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Clinical paper

Serum neurofilament light chain and multimodal neuroprognostication after cardiac arrest – A retrospective cohort study

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Abstract

Background and purpose: Most patients remain comatose within the first days after cardiac arrest (CA) and resuscitation. Guidelines recommend multimodal neuroprognostication including neuron specific enolase (NSE) as serum biomarker. Neurofilament light-chain (NFL) may have higher prognostic accuracy earlier after cardiac arrest and a lower risk of confounders. This study investigates the prognostic value of serum NFL in clinical routine compared to established prognostic tests.

Methods: Monocentric retrospective observational study of patients with serum NFL between 24–96 h after CA. Neurological outcome was evaluated at hospital discharge via the Cerebral Performance Category score (CPC), dichotomized as good (CPC 1–3) and poor (CPC 4–5). Prognostic performance for good and poor neurological outcome prediction was analysed for NFL, NSE, electroencephalography (EEG), somatosensory evoked potentials (SSEP), and head computed tomography (CT). NFL was measured using the SIMOA Quanterix assay.

Results: 152 patients were included, median age was 61 years, 24% were female. 10 patients were discharged in vegetative state or comatose (7%), and 78 died before discharge (51%). NFL > 2000 pg/ml predicted poor outcome with 53% (43–63%) sensitivity and 100% (94–100%) specificity. Most patients (69%) with NFL < 55 pg/ml had a good outcome. Predictive accuracy was similar to other neuroprognostic tests (AUC 0.89, 0.84–0.94). In head-to-head comparisons with the other neuroprognostic tests, NFL identified 16–41% additional poor outcome patients.

Conclusion: NFL (SIMOA) > 2000 pg/ml predicts poor neurological outcome with high specificity, while low concentrations strongly argue against severe HIE. Adding NFL to established neuroprognostication tests increases sensitivity of poor outcome prediction.

Keywords: Cardiac Arrest, Biomarkers, Neurofilament light chain, Neuron-Specific-Enolase, Electroencephalography, Somatosensory Evoked Potentials, Computed Tomography

Introduction

Following cardiac arrest (CA) and return of spontaneous circulation (ROSC), most patients remain comatose. International guidelines recommend multimodal neuroprognostication consisting of clinical examination, brain imaging, cortical somatosensory evoked potentials (SSEP), electroencephalography (EEG), and blood biomarkers to predict long-term neurological outcome.[1,2] A specificity close to 100% for prediction of poor outcome is needed to prevent withdrawal of life-sustaining therapy (WLST) in comatose patients with a chance of recovery. The best-established serum biomarker is Neuron-specific enolase (NSE), which has a moderate sensitivity (around 50%) and high specificity for poor neurological outcome prediction at thresholds above 60–90 μg/ml.[3,4] NSE is widely available at a reasonable cost but can be confounded by NSE from extracerebral sources such as malignancies or haemolysis, for example during treatment with extracorporeal membrane oxygenation (ECMO).[5]

Neurofilament light chain (NFL) is an axonal cytoskeletal protein whose serum concentration increases in diseases with neuroaxonal injury such as amyotrophic lateral sclerosis, multiple system atrophy, multiple sclerosis, and psychiatric diseases.[6–9] In these

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diseases, however, serum concentrations are far lower than in patients with severe hypoxic-ischemic encephalopathy (HIE) after CA.[10] Confounders from extracerebral sources are less common than for NSE.[7]

Although NFL has been shown to predict neurological outcome after CA with high specificity and a sensitivity potentially superior to NSE and at earlier timepoints, the added value of NFL in addition to already established prognostic tests in the prognostication algorithm remains unclear.[11–21] Our study aims to evaluate NFL as a biomarker for neuroprognostication after CA in clinical routine and to compare it to established prognostication methods.

Methods

Patients

The study was approved by our local ethics committee (Ethikkommission der Charité, approval number: EA2/066/23), which waived the need for informed consent. We retrospectively included consecutively admitted adult out-of-hospital (OHCA) and in-hospital-CA (IHCA) patients from three medical ICUs at *Charité University Hospital Berlin*, Germany between January 2021 and March 2023 with serum NFL testing within 24–96 h after CA (eFig. 1). Post-resuscitation care protocols were consistent during the whole study period and followed international guidelines including treatment with targeted temperature management at 33° for 24 h irrespective of location of cardiac arrest or initial rhythm.[22–24] WLST for neurological reasons was carried out only after a considerable observation period and multimodal neuroprognostication according to the national guidelines[23–24]. The results of prognostic tests presented in this study were available to the treating team. Neurological outcome was assessed by the treating physician at hospital discharge using the Cerebral Performance Category Scale (CPC).[25]

Prognostic tests

Serum biomarkers

Serum biomarkers were sampled between 24–96 h after CA by request of the treating ICU physician. Serum NFL measurements were carried out using a single molecule array (SIMOA) analyzer by Quanterix (Billerica, USA).[26] For NSE, an Electro-Chemi-Luminescent-Immuno Assay (ECLIA) test kit by Roche Diagnostics (Rotkreuz, Switzerland) was used. The haemolysis index (h-index) was measured from the same blood sample; samples with an h-index > 50, corresponding to a free hemoglobin (fHb) concentration > 50 mg/dL, were excluded.[5,27] For statistical analysis, we used the NSE serum concentration of day 3 and for NFL the highest NFL value within 24 and 96 h of CA.

Neuroimaging

Head CTs were obtained on Toshiba Medical (Otawara, Japan) or GE Healthcare (Chicago, USA) scanners using 120 kV peak kilovoltage. Five-millimetre reconstructions were assessed qualitatively for signs of HIE and quantitatively to determine the gray-white-matter ratio (GWR) by two neurologists experienced in post-CA care (CL, CE) using a previously published standard operating procedure (SOP).[28]

Neurophysiology

Patients received standard electroencephalography (EEG), including reactivity testing, which was evaluated by the on-duty EEG neurologist and categorized according to the ACNS criteria[29] and Westhall et al..[30] Suppression, suppression with generalized periodic discharges and burst-suppression were classified as "highly malignant" EEGs. Somatosensory evoked potentials (SSEP) were recorded following current international guidelines[29,31] and cortical SSEP amplitudes determined as described previously.[32,33] An SSEP was categorized as bilaterally absent when there was no reproducible cortical SSEP, the noise levels did not exceed 0.25 μV in all cortical recordings and spinal SSEPs (N13) were reproducible bilaterally.

Statistics and visualization

For statistical analysis, neurological outcome was dichotomized into "good" (CPC 1–3) and "poor" (CPC 4–5) to acknowledge the possibility of further improvement after hospital discharge. Additionally, we provide a separate good outcome prediction analysis for an alternative dichotomization (CPC 1–2 vs. 3–5) in the supplementary material. We analysed descriptive measures of prognostic performance (sensitivity, specificity and contingency tables) and receiver operating characteristics (ROC) for predicting neurological outcome with NFL at the pre-specified threshold > 2000 pg/ml (poor outcome) and < 55 pg/ml (good outcome)[12,34] with NSE at > 90 ng/ml (poor) and < 17 ng/ml (good),[3] with cortical SSEP amplitude at < 0.5 μV (poor) and > 2.5 μV (good),[32] with highly malignant EEG pattern (poor) and EEG reactivity (good)[30,35,36] and with CT GWR at < 1.10 (poor) and > 1.20 (good).[28] For data visualization we used the *ggpubr*[37] and *ComplexUpset*[38] packages in RStudio (Version 1.4.1653, *Posit PBC*).

Results

Patient characteristics

Of 587 patients in the registry between January 2021 and March 2023, 152 (26%) had serum NFL testing on day 1 to 4 after CA (eFig. 1). Patient and CA characteristics of the study cohort and all patients in the registry are presented in Table 1. 84% of patients with NFL testing had an OHCA, 85% received bystander CPR, and 51% of patients had an initially shockable rhythm. Of all patients in the registry, 403 (69%) patients died: 325 (75%) patients without and 78 (51%) patients with NFL testing. 64 (43%) patients with NFL measurements were discharged with a good neurological outcome (CPC 1–3).

Prognostic value of NFL for poor outcome prediction

The association between serum NFL concentrations and clinical outcome are plotted in Fig. 1. Median (interquartile, IQR) NFL concentration in patients with good neurological outcome were 50 pg/ml (20–101 pg/ml) and 1480 pg/ml (346–5210 pg/ml) in poor neurological outcome patients ($p < 0.01$). From CPC 1 to CPC 4, median NFL concentrations increased, whereas NFL concentrations of CPC 5 patients were widely distributed (Fig. 1). The lowest NFL value in a patient with definitive clinically severe HIE (CPC 4) was 536 pg/ml (Fig. 1, eTable3A). At the pre-specified threshold of above 2000 pg/ml, serum NFL had a specificity of 100% (94–100%) and sensitivity of 53% (43–63%) for poor neurological outcome prediction (Table 2).

Prognostic value of NFL for good outcome prediction

The highest NFL serum concentration in a good outcome patient discharged with moderate neurological deficits (CPC 2) was 1770 pg/ml (Fig. 1, eTable3B, details see below). NFL < 55 pg/ml had a speci-

Table 1 – Baseline Table of the study cohort

	All Patients	Patients without NFL at 24–96 h	Patients with NFL at 24–96 h	Patients with all 5 prognostic investigations
No. of Patients	587	435	152	44
Out-of-Hospital Cardiac Arrest, n (%)	420 (73%)	293 (70%)	127 (84%)	39 (89%)
Sex (female), n (%)	174 (30%)	138 (32%)	36 (24%)	34 (23%)
Age, years (median, IQR)	61 (52–71)	61 (51–71)	61 (55–69)	60 (55–68)
Initial Rhythm shockable, n (%)	205 (40%)	132 (36%)	73 (51%)	20 (47%)
tROSC, min (median, IQR)	15 (10–30)	15 (5–25)	20 (10–30)	20 (14–30)
Bystander CPR, n (%)	436 (82%)	310 (80%)	126 (85%)	35 (83%)
CPC 1, n (%)	110 (19%)	74 (17%)	36 (24%)	7 (16%)
CPC 2, n (%)	16 (3%)	7 (2%)	9 (6%)	2 (5%)
CPC 3, n (%)	40 (7%)	21 (5%)	19 (13%)	7 (16%)
CPC 4, n (%)	18 (3%)	8 (2%)	10 (7%)	5 (11%)
CPC 5, n (%)	403 (69%)	325 (75%)	78 (51%)	23 (52%)

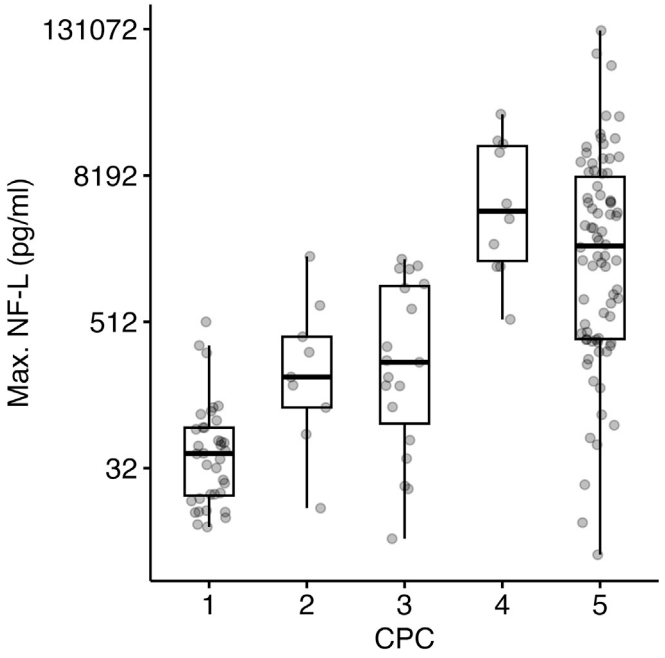

Fig. 1 – Scatter-/Boxplot for median (IQR) maximum NFL between 24 h-96 h after CA and outcome category (CPC) at hospital discharge in 153 patients. Logarithmic y-axis.

ficity of 95% (95%-CI: 89–98%, n = 152) and sensitivity of 48% (37–60%) to predict good neurological outcome (Table 2B). In a subgroup of 55 patients with repeated measurements of NFL, poor outcome patients had their peak NFL on day 2 after CA while good outcome patients largely remained at their initial NFL serum concentration (eFig. 2).

NFL and multimodal neuroprognostication of poor outcome

Multiple prognostic investigations were used in most patients. Of the 152 patients with NFL measurements available, 114 received serum NSE measurements on day 3 after CA, 116 had SSEP recordings, 69 patients a late head CT (median 4 days after CA), and 106 patients had an EEG (Table 2, eTable 2). In 44 patients, all five prognostic investigations were carried out (Table 1).

Fig. 2A-C illustrates the relationship between NFL, NSE, CT GWR and cortical SSEP amplitude. All poor outcome prognostic investigations had zero false positives at our pre-specified thresholds, resulting in 100% specificity. Sensitivity ranged from 41% (43–63%) for CT GWR to 56% (43–68/44–66%) for NSE and SSEP amplitude, AUC ranged from 0.86 (0.78–0.95) for CT GWR to 0.92 (0.87–0.97) for NSE (Table 2A). The combination of NFL and any other neuroprognostic test identified 72–79% of patients with poor outcome. NFL identified 16–41% additional patients with poor outcome when added to any single other neuroprognostic test (eTable 5A).

Among the subgroup with all 5 prognostic tests available (NFL, NSE, SSEP, EEG and CT), 57% (16/28) of patients with poor outcome had two positive tests among those included in the ERC/

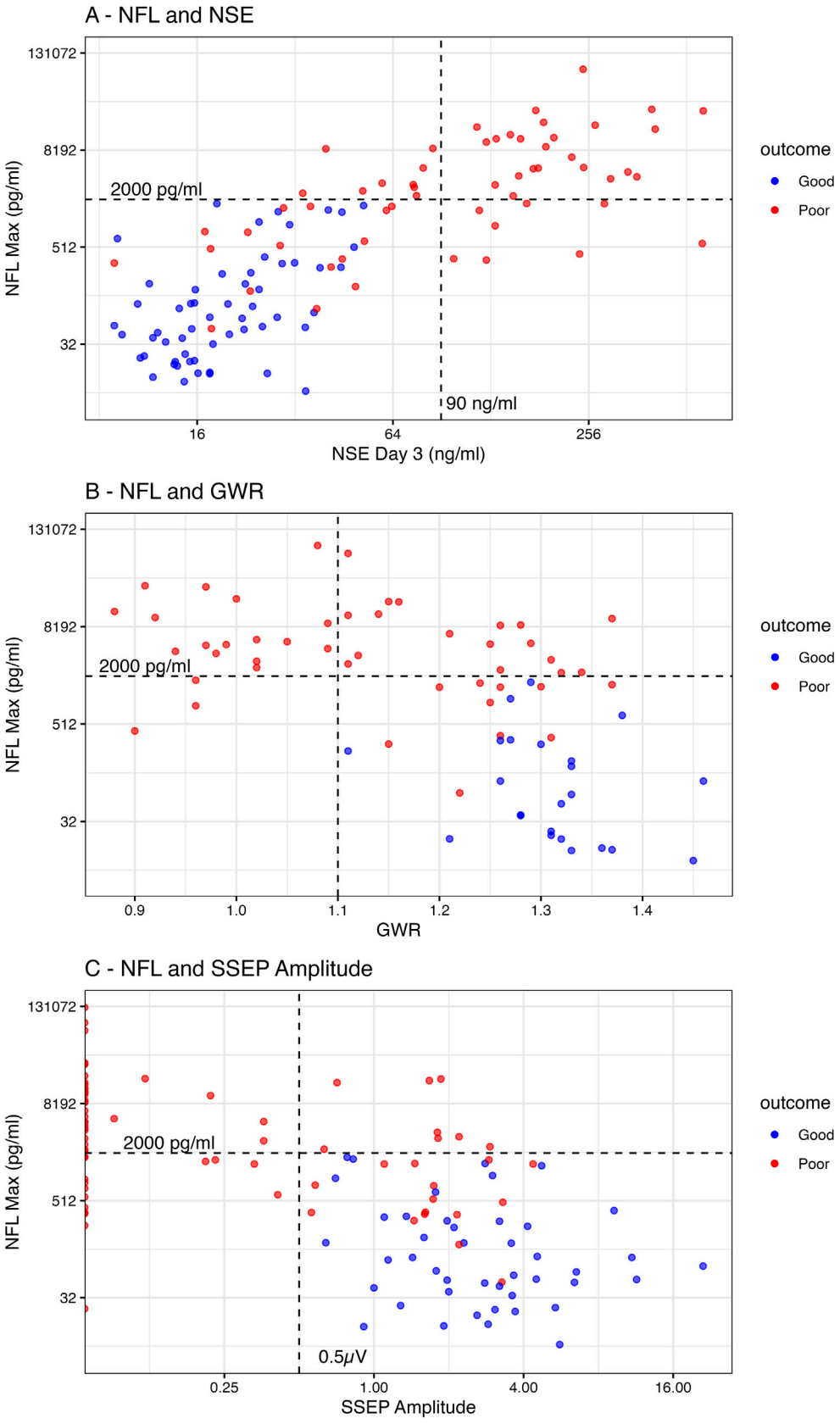

Fig. 2 – Scatterplot NFL for highest NFL between 24–96 h after CA and A – NSE (ng/ml) at day 3 after CA, n = 114, B – GWR in CT > 24 h after CA, n = 69, C – Cortical SSEP Amplitude (μV), n = 116. Dashed lines at poor outcome thresholds. Logarithmic scale except for x-axis in B.

ESCIM algorithm (NSE, SSEP, EEG, CT).[1] Including NFL increased the proportion of poor outcome patients with at least two positive tests to 75% (21/28) (Fig. 3).

NFL and multimodal prognostication of good outcome

Specificity for good outcome prediction was high for EEG reactivity (97%; 89–99%), NFL < 55 pg/ml (95%; 89–98%), NSE < 17 ng/ml (96%; 88–99%), SSEP-Amplitude > 2.5 μV (93%; 85–97%), and lowest for CT GWR > 1.20 (61%; 46–74) (Table 2B). Sensitivity was 48% (37–60%) for NFL, 44% for EEG reactivity (30–59%) and NSE < 17 ng/ml (32–57%) and 55% (40–68%) for cortical SSEP amplitude > 2.5 μV. Combining NFL and any prognostic test other than CT increased the proportion of correctly predicted good outcome patients up to + 26% (EEG) (eTable 5B).

Patients with low serum NFL and severe HIE

One poor outcome patient had a low NFL serum level on day 1 after CA (23 pg/ml) (Fig. 1). This 27-year-old patient was treated with an VA-ECMO due to ongoing ventricular fibrillation after an OHCA. He was found to have extensive cerebral oedema in the early CT scan only hours after CA, dilated and fixed pupils, and no cortical SSEP amplitudes. Death by neurological criteria (DNC) was determined

Table 2A – Prediction of poor functional outcome (CPC 4–5) by prognostic investigation

Method	Specificity (95% CI)	Sensitivity (95% CI)	TP	TN	FP	FN	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)	N
NFL max. Day 1–4 > 2000 pg/ml	100 (94–100)	53 (43–63)	47	64	0	41	1 (0.92–1)	0.61 (0.51–0.70)	0.89 (0.84–0.94)	152
NSE Day 3 > 90 ng/ml	100 (94–100)	56 (43–68)	32	57	0	25	1 (0.89–1)	0.70 (0.59–0.78)	0.92 (0.87–0.97)	114
Cortical SSEP amplitude Day 3 < 0.5 μV	100 (92–100)	56 (44–66)	40	44	0	32	1 (0.91–1)	0.58 (0.47–0.68)	0.90 (0.84–0.95)	116
EEG Day 4 "Highly malignant"	100 (92–100)	51 (39–63)	32	43	0	31	1 (0.89–1)	0.58 (0.47–0.69)	–	106
CT Day 4 "Signs of severe HIE"	100 (86–100)	48 (34–62)	22	23	0	24	1 (0.85–1)	0.49 (0.35–0.63)	–	69
CT Day 4 GWR < 1.10	100 (86–100)	41 (28–56)	19	23	0	27	1 (0.83–1)	0.46 (0.33–0.60)	0.86 (0.78–0.95)	69

Table 2B – Prediction of "good" functional outcome (CPC 1–3) by prognostic investigation

Method	Specificity (95% CI)	Sensitivity (95% CI)	TP	TN	FP	FN	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)	N
NFL max. Day 1–4 < 55 pg/ml	95 (89–98)	48 (37–60)	31	84	4	33	0.89 (0.74–0.95)	0.72 (0.63–0.79)	0.89 (0.84–0.94)	152
NSE Day 3 < 17 ng/ml	96 (88–99)	44 (32–57)	25	55	2	32	0.93 (0.77–0.98)	0.63 (0.53–0.73)	0.92 (0.87–0.97)	114
Cortical SSEP amplitude Day 3 > 2.5 μV	93 (85–97)	55 (40–68)	24	67	5	20	0.83 (0.65–0.92)	0.77 (0.67–0.85)	0.90 (0.84–0.95)	116
EEG reactivity Day 4	97 (89–99)	44 (30–59)	19	60	2	24	0.90 (0.71–0.97)	0.71 (0.61–0.80)	–	105
CT Day 4 GWR > 1.20	61 (46–74)	96 (79–99)	22	28	18	1	0.55 (0.40–0.69)	0.97 (0.83–0.99)	0.86 (0.78–0.95)	69

Prognostic accuracies for prediction of neurological outcome (CPC) at hospital discharge post-arrest in N = 68–152 patients. TP; true positive, TN; true negative, FP; false positive, FN; false negative; max; Maximum.

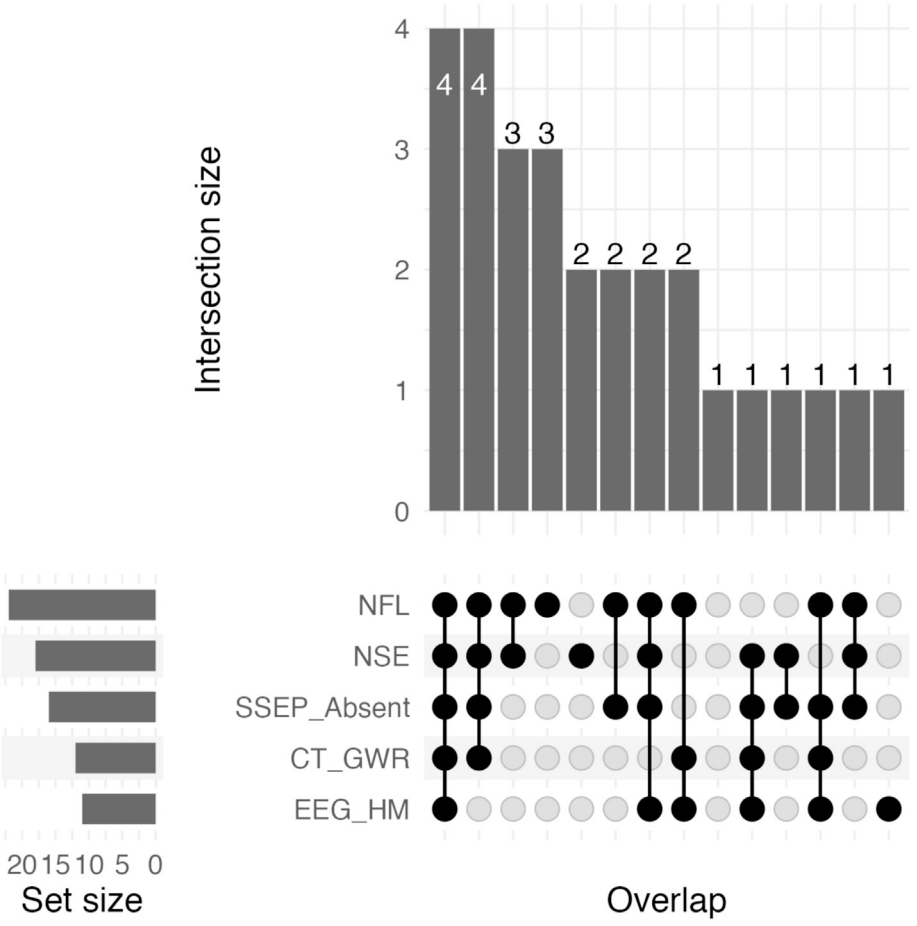

Fig. 3 – Frequency and overlap of combinations of poor outcome predictors in 44 patients with all 5 diagnostic tests available. Black dots indicate positive tests. Each column represents one possible combination of tests. Horizontal bars show the number of positive patients for each single marker. For example, column 1 represents 4 cases, where all prognostic markers for poor outcome were positive whereas in column 6 shows 2 patients where only NFL and SSEP were positive.

at 48 h after CA. We observed a similar case which was not included in our statistical analysis because NFL was sampled at 11 h after CA. A 37-year-old patient with an initial subarachnoid haemorrhage had a serum NFL concentration of 49 pg/ml. The first measured intercranial pressure (ICP) was 50 mmHg, and the patient was also declared dead by neurological criteria within 24 h after arrest.

Patient with high serum NFL and a good neurological outcome

One 62-old-patient had a good outcome (CPC 2) despite having an NFL serum level of 1770 pg/ml on day 3. This patient had a witnessed hypoxia-induced CA due to an exacerbated COPD with bystander CPR performed by paramedics, 5 min tROSC and developed a candida blood stream infection and an acute kidney injury with haemodialysis in the clinical course. The patient had no definite signs of HIE in head CT, NSE was low at 18.4 ng/ml three days after CA, cortical SSEPs were reproducible bilaterally and EEG was not highly malignant. The patient was discharged to rehabilitation with ventilation via a tracheostoma in an awake, alert, and partly oriented state.

Discussion

Our main study results

(1) Serum NFL between 24 and 96 h after CA is a highly specific and moderately sensitive biomarker for both good and poor neurological outcome prediction in comatose CA patients.
(2) Serum NFL added prognostic information for both good and poor outcome prediction to the established neuroprognostic tests.
(3) In patients with a rapid increase in intracranial pressure, NFL serum concentrations may remain normal despite severe brain injury, most likely due to absent outflow of NFL from the injured brain to the systemic circulation.

In this retrospective observational study, we present data from a distinct cohort of CA patients with comprehensive neuroprognostic assessment after the introduction of routine serum NFL testing. In line with previous studies, we found that serum NFL is a reliable prognostic biomarker in CA patients. Our conservatively chosen, pre-specified threshold of 2000 pg/ml (SIMOA) yielded a specificity of 100% at a sensitivity of 53%, which is lower than the 60–89% sensitivity reported

by previous studies with lower thresholds of 241–1539 pg/ml.[20,39,11–14] The prognostic performance of NFL to predict good outcome is also comparable with a large cohort reported by Moseby-Knappe et al..[40] It is important to note that absolute NFL serum concentrations can vary by up to 85% between available tests, especially between single molecule analyzers and a new electrochemiluminescence method.[41] As R^2 between assays has been found to be > 0.95, it is reasonable to convert thresholds between assays, adding a safety margin. A recent review also underscores multimodal diagnostics and serial testing until fixed exchange rates for each test have been established. Also, correcting NFL for age and BMI might increase the reliability in future studies.[7] Apart from one case with CPC 2 despite an NFL of 1.770 pg/ml all five other patients with NFL > 1.000 pg/ml which had regained consciousness had severe neurological deficits (CPC 3). Thus, lower NFL cut-offs than used in our study within a multimodal prognostication approach may also be reasonable. Furthermore, our data suggests that the optimal NFL sampling time within the first 3 days after CA is on day 2 to 3.

We analyzed patients with low NFL concentrations despite severe brain injury (DNC in both cases). These patients had a rapid increase in intracranial pressure which likely explains low NFL concentrations by absent outflow of NFL from the injured brain to the systemic circulation. NFL serum concentrations in patients with possible rapid ICP elevation could therefore not always argue against severe brain injury.

Guidelines recommend a multimodal approach to neuroprognostication.[1,2,24] Adding NFL to a clinical information risk score can improve its predictive accuracy.[15] In our cohort, combining NFL with any established neuroprognostic tests increased the proportion of poor neurological outcome patients detected by 16–41%. Vice versa, single neuroprognostic tests identified 7–21% poor outcome patients in addition to NFL. It is important to note that these proportions depend on the thresholds/definitions used. The ERC/ESCIM guideline recommends predicting poor outcome in cases with at least two poor prognostic findings.[1] This approach has been externally validated in a cohort with very little risk of a self-fulfilling prophecy.[42] Applying NFL to the ERC/ESICM strategy increased the proportion of poor outcome patients with at least two poor prognostic markers from 57% to 75%. While selection bias should be considered as a potential confounder for this finding, our data highlight the potential added value of serum NFL in a multimodal neuroprognostication strategy: It will likely increase the number of patients safely predicted as poor outcome. We therefore suggest prospectively validating a multimodal neuroprognostication approach including serum NFL in future studies.

Similarly, combining NFL with one other parameter increased sensitivity for good outcome prediction by up to 27%. In a recent Korean study without NFL, performance for good outcome prognostication also increased for any combination of two prognostic tests.[43] Since the therapeutic implications of falsely optimistic neuroprognostication are less severe than of falsely pessimistic, recommendations on good outcome prediction are less standardized.[44] Nevertheless, caregiver burden, patient will, and economical aspects should be arguments for applying good outcome predictors in clinical routine.[45]

Limitations

This is a single-center study with a relatively small cohort. A strength of this cohort is that patients in this study had extensive high-quality multimodal testing. As not all patients received NFL testing, there is some degree of selection bias: patients without NFL measurements had less shockable rhythms and overall poorer outcomes but similar time to return of spontaneous circulation (tROSC) and similar demographics. Patients with an unstable circulatory situation or ECMO might have been too impaired for some of the extensive neurological testing and as NFL was usually measured at day 3 after CA, some patients have died before the timepoint of NFL measurement. Head-to-head comparison of all 5 tests in the same patients was only possible in a smaller subset of our cohort.

Furthermore, the results of clinical neurological examination were not collected in our registry. Due to the structure of the registry, we could only assess neurological outcome at hospital discharge. As in most studies in the field, the results were available to the treating physicians, generating the risk of an incorporation bias ("self-fulfilling prophecy"). Future prospective trials with more restrictive use of WLST or using neuropathological analyses could address this concern. Since our study utilized only one NFL assay, potential analytical differences should be considered when applying the thresholds reported here, as mentioned above.

Conclusion

Serum NFL within the first days after CA is a highly specific and moderately sensitive predictor of poor neurological outcome and absence of severe HIE. Threshold values should be interpreted in the context of the specific assay used (here: SIMOA). When integrated into a multimodal neuroprognostication approach with standardized thresholds, serum NFL can significantly enhance the early and reliable identification of patients with poor outcomes or absence of HIE after CA.

Declarations of interest

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CRediT authorship contribution statement

Constanze Czimmeck: Writing – original draft, Investigation, Data curation, Conceptualization. **Jens Nee:** Writing – review & editing, Project administration, Data curation. **Carl Hinrichs:** Investigation, Data curation. **Christian Endisch:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Péter Körtvélyessy:** Writing – review & editing, Validation. **Christoph J. Ploner:** Writing – review & editing. **Christoph Leithner:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Conceptualization. **Martin Kenda:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2025.110650.

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