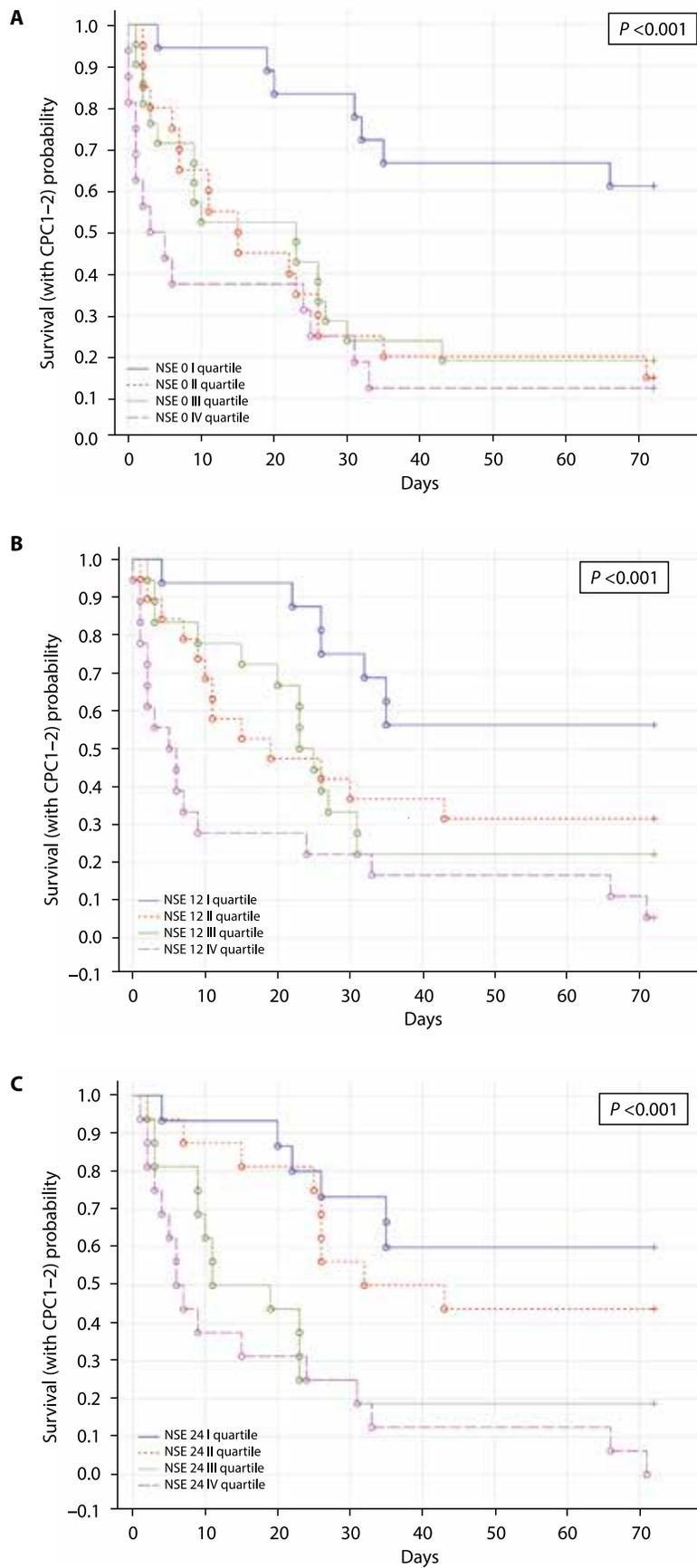
Figure 3. Kaplan–Meier curves showing the probability of a good outcome in relation to the quartile of neuron-specific enolase (NSE) level.
A. At admission; **B.** After 12 hours; **C.** After 24 hours.

Abbreviations: see Table 1

with 100% in the TTM Trial. Nevertheless, the observed differences in cutoff levels support the relatively cautious position of the ERC and prove the necessity for establishing diagnostic thresholds at each center in order to use NSE levels for neurological prognosis.

While NSE concentrations remain constant in patients with a good prognosis, patients with poor neurologic outcomes typically have elevated NSE levels, and in serial measurements, there is also a significant rise in NSE concentrations [6, 19]. This observation was also confirmed by our results, showing an increase in NSE concentrations over time and, therefore, providing additional prognostic value.

Our results seem to have important clinical implications. The use of proposed NSE cutoffs, highly specific to poor neurological outcome, could be useful in determining therapeutic strategy. Objective, biochemical confirmation of serious brain injury may facilitate the withdrawal of life-sustaining therapy. We hope that our results will encourage other Polish cardiac intensive care unit teams to implement NSE assessment in their prognostication algorithms for patients after OHCA.

Limitations

The main limitation of NSE testing is that NSE may also have extracerebral origins. Hemolysis is the main cause of false-positive results, and even if undetectable, it may affect NSE concentration test results [20]. There is also a low risk that some of the individuals in our cohort may have had undiagnosed neuroendocrine tumors. The possibility of non-neuronal sources of NSE affecting NSE levels can be avoided by testing concentrations directly in the cerebrospinal fluid. NSE determined in the cerebrospinal fluid may have more diagnostic accuracy than serum measurements [21]. However, the technically demanding procedure for obtaining cerebrospinal fluid for diagnostic purposes makes this approach highly impractical.

CONCLUSIONS

Our results revealed that in the environment of our center the NSE cutoffs measured at 48 hours and 72 hours may be useful in the prediction of poor prognosis after OHCA. The concentrations at first 24 hours are also of prognostic value, however, lower than those at 48 hours and 72 hours. The elevation of NSE levels and their rise in serial measurements are confirmed to be a valuable prognostic tool in patients after OHCA and should be considered in everyday clinical practice.

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