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Clinical paper

Neurofilament light compared to neuron-specific enolase as a predictor of unfavourable outcome after out-of-hospital cardiac arrest ☆

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Abstract

Aim: We compared the prognostic abilities of neurofilament light (NfL) and neuron-specific enolase (NSE) in patients resuscitated from out-of-hospital cardiac arrest (OHCA) of various aetiologies.

Methods: We analysed frozen blood samples obtained at 24 and 48 hours from OHCA patients treated in 21 Finnish intensive care units in 2010 and 2011. We defined unfavourable outcome as Cerebral Performance Category (CPC) 3–5 at 12 months after OHCA. We evaluated the prognostic ability of the biomarkers by calculating the area under the receiver operating characteristic curves (AUROCs [95% confidence intervals]) and compared these with a bootstrap method.

Results: Out of 248 adult patients, 12-month outcome was unfavourable in 120 (48.4%). The median (interquartile range) NfL concentrations for patients with unfavourable and those with favourable outcome, respectively, were 689 (146–1804) pg/mL vs. 31 (17–61) pg/mL at 24 h and 1162 (147–4360) pg/mL vs. 36 (21–87) pg/mL at 48 h, $p < 0.001$ for both. The corresponding NSE concentrations were 13.3 (7.2–27.3) μg/L vs. 8.5 (5.8–13.2) μg/L at 24 h and 20.4 (8.1–56.6) μg/L vs. 8.2 (5.9–12.1) μg/L at 48 h, $p < 0.001$ for both. The AUROCs to predict an unfavourable outcome were 0.90 (0.86–0.94) for NfL vs. 0.65 (0.58–0.72) for NSE at 24 h, $p < 0.001$ and 0.88 (0.83–0.93) for NfL and 0.73 (0.66–0.81) for NSE at 48 h, $p < 0.001$.

Conclusion: Compared to NSE, NfL demonstrated superior accuracy in predicting long-term unfavourable outcome after OHCA.

Keywords: Neurofilament light (NfL), Neuron-Specific Enolase (NSE), Out-of-hospital cardiac arrest, OHCA, Resuscitation, Cardiac arrest, Neurological outcome, Biomarkers

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Introduction

Prognostication after cardiac arrest (CA) should be performed using a multimodal approach, including clinical assessment, neurophysiology, radiological investigations and biomarkers.[1–3] The updated European Resuscitation Council (ERC)-European Society of Intensive Care Medicine (ESICM) guidelines recommend using neuron-specific enolase (NSE) as one component of multimodal prognostication.[1] However, the recommended high NSE cut-off values that are necessary to achieve high specificity may result in low sensitivity in detecting patients with poor prognosis.[4,5] One example is the decreased prognostic accuracy in elderly patients and patients with a short time from collapse to return of spontaneous circulation (ROSC).[6] NSE also has well-known sources of error, resulting in falsely elevated levels further weakening its prognostic accuracy.[7–12]

A novel axonal biomarker, neurofilament light (NfL), can be measured in plasma with an ultrasensitive novel single molecule array (SIMOA) method.[13] NfL demonstrated a very high capacity to predict unfavourable six-month outcome after out-of-hospital cardiac arrest (OHCA) with a presumed cardiac cause.[14,15] NfL also appeared to have the best ability among a group of neurobiomarkers, including NSE, to find patients with a favourable outcome despite the indeterminate prognosis given by examinations recommended in the ERC-ESICM guidelines.[16] Before wider adoption, the utility and presumed superiority of NfL over NSE should be validated also in unselected CA populations. Accordingly, we analysed NfL concentrations and its prognostic capacity in an unselected OHCA population, including patients with shockable and non-shockable initial rhythms and resuscitated from different CA aetiologies. We hypothesised that NfL would be superior to NSE in predicting unfavourable long-term outcome in patients treated in the intensive care unit (ICU) following OHCA. The secondary hypothesis was that NfL would have better prognostic value in those patient subgroups (high age, short time from collapse to ROSC) where NSE has demonstrated poor prognostic accuracy.

Methods

Study population and definitions

This was a post hoc analysis of the prospective multicentre FINNRESUSCI study of 548 adult patients resuscitated after OHCA and treated in 21 Finnish ICUs between 2010 and 2011.[17] All five university hospitals and 14 out of 15 non-university central hospitals participated in FINNRESUSCI. Over 98% of the Finnish population live in the referral areas of these hospitals. The FINNRESUSCI study protocol was approved by the Helsinki University Hospital Ethics Committee and by each participating hospital. A post-hoc substudy of NSE values was published earlier.[6] In this post-hoc study, we included 248 patients whose blood samples were stored (Fig. 1). We defined outcome according to the Cerebral Performance Category (CPC)[18] at 12 months after CA: CPC 1–2 indicates favourable outcome and CPC 3–5 indicates unfavourable outcome. The CA cause was defined with clinical criteria.

Data collection

The patient data were collected using Internet-based forms. Data on previous health status were collected from the patients' medical history and mortality data from Statistics Finland. The outcome according to CPC classification was assessed 12 months after CA with phone interviews conducted by a neurology specialist blinded to the hospital treatment and the laboratory analysis.

Blood samples

The blood samples were from patients in the FINNRESUSCI study for whom the next of kin had provided written informed consent. The plasma samples were collected at 24 and 48 hours from OHCA, stored at −80 °C and thawed for this analysis. We measured the NfL levels quantitatively using a commercially available two-step digital immunoassay using the single molecule array Quanterix SIMOA™ NF-light® Kit and SIMOA™ HD-1 Analyzer (SIMOA™, Quanterix Corporation, Lexington, MA, USA). The plasma NfL concentrations were expressed in picograms per millilitre (pg/mL). For comparison, we used NSE samples from the same time points determined according to previously described methods.[6] The obtained serum samples were stored at −70 °C during the original study and analysed with a commercially available electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) in April 2015. We excluded all NSE samples with significant haemolysis, ≥ 500 mg/L.[19]

Statistical analysis

We present categorical data as absolute numbers with percentages (95% confidence intervals [CIs]) and continuous data as medians with interquartile ranges (IQRs). For continuous data, we used Student's t test (normal distribution) and the Mann-Whitney U test or the Kruskal-Wallis test (skewed distribution) for comparison. We compared the categorical variables with the Chi square test or Fisher's exact test. We divided the study population into quartiles according to patients' age and time to ROSC[6] to detect differences in prognostic values between NfL and NSE.

We calculated the areas under the receiver operating characteristic curves (AUROCs) with 95% CIs to assess the ability of NfL and NSE to discriminate between patients in favourable (CPC 1–2) and those in unfavourable (CPC 3–5) outcome groups. We compared the AUROCs of NfL to NSE at 24 and 48 h after CA using the bootstrap method. We constructed a multivariable model with clinical factors such as age, initial rhythm, delay to ROSC and witnessed collapse for the prediction of poor functional outcome. Into this model, with a backward stepwise approach, we subsequently inserted NfL and NSE and report results with odds ratios and 95% CIs.

We defined the NfL cut-off values to predict unfavourable outcome at 24 and 48 h after CA from the receiver operating characteristic curve and for NSE at 48 h, accordingly. The cut-off values for NSE at 24 h were not calculated because of its poor prognostic accuracy.[6] We determined biomarker concentrations for high specificity (low false positive rate, [FPR]) to detect patients with a high probability for unfavourable outcome and concentrations for high sensitivity to detect those with a high probability for favourable outcome (low false negative rate). We calculated the Youden-based[20,21] cut-off values to assess the concentrations that simultaneously have as high specificity and sensitivity as possible, to promote their comparability. Furthermore, we defined cut-offs for high sensitivity (95% and 99%) and used normal levels of NfL to detect patients with favourable outcome. We used concentrations of 55 pg/mL for NfL[16] and 17 μg/mL for NSE[7] as the highest normal value. We also calculated the sensitivity, specificity, positive predictive value (PPV), negative

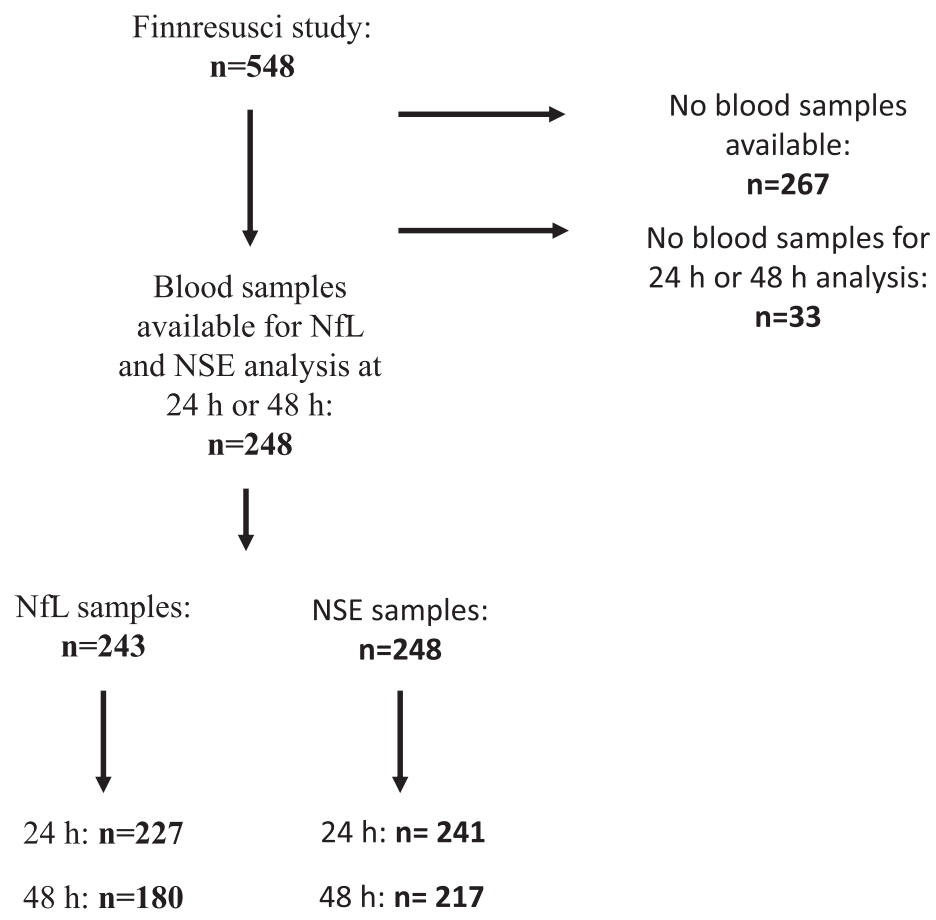

Fig. 1 – Flowchart of the study population. Abbreviations: NfL: neurofilament light. NSE: neuron-specific enolase.

predictive value (NPV), positive likelihood ratio (LR+) or negative likelihood ratio (LR-), if suitable, for these cut-off values. We considered *p* values < 0.05 as significant. We performed statistical analyses with SPSS version 27 (SPSS, Il, Chicago, USA) and R program, version 4.0.0.

Results

The 12-month outcome was unfavourable in 120/248 (48.4%) of the patients. Of these patients, 177 (71.4%) had a shockable initial rhythm. Blood samples enabled NfL analysis in 243 patients and NSE analysis in 248 patients (Fig. 1). Table 1 shows the outcome data and patient characteristics. The comparison of the study patients to the FINNRESUSCI patients in whom blood samples were unavailable are shown in Table S1.

NfL and NSE concentrations and prognostic ability

The NfL concentrations were significantly higher for the patients with unfavourable outcome than for those with favourable outcome at all time points. At 24 h, the median concentrations (IQR) were 688.9 pg/mL (146.1–1803.8) for the patients with unfavourable outcome vs. 30.9 pg/mL (16.9–61.2) pg/mL for those with favourable outcome ($p < 0.001$). Accordingly, the concentrations at 48 h were 1162.4 pg/mL (146.8–4360.5) vs. 35.6 pg/mL (21.3–86.7), $p < 0.001$. Fig. 2 shows the concentrations indexed by outcome. The NSE concentrations were higher for the patients with unfavourable outcome than for those with favourable outcome; at 24 h, the concentrations were 13.3 μg/L (7.2–27.3) for the patients with unfavourable outcome vs. 8.5 μg/L (5.8–13.2) for those with favourable outcome, $p < 0.001$. At 48 h, the concentrations were 20.4 μg/L (8.1–56.6) vs. 8.2 μg/L (5.9–12.1), respectively ($p < 0.001$) (Fig. 2). The NfL and NSE concentrations were not different for the patients with a cardiac aetiology of arrest compared to those with a non-cardiac aetiology, according to outcome Table S2.

The prognostic ability assessed with AUROC (with 95% CI) was significantly higher at 24 h after CA to predict unfavourable outcome for NfL (0.90 [0.86–0.94]) than NSE (0.65 [0.58–0.72]), $p < 0.001$. At 48 h, the AUROC was higher for NfL (0.88 [0.83–0.94]) than NSE (0.72 [0.66–0.81]), $p < 0.001$. The AUROC for NfL at 24 h was also higher than NSE at 48 h, $p < 0.001$. NfL at 24 h was a significant predictor of unfavourable outcome in the multivariable model, whereas NSE at 48 h was not (Table S3). The AUROCs for NfL and NSE according to the CA aetiology are presented in Table S2.

Cut-off values

The NfL cut-off values to predict unfavourable outcome using the Youden method (maximising sensitivity and specificity) were 97 pg/mL at 24 h and 231 pg/mL at 48 h. For those cut-offs, the specificities (with 95% CIs) were 86.8% (80.6–93.0) and 92.1% (86.8–97.3), and the sensitivities were 81.8% (74.2–88.6) and 72.2 (62.3–82.0), respectively. For 99% specificity, the cut-offs were 589 pg/mL and

Table 1 – Characteristics of the study patients according to Cerebral Performance Category classification.

		CPC 1-2	CPC 3-5
Number of patients, n (%)		128 (51.6)	120 (48.4)
Initial rhythm[a]			
Shockable rhythms, n (%)	VF	104 (81.3)	70 (58.3)
	VT	2 (1.6)	1 (0.8)
Non-shockable rhythms, n (%)	PEA	9 (7.0)	23 (19.2)
	ASY	13 (10.2)	25 (20.8)
Witnessed, n (%)		123 (96.1)	103 (85.8)
Bystander CPR, n (%)		78 (60.9)	67 (55.8)
ROSC, min (IQR)		16 (11–23)	24 (19–31)
CA aetiology, n (%)			
	Cardiogenic	106 (82.8)	90 (75.0)
	Hypoxia	4 (3.1)	7 (5.8)
	Drowning	2 (1.6)	3 (2.5)
	Hypothermia	1 (0.8)	0 (0)
	Intoxication	3 (2.3)	3 (2.5)
	Trauma	1 (0.8)	0 (0)
	Other etiologies	2 (1.6)	6 (5.0)
	Unknown	5 (3.9)	4 (3.3)
	Missing	4 (3.1)	7 (5.8)
SAPS II, points (IQR)		47 (34–60.8)	64.5 (55.3–71)
Male gender, n (%)		107 (89.2)	101 (84.2)
TTM, n (%)		100 (78.1)	92 (76.7)

Abbreviations: ASY: asystole. CA: cardiac arrest. CPC: Cerebral Performance Category. CPR: cardiopulmonary resuscitation. IQR: interquartile range. PEA: pulseless electrical activity. ROSC: return of spontaneous circulation. SAPS II: Simplified acute physiology score. TTM: targeted temperature management. VF: ventricular fibrillation. VT: ventricular tachycardia.

[a] Data missing in 1 (0.8%) of the patients with CPC 3-5.

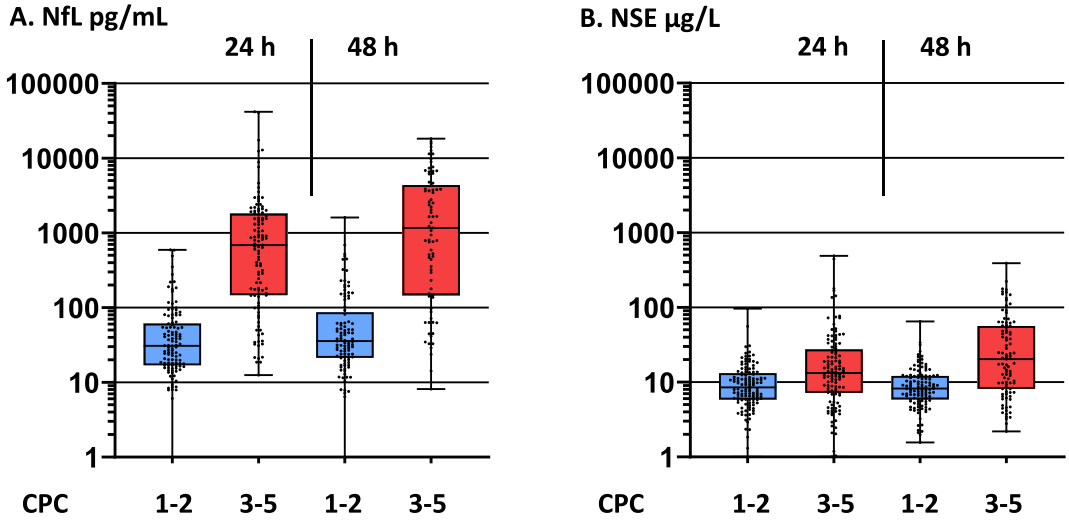

Fig. 2 – Boxplots for NfL (A) and NSE (B) concentrations at 24 h and 48 h after cardiac arrest for patients with favourable (CPC 1–2) and unfavourable (CPC 3–5) outcomes with a 10-based logarithmic scale. Each box presents the interquartile range. The line inside the box shows the median value, the whiskers show the lowest and the highest concentrations, and the dots show the concentrations for each individual. Abbreviations: CPC: Cerebral Performance Category. NfL: neurofilament light. NSE: neuron-specific enolase.

721 pg/mL, respectively with sensitivities of 54.0% (44.8–63.2) and 59.5% (48.7–70.3), respectively (Table 2).

Regarding NSE at 48 h, using a 35 µg/L cut-off value with 99% specificity resulted in a 37.1% (27.5–46.7) sensitivity. Table 2 shows the cut-off values with corresponding characteristics for NfL at 24 h and 48 h and for NSE at 48 h using the Youden method and 95% and 99% specificity. The cut-off values for NfL and NSE to predict favourable outcome are presented in Table S4.

Combining NfL and NSE, 0.3% of the patients who exceeded the cut-offs for 95% specificity had a favourable outcome (Table S5).

Table 2 – Characteristics (with 95% CIs) of cut-off values for NfL at 24 h and 48 h and for NSE at 48 h after cardiac arrest for high demand of specificities to predict unfavourable outcome.

	Basis for cut-off setting	Cut-off	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)	LR+	p
NfL 24 h	Youden	97 pg/mL	86.8 (80.6–93.0)	81.8 (74.2–88.6)	86.0 (79.4–92.6)	82.5 (75.7–89.3)	6.2 (3.8–10.0)	<0.001
	95% specificity	232 pg/mL	95.6 (91.9–99.4)	65.5 (56.7–74.3)	93.7 (88.3–99.0)	73.6 (66.6–80.7)	14.9 (6.3–35.5)	<0.001
	99% specificity	589 pg/mL	99.1 (97.4–100)	54.0 (44.8–63.2)	98.4 (95.3–100)	68.5 (61.4–75.6)	61.5 (8.7–436.4)	<0.001
NfL 48 h	Youden	231 pg/mL	92.1 (86.8–97.3)	72.2 (62.3–82.0)	87.7 (79.7–95.7)	80.9 (73.7–88.1)	9.1 (5.6–18.0)	<0.001
	95% specificity	445 pg/mL	95.1 (90.8–99.3)	65.8 (55.4–76.3)	91.2 (83.9–98.6)	78.0 (70.7–85.4)	13.3 (5.6–31.7)	<0.001
	99% specificity	721 pg/mL	99.0 (97.1–100)	59.5 (48.7–70.3)	97.9 (93.9–100)	75.8 (68.4–83.1)	60.1 (8.5–426.0)	<0.001
NSE 48 h	Youden	20 μg/L	94.2 (90.0–98.4)	50.5 (40.6–60.5)	87.5 (78.8–96.2)	70.2 (63.1–77.3)	8.7 (4.1–18.2)	<0.001
	95% specificity	22 μg/L	95.0 (91.1–98.9)	46.4 (36.5–56.3)	88.2 (79.4–97.1)	68.7 (61.6–75.7)	9.3 (4.1–20.8)	<0.001
	99% specificity	35 μg/L	99.2 (97.5–100)	37.1 (27.5–46.7)	97.3 (92.1–100)	66.1 (59.2–73.0)	44.5 (6.2–319.0)	<0.001

Abbreviations: CI: confidence interval. LR+: positive likelihood ratio. NfL: neurofilament light. NPV: negative predictive value. NSE: neuron-specific enolase. PPV: positive predictive value.

NfL in different subgroups

Age quartiles

In all age groups, the NfL concentrations were significantly higher for the patients with unfavourable outcome than for those with favourable outcome at 24 h and 48 h after CA (Fig. 3). The prognostic ability of NfL was significantly better at 24 h than that of NSE in all age subgroups (Table S6). At 48 h, the prognostic ability of NfL was better than that of NSE in the patients aged 57–63 years (p = 0.005) and in the oldest subgroup, ≥72 years (p = 0.020) (Table S6). The AUROC for NfL to predict unfavourable outcome was lower in the oldest quartile compared to the youngest quartile (18–56 years) both at 24 h (p = 0.016) and 48 h (p = 0.032). The AUROC was also lower in the fourth quartile (≥72 years) at 48 h than in the second quartile (57–63 years), p = 0.020. The NfL concentrations in the patients with favourable outcome were significantly different according to age group at 24 h (p < 0.001) and at 48 h (p = 0.001).

ROSC quartiles

The NfL concentrations were significantly higher for the patients with unfavourable outcome compared to those with favourable outcome at all times from collapse to ROSC quartiles at 24 h and 48 h (Fig. 4). The prognostic ability of NfL was also better than that of NSE in all ROSC subgroups at 24 h and 48 h after CA (Table S7). The AUROC for NfL to predict unfavourable outcome was lower in the quartile with the shortest time from collapse to ROSC (1–13 min) than in the quartile with the longest time to ROSC (≥29 min) at 24 h (p = 0.014) and at 48 h (p = 0.019). The AUROC was also lower for the patients in the second quartile (ROSC 14–

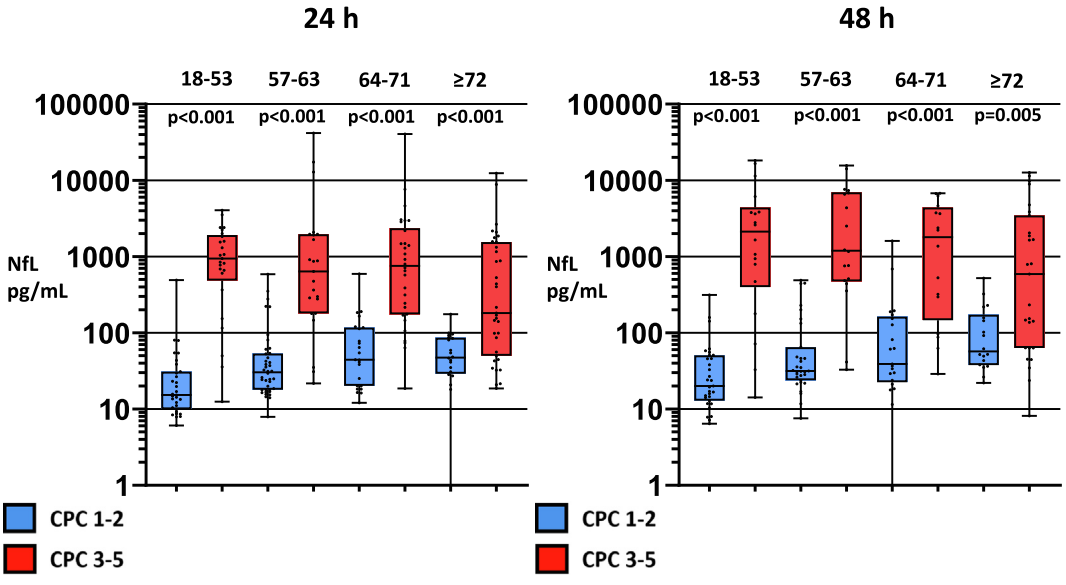

Fig. 3 – Boxplots for NfL concentrations at 24 h and 48 h after cardiac arrest for patients with favourable (CPC 1–2) and unfavourable (CPC 3–5) outcomes with a 10-based logarithmic scale, according to different age quartiles. Each box presents the interquartile range. The line inside the box shows the median value, the whiskers show the lowest and the highest concentrations, and the dots show the concentrations for each individual. Age intervals (years) with p values (for differences in concentrations for patients with favourable [CPC 1–2] and unfavourable [CPC 3–5] outcomes in each quartile) are presented above each figure. Abbreviations: CPC: Cerebral Performance Category. NfL: neurofilament light.

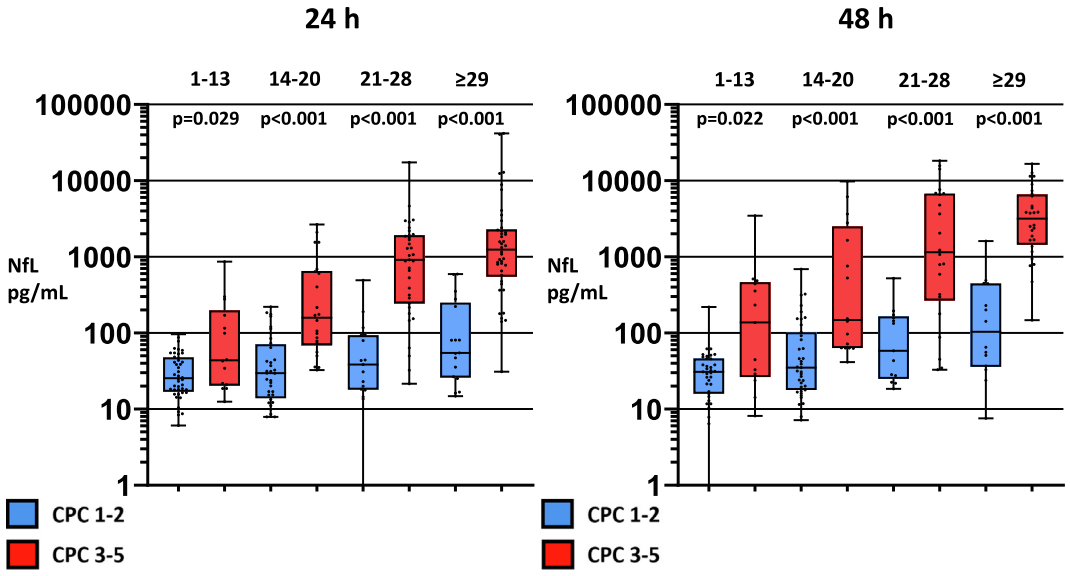

Fig. 4 – Boxplots for NfL concentrations at 24 h and 48 h after cardiac arrest for patients with favourable (CPC 1–2) and unfavourable (CPC 3–5) outcomes with a 10-based logarithmic scale, according to different ROSC quartiles. Each box presents the interquartile range. The line inside the box shows the median value, the whiskers show the lowest and the highest concentrations, and the dots show the concentrations for each individual. ROSC intervals (minutes) with p values (for differences in concentrations for patients with favourable [CPC 1–2] and unfavourable [CPC 3–5] outcomes in each quartile) are presented above each figure. Abbreviations: CPC: Cerebral Performance Category. NfL: neurofilament light. ROSC: return of spontaneous circulation.

20 min) than for those in the fourth quartile (≥29 min) at 48 h, p = 0.032. The distributions of NfL concentrations were significantly different according to outcome in the ROSC subgroups: for the patients with favourable outcome (at 24 h p = 0.034; at 48 h p = 0.004) and for those with an unfavourable outcome (p < 0.001 at 24 h and 48 h).

Discussion

In this post-hoc analysis of OHCA patients resuscitated from various arrest aetiologies, NfL was significantly more accurate than NSE in predicting unfavourable 12-month outcome. The prognostic ability of NfL was already excellent at 24 hours after CA. The median concentrations for the patients with unfavourable outcome were about 20-fold greater than for those with favourable outcome. Importantly, NfL was also accurate in the patients resuscitated from a likely non-cardiac cause of arrest. We also found a less clear association between age and time to ROSC and predictive accuracy than we previously showed with NSE.[6] As our sample presents heterogeneous OHCA patients, our findings support wider utilisation of NfL in clinical prognostication after CA.

The lack of wider adoption of NfL thus far may have been due to the unavailability of a commercial assay, but given the introduction of the ultrasensitive SIMOA method, this is likely to change.

However, few studies exist about prognostication after CA using the ultrasensitive SIMOA method. NfL measurement within the first 24 h after ROSC demonstrated an AUROC of 0.82 to predict in-hospital death.[22] In a Targeted Temperature Management (TTM) substudy including 782 OHCA patients with a likely cardiac aetiology of arrest, the AUROCs at 24–72 h to predict poor six-month outcome were 0.94–0.95.[14] In our study of OHCA patients with VF as the initial rhythm, the AUROCs were very high at 0.98.[15] The present study, including an unselected population with both shockable and non-shockable rhythms, found AUROCs to predict CPC 3–5 at 12 months of 0.88–0.90, demonstrating slightly worse but still excellent discriminative ability. Pouplet et al demonstrated AUROC of 0.87 to predict CPC 3–5 at 90 days after CA in patients with shockable rhythms using different but comparable commercial laboratory method.[23] In Stammet et al.'s TTM substudy,[19] NSE had an AUROC of 0.85–0.86 at 48–72 h, and Streitberger et al. found an AUROC of 0.85–0.90 at 72 h.[7] In summary, studies conducted to date suggest better accuracy for NfL compared to NSE.[14,15] We found a slightly lower discriminative ability, especially for NSE, than previously reported. The likeliest explanation is the inclusion of different types of CA patients in whom the reason for the unfavourable outcome may not only be due to post-cardiac arrest brain injury (PCABI), which is the most common cause of death after CA.[24] Clearly, NfL and NSE can only work for predicting death or poor outcome related to brain injury.

The levels of NSE for patients with unfavourable outcome were somewhat lower in this study compared to some previous studies. There are several possible explanations for this. Firstly, the laboratory methods used may be important.[25] Secondly, it is possible that the lower levels and prognostic ability of NSE seen in the present study compared to previous studies are related to differences in the definition of unfavourable outcome[7] and follow-up time.[7,19]

Our secondary finding was that NfL's prognostic ability was better than NSE in subgroups where the prognostic value of NSE was poor, such as the elderly and those with a shorter arrest duration. In our study, the NfL levels were higher in those with longer time from collapse to ROSC, and the accuracy was highest in those with the longest time to ROSC. However, even in the group with a short time to

ROSC, the discriminative ability was satisfactory. This may suggest that NfL is more sensitive even in detecting milder hypoxic brain injury. Importantly, for patients with a short time from collapse to ROSC and patients aged ≥72 years, the prognostic value of NfL was superior to NSE. Increasing age is one confounding factor of NfL; the concentrations increase about 2% per year,[26,27] and for individuals over 60 years of age, the variability of NfL levels increases.[28] We also found a rising trend of NfL levels in CPC 1–2 patients with increasing age. This finding may provide an additional explanation for the worse discriminative ability of NfL in the oldest patient group.

The ERC-ESICM guidelines recommend a 60 μg/L NSE cut-off.[1] In this study, the 35 μg/L NSE cut-off at 48 h yielded 99% specificity but 37% sensitivity. Generally, demanding a very high specificity results in low sensitivity if the diagnostic method's performance is insufficient.

Targeting specificities of 95% and 99%, the cut-off values for NfL at 24 h were 232 pg/mL and 589 pg/mL, respectively; the cut-off values for NfL at 48 h were 445 pg/mL and 721 pg/mL, respectively.

Those cut-off concentrations are comparable to corresponding values in a TTM substudy.[14] Lower NfL cut-off values with higher sensitivities were presented in our study of a highly selected population with shockable rhythms.[15] The Youden-based NfL cut-offs showed 72–82% sensitivities and 87–91% specificities. In this study population, NfL presented better sensitivity than NSE, even with clinically useful specificities. The combination of cut-offs of NfL and NSE for 95% specificity resulted in a 0.3% FPR.

Recent studies have raised the concern that there might be CA patients with potentially favourable outcome despite poor prognosis given by prognostic methods.[29,30] Targeting 95% and 99% specificity to find patients with favourable outcome, the NfL cut-offs were 14–29 pg/mL, which are in the normal range. NSE demonstrated insufficient capacity to detect patients with favourable outcome. NfL has a better ability than NSE to find patients with favourable outcome using normal or lower values.

Strengths and limitations

Our study has several strengths. It was a nationwide multicentre study with a large patient sample from many ICUs. Importantly, we included CA patients of various arrest aetiologies. The treating clinicians were blinded to the NfL results. Neurological outcome was defined by an experienced neurologist blinded to the biomarker results. However, some limitations exist. First, the original study is 10 years old, and prognostication and clinical care of resuscitated patients are likely to have changed. Second, our study population was selected by consent availability, and, consequently, the proportion of patients with bystander cardiopulmonary resuscitation, shockable rhythm and TTM was significantly higher in those included than those excluded. Third, we do not have conclusive data on the patients' cause of death or prognostication; the patients were managed according to protocols available at the time. Fourth, the numbers of patients in the subgroups were small.

Conclusion

NfL is more valuable than NSE in prognostication of unfavourable outcome after OHCA, also in cases with non-cardiac aetiologies. Contrary to NSE, NfL retained its accuracy in the elderly and those with a short delay to ROSC, suggesting the ability of NfL to also identify milder forms of hypoxic brain injury.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

L. Wihersaari: Writing – original draft, Formal analysis, Visualization, Software, Data curation. **M. Reinikainen:** Conceptualization, Methodology, Writing – original draft, Supervision. **R. Furlan:** Resources, Validation. **A. Mandelli:** Resources, Validation. **J. Vaahersalo:** Validation, Investigation. **J. Kurola:** Validation, Conceptualization. **M. Tiainen:** Validation, Investigation. **V. Pettilä:** Validation, Supervision. **S. Bendel:** Validation, Supervision. **T. Varpula:** Validation, Conceptualization. **R. Latini:** Resources, Validation. **G. Ristagno:** Resources, Validation. **MB. Skrifvars:** Writing – original draft, Conceptualization, Methodology, Project administration, Supervision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2022.02.024.

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