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Relationship between serum neuron-specific enolase and EEG after cardiac arrest: A reappraisal

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HIGHLIGHTS

- The relationship between EEG and neuron specific enolase (NSE) has been previously described, but without considering the influence of EEG background.
- NSE is higher in patients with repetitive epileptiform discharges on continuous, discontinuous, and burst-suppression.
- NSE is however lower with epileptiform features on suppression, likely reflecting the need of viable neurons to generate them.

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ABSTRACT

Objective: Electroencephalogram (EEG) and serum neuron specific enolase (NSE) are frequently used prognosticators after cardiac arrest (CA). This study explored the association between NSE and EEG, considering the role of EEG timing, its background continuity, reactivity, occurrence of epileptiform discharges, and pre-defined malignancy degree.
Methods: Retrospective analysis including 445 consecutive adults from a prospective registry, surviving the first 24 hours after CA and undergoing multimodal evaluation. EEG were interpreted blinded to NSE results.
Results: Higher NSE was associated with poor EEG prognosticators, such as increasing malignancy, repetitive epileptiform discharges and lack of background reactivity, independently of EEG timing (including sedation and temperature). When stratified for background continuity, NSE was higher with repetitive epileptiform discharges, except in the case of suppressed EEGs. This relationship showed some variation according to the recording time.
Conclusions: Neuronal injury after CA, reflected by NSE, correlates with several EEG features: increasing EEG malignancy, lack of background reactivity, and presence of repetitive epileptiform discharges. The correlation between epileptiform discharges and NSE is influenced by underlying EEG background and timing.
Significance: This study, describing the complex interplay between serum NSE and epileptiform features, suggests that epileptiform discharges reflect neuronal injury particularly in non-suppressed EEG.
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1. Introduction

The number of successfully resuscitated patients from cardiac arrest (CA) is increasing as pre-hospital care advances (Gräsner et al., 2020). As a result, there is a growing number of comatose patients in the Intensive Care Unit (ICU), with the leading cause of death being withdrawal of life-sustaining treatment (WSLT) due to poor outcome prognostication (Sandroni et al., 2018). This emphasizes the need for reliable risk stratification and the importance of a multimodal approach in defining outcome. Currently used tools of multimodal prognostication include neurological examination, neurophysiology (electroencephalography (EEG) and somatosensory evoked potentials (SSEP), serum biomarkers (mostly neuron-specific enolase (NSE)), and brain imaging (Cronberg et al., 2020).

Abbreviations: NfL, Neurofilament light; WLST, Withdrawal of life-sustaining treatment; NSE, Neuron-specific enolase; CA, Cardiac arrest; CPC, Cerebral performance category; ROSC, Return of spontaneous circulation.

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EEG represents one of the most commonly used tools for outcome prognostication (Friberg et al., 2015), as it is non-invasive and widely available. A stratified classification of standardized EEG patterns based on guidelines of the American Clinical Neurophysiology Society (Hirsch et al., 2013; Hirsch et al., 2021; Westhall et al., 2015) has been proposed, and its validity in predicting poor and good neurological outcome after cardiac arrest has been extensively studied (Rossetti et al., 2017; Rossetti et al., 2012; Westhall et al., 2016, 2015). Background EEG continuity (Hofmeijer et al., 2015; Sivaraju et al., 2015) and reactivity (Rossetti et al., 2012; Tsetsou et al., 2013) have been identified as predictors of neurological outcome; background suppression (<10 μV) and burst-suppression (>50% of suppressed trace) are considered as "highly malignant" patterns, as they have very high specificity for poor outcome (Ruijter et al., 2019; Westhall et al., 2016).

Biomarkers are less affected by temperature and sedation than clinical examination and EEG. Serum NSE is an intracellular enzyme released after CA, with a biological half-life of about 24 hours (Cronberg et al., 2011; Rossetti et al., 2012); it has a good prognostic performance towards poor outcome (sensitivity: 52–63%, specificity: 95–100%) (Cronberg et al., 2020), nevertheless, unlike EEG, it is a continuous variable and has a limited temporal resolution (Nolan et al., 2021). Recently, a cutoff value has been proposed at 60 μg/L for a poor neurological outcome (Nolan et al., 2021), while cutoffs for good outcomes are less clear (Moseby-Knappe et al., 2021; Vanat et al., 2023).

Relationships between EEG and NSE have been previously described (Beuchat et al., 2018; Cronberg et al., 2011; Moseby-Knappe et al., 2021; Rossetti et al., 2012; Stammet et al., 2015), and are relevant to understand the reciprocal influence between these two frequently used prognosticators in clinical practice. However, as opposed to a recent study (Grindegård et al., 2022) analyzing serum Neurofilament light (NfL), a biomarker of neuroaxonal injury, the interaction between EEG background and serum NSE has received little attention. The aim of the current study was to explore the relationship between the severity of pre-defined EEG patterns (highly malignant, malignant, benign) (Westhall et al., 2016, 2015), and serum NSE. We hypothesized that underlying EEG background activity, absence of its reactivity, and presence of repetitive epileptiform discharges would have an impact on NSE levels.

2. Methods

2.1. Design

This cohort study involves consecutive comatose adults treated in our ICU following CA, identified from our prospective registry (not dying within 24 h and receiving at least one EEG recording within 72 h of CA), between January 2018 and April 2022. The registry is approved by the local ethics committee (CER-VD, 116/13), with consent waiver (procedures and treatments are part of standard care).

2.2. Procedures

Details of the registry have been published elsewhere (Oddo and Rossetti, 2014; Rossetti et al., 2017). The protocol included temperature management (TTM) during the first 24 h, i.e. controlled normothermia at 36 °C (or occasionally mild hypothermia to 33–34 °C), with standard sedation including propofol (2–3 mg/kg/h) or midazolam (0.1–0.15 mg/kg/h); fentanyl (1.5 μg/kg/h), neuromuscular blocking agents, and noradrenaline (mean arterial pressure target: ≥65 mmHg) were administered if needed. Clinical and non-convulsive (electrical) seizures were treated with intravenous valproate and levetiracetam; in selected cases, propofol was added. The standardized prognostic evaluation included clinical examination after TTM (at 72 hours), video-EEG recordings at 12–36 and 36–72 hours (mostly lasting 20 min. each; in some cases recordings > 18 hrs were performed), median nerve SSEP after 24 hours, and serum NSE at 24 and 48 hours (assessed with an automated immunofluorescent assay (Thermo Scientific BrahmsNSE Kryptor®Immunoassay); hemolysis was avoided by manually handling samples. Withdrawal of life sustaining intensive treatment (WLST) was considered after multimodal evaluation, in the presence of at least 2 items among: lack of return of pupillary or corneal reflexes; unreactive, "highly malignant" EEG after TTM; bilateral lack of cortical responses on SSEP; treatment-resistant myoclonus and/or repetitive epileptiform EEG discharges; peak serum NSE (threshold: ≥μ75g/l) (Oddo and Rossetti, 2014; Rossetti et al., 2017). Brain magnetic resonance diffusion weighted imaging alterations were also considered in unclear cases. Neurologic outcome in survivors was assessed at 3 months, as part of clinical follow-up, through telephone interviews using the Cerebral Performance Category (CPC) Scale, categorized as 1–2: good; 3–5: poor.

EEG were interpreted upon recording by certified neurophysiologists (AOR, JN), without knowing NSE levels, according to published recommendations (Hirsch et al., 2013; Hirsch et al., 2021). In case of prolonged EEG, the timing of reactivity testing was considered for the EEG scoring. Background activity was categorized as continuous or nearly continuous (<10% suppression); discontinuous (suppression 10–<50%); burst-suppression (suppression ≥ 50%); and suppressed (>99% at < 10 μV) (Hirsch et al., 2013). We also took into consideration the presence of EEG reactivity, defined as reproducible alteration of amplitude or frequency upon stimulation (Tsetsou et al., 2015), tested and interpreted on the same day (typically within 2 hours of recording), and repetitive epileptiform discharges, defined as any periodic or rhythmic spikes, sharp waves, spike-waves, or (seizures) rhythmic waves evolving in amplitude, frequency, or field (Rossetti et al., 2012). Traces were also classified according to the Westhall grading system (Westhall et al., 2016):

- Highly malignant: Suppressed or burst-suppressed background, with or without repetitive epileptiform discharges.
- Malignant: periodic or rhythmic patterns, electrographic seizures, discontinuous or low-voltage background or reversed anterior-posterior gradient, lack of background reactivity.
- Benign: absence of all highly malignant or malignant features above.

2.3. Statistical analysis

Kruskal-Walllis tests were used to estimate correlations between peak NSE and Westhall EEG patterns, or background continuity. Association of background reactivity and epileptiform discharges with peak NSE was analyzed using Mann-Whitney U tests, and the relationship between different EEG patterns and neurological outcome was examined using chi^2 or 2-sided Fischer exact tests, as appropriate. Calculations were performed using excel and the STATA software (Version 16; College Station, TX), and significance was assumed at $p < 0.05$.

3. Results

3.1. Patients and outcome

During 52 months, 449 CA events occurring in 445 patients (4 presented with 2 events each) were entered in the registry; NSE

was measured twice in 357, and at least once in 430 patients, and we recorded a total of 426 early (at 12–36 hours; mean temperature ± standard deviation: 35.7 ± 0.8 °C, 71.9% being sedated) and 356 late (at 36–72 hours; mean temperature ± standard deviation: 36.8 ± 0.6 °C, 34.9% being sedated) EEGs. Demographics and patients' characteristics are described in Table 1. Almost half of patients (45.8%) presented with a shockable rhythm and the mean time to return of spontaneous circulation (ROSC) was 24.3 ± 18.81 minutes; 221 patients (51.4%) survived at 3 months, with 147 patients (34.2%) reaching a good outcome (CPC 1–2).

3.2. Correlation between EEG patterns and NSE

Table 2 summarizes the relationship between EEG patterns and peak serum NSE. At both timepoints, NSE was significantly higher with increasing EEG "malignancy", as well as in case of lack of background reactivity, or presence of repetitive epileptiform discharges. Clinical outcome followed the inverse pattern, also at both timepoints. While few subjects with early highly malignant EEG reached a good outcome (false positive rate 4%), no patient with suppressed early EEG (or late highly malignant recording) had good neurological outcome at 3 months. We further restricted analyses to patients without sedation at the later EEG timepoint (in normothermia): all relationships with peak NSE and clinical outcomes remained basically unchanged.

Peak serum NSE values, stratified for background EEG continuity (Figs. 1 and 2), were higher in patients with repetitive epileptiform discharges if the EEG was continuous (both timepoints, p: 0.003 and $p < 0.001$, respectively), discontinuous or burst-suppressed (early EEG only, p: 0.018 and p: 0.003, respectively). Conversely, in suppressed recordings, NSE tended to be higher if not associated with epileptiform features; this relationship reached significance in late EEGs (p: 0.011).

4. Discussion

This analysis offers a detailed view on the relationship of distinct EEG features and serum NSE. Besides confirming the correlation between abnormal EEG patterns (regarding continuity, reactivity, and occurrence of repetitive epileptiform features) and elevated serum NSE in the first few days after CA, this study shows that the relationship between NSE and epileptiform features depends on EEG background continuity. As shown in Figs. 1 and 2, when peak serum NSE is stratified for background EEG continuity, NSE is higher in patients with epileptiform features and continuous EEG at both time-points (in early recordings, the same applies also for discontinuous or burst-suppressed background); conversely, in late EEGs, NSE is significantly lower in those with epileptiform discharges and suppressed background. Finally, this study correlates the standardized EEG Westhall classification with NSE and thus the degree of neuronal injury.

NSE measured at 24–48 hours correlates with abnormal EEG findings. Of relevance, restricting analysis to patients off sedation and in normothermia did not change the results, thus showing that these two variables probably exert a negligible influence on NSE (at least as compared to EEG features). Even though exact cutoff levels for poor neurologic outcome may be still debated (Cronberg et al., 2020; Nolan et al., 2021; Oddo and Rossetti, 2014; Stammet et al., 2015), NSE has a reasonable prognostic performance towards poor outcome, and is still more extensively used than other blood biomarkers (Cronberg et al., 2020). Our results highlight that higher degree of EEG background continuity is associated with lower NSE (Ruijter et al., 2019; Sivaraju et al., 2015; Westhall et al., 2018). This is in accordance with the histopathologic association between highly malignant EEG, injury after CA and high NSE (Endisch et al., 2020). In line with previous studies, EEG background reactivity is associated with markedly lower serum NSE and represents a favorable outcome predictor (Admiraal et al., 2020; Juan et al., 2015; Oddo and Rossetti, 2014).

The strong correlation between the standardized Westhall EEG classification and increasing NSE replicates recent findings on NfL, and pinpoints the general validity of this scoring approach that parallels neuronal and neuro-axonal injury (Grindegård et al., 2022). Highly malignant EEG activity was originally described as a predictor of poor outcome with 100% specificity (Westhall et al., 2016). Even though our results are in global accordance with this relationship, the presence of false positives (patients with highly malignant EEG reaching a good neurological outcome), was 4% in early and 0% in late recordings (broadly comparable to 9% in early and 2% in late EEG (Beuchat et al., 2018), and to 1% in late EEG (Grindegård et al., 2022). This underscores the importance of a multimodal prognostic approach at normal temperature and without sedation to minimize false-positivity (Cronberg et al., 2020; Nolan et al., 2021), as sedation might indeed generate a bias by favoring early background burst-suppression (Westhall et al., 2016).

We also examined the influence by the underlying EEG background on the relationship between NSE and the presence of repetitive epileptiform discharges. To our knowledge, this approach was explored recently analyzing NfL (Grindegård et al., 2022), but the present study represents the first analysis on NSE data. Contrary to the NfL findings (describing higher serum values only in continuous backgrounds, and based on EEGs recorded after TTM only), we show that the relationship between NSE and epileptiform features is more robust during early EEGs (under TTM), as it is significant for continuous, discontinuous, and burst-suppressed backgrounds, but only continuous backgrounds in late recordings (which are thus reminiscent of the NfL findings). Additionally, suppressed background activity showed a reverse tendency, as NSE was significantly higher in the absence of epileptiform discharges, reaching significance in late EEGs. This may suggest that viable cells are needed for epileptiform discharges in this EEG background setting (Snider et al., 2022). It is worth noting that despite the statistical significancy of our results, ranges of NSE levels overlap to some extent. However, along with the evidence that EEG suppression is associated with the highest serum NSE peak and poor neu-

Table 1
Patients' demographics and clinical characteristics of 430 cardiac arrest episodes (426 patients).

Age (years) mean (±SD)	61.61 ± 15.21
Women, number (%)	110 (25.80%)
Cardiac variables	
• Shockable rhythm, n (%)	197 (45.80%)
• Time (min) to ROSC, mean (±SD)	24.3 ± 18.81
Recording of continuous EEG (>18hrs), n (%)	32 (7.4%)
EEG latency (hrs) mean (±SD)	
• Early EEG	18.82 ± 5.62
• Late EEG	51.69 ± 10.0
Presence of pharmacological sedation, n (%)	
• Early EEG	309 (71.9%)
• Late EEG	157 (34.9%)
Temperature (°C) during EEG recording, mean (±SD)	
• Early EEG	35.72 ± 0.73
• Late EEG	36.80 ± 0.65
Outcome at 3 months, n (%)	
• CPC 1	57 (13.2)
• CPC 2	90 (20.9)
• CPC 3	73 (16.9)
• CPC 4	1 (0.2)
• CPC 5	208 (48.3)

ROSC: return of spontaneous circulation; CPC: Cerebral Performance Category; SD: standard deviation.

Table 2
Correlations between EEG and peak serum NSE, and clinical outcome.

			number (%)	Peak NSE (μg/L) (Median, range)	Test	P*	CPC 1–2 at 3 m, n (%*)	Test	P**
Early EEG (n = 426)	Westhall	benign	91 (22)	25.5 (4.1–129.1)			69 (68)		
		malignant	153 (38)	29.2 (4.4–333.4)	Kruskal-Wallis	<0.001	71 (44)		
		highly malignant	163 (40)	69.3 (10.3–1400.0)			7 (4)	Chi^2	<0.001
	Background	continuous	149 (37)	27.0 (4.1–333.4)			93 (62)		
		discontinuous	103 (25)	28.0 (8.1–532.6)	Kruskal-Wallis		47 (46)		
		burst-suppressed	114 (28)	121.0 (10.3–845)		<0.001	7 (6)	Fisher	<0.001
		suppressed	42 (10)	231.0 (11.3–1400.0)			0 (0)		
	Reactivity	yes	249 (61)	27.0 (4.1–321.7)	U	<0.001	139 (56)	Chi^2	<0.001
		no	159 (39)	83.0 (9.9–1400.0)			8 (5)		
	Repetitive epileptiform discharges	yes	62 (15)	79.0 (12–450.7)			2 (3)		
		no	346 (85)	29.0 (4.1–1400.0)	U	<0.001	145 (42)	Fisher	<0.001
Late EEG (n = 356)	Westhall	benign	132 (39)	26.5 (4.1–224.4)			81 (56)		
		malignant	130 (38)	42.0 (8.1–335.2)	Kruskal-Wallis	<0.001	29 (25)	Fisher	<0.001
		highly malignant	81 (24)	107.9 (18.6–1400.0)			0 (0)		
	Background	continuous	204 (59)	29.0 (4.1–388.3)			99 (49)		
		discontinuous	66 (19)	44.0 (8.1–293.7)	Kruskal-Wallis		11 (17)	Fisher	<0.001
		burst-suppressed	34 (10)	70.0 (18.6–333.4)		<0.001	0 (0)		
		suppressed	44 (13)	196.0 (39.4–1400.0)			0 (0)		
	Reactivity	yes	217 (62)	28.0 (4.1–335.2)	U	<0.001	106 (44)	Fisher	<0.001
		no	131 (38)	93.0 (13.4–1400.0)			4 (3)		
	Repetitive epileptiform discharges	yes	63 (18)	60.0 (15.4–450.7)			4 (6)		
		no	285 (82)	32.0 (4.1–1400.0)	U	<0.001	106 (37)	Fisher	<0.001
Late EEG without sedation (n = 229)	Westhall	benign	91 (40)	26.3 (4.1–224.4)			51 (54)		
		malignant	77 (35)	48.0 (12.0–335.2)	Kruskal-Wallis	<0.001	16 (21)	Fisher	<0.001
		highly malignant	57 (25)	113.2 (18.6–1400.0)			0 (0)		
	Background	continuous	140 (61)	28.2 (4.1–388.3)			63 (44)		
		discontinuous	31 (13)	48.3 (15.6–293.7)	Kruskal-Wallis		4 (13)	Fisher	<0.001
		burst-suppressed	20 (9)	91.3 (18.6–333.4)		<0.001	0 (0)		
		suppressed	39 (17)	235.4 (40.1–1400.0)			0 (0)		
	Reactivity	yes	132 (58)	27.4 (4.1–335.2)	U	<0.001	65 (48)	Fisher	<0.001
		no	98 (42)	105.2 (13.4–1400.0)			2 (2)		
	Repetitive epileptiform discharges	yes	46 (20)	60.6 (18.6–450.7)			3 (7)		
		no	184 (80)	32.5 (4.1–1400.0)	U	<0.001	64 (34)	Fisher	<0.001

NSE: Neuron specific enolase. CPC: Cerebral Performance Category. U: Mann-Whitney U test.
P*: significant between peak NSE values when comparing different EEG patterns.
P**: significant between CPC 1–2 at 3 months, when comparing different EEG patterns.

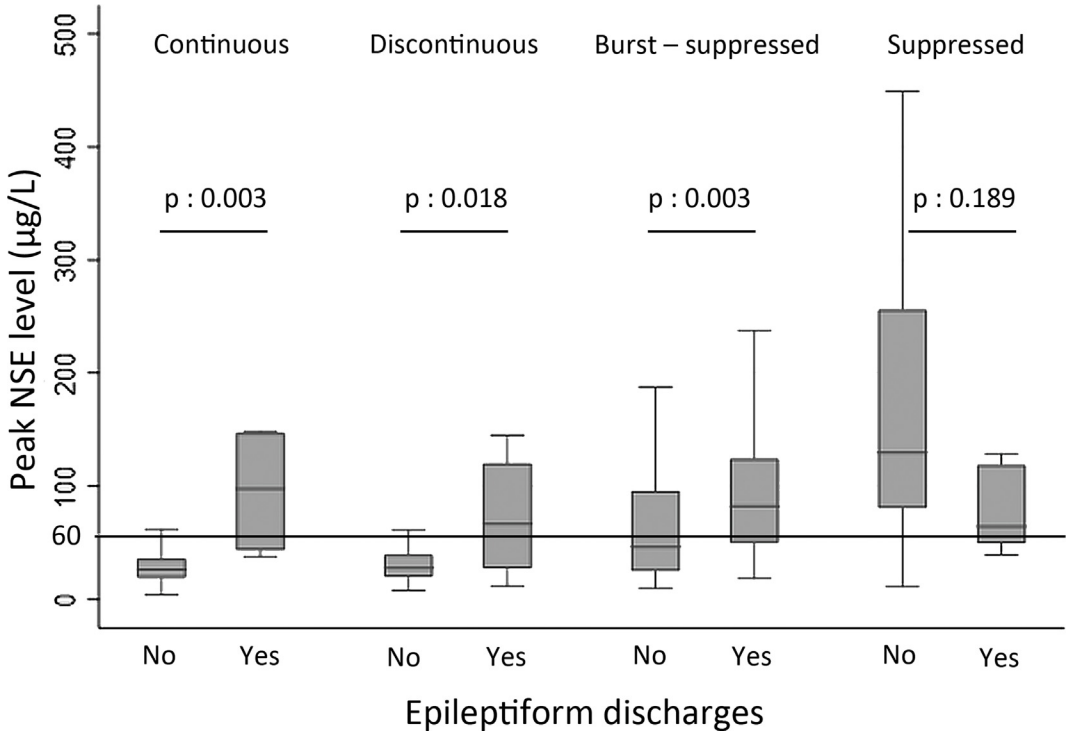

Fig. 1. Peak serum NSE (neuron specific enolase), stratified for background continuity (top) and occurrence of repetitive epileptiform discharges (bottom) on early EEG. The horizontal line at 60 µg/l shows the recommended threshold for poor outcome in multimodal assessments (Nolan et al., 2021).

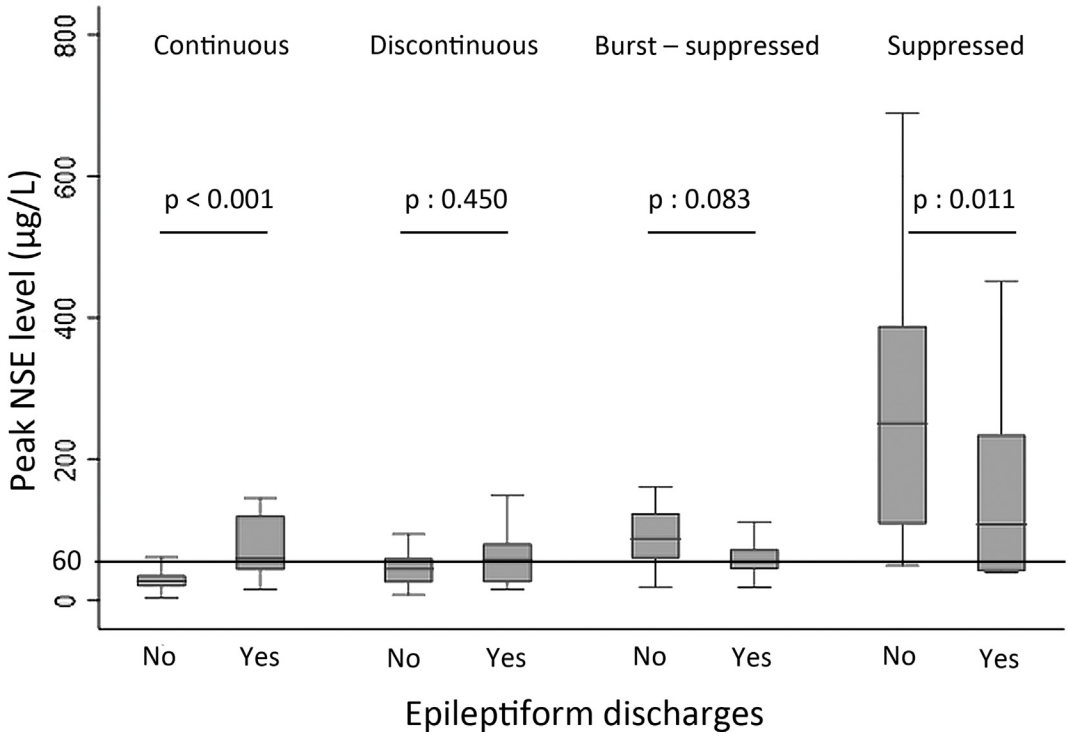

Fig. 2. Peak serum NSE (neuron specific enolase), stratified for background continuity (top), and occurrence of repetitive epileptiform discharges (bottom) on late EEG. The horizontal line at 60 µg/l shows the recommended threshold for poor outcome in multimodal assessments (Nolan et al., 2021).

rological outcome (with 100% specificity in the present cohort), our findings support the hypothesis that the global extent of neuronal injury is better represented by EEG suppression than epileptiform discharges.

This study, performed on a large dataset with reasonable internal (EEGs scored by two experienced neurophysiologists, JN and AOR, working together since many years) and external validity (patients' characteristics similar to other cohorts (Ruijter et al., 2019;

Sivaraju et al., 2015), has limitations. Firstly, our findings are based on routine EEG recordings. However, even though continuous EEG is sometimes preferred (Sivaraju et al., 2015), routine EEGs have been found to provide comparable information in terms of prognostication and outcome (Alvarez et al., 2013; Crepeau et al., 2014; Rossetti et al., 2020; Urbano et al., 2022). Secondly this is a single cohort, and results should be replicated in further studies. Moreover, we recognize that a self-fulfilling prophecy cannot be excluded, as EEG recordings and NSE values were some of the predictors used to decide on withdrawal of intensive care support. Nonetheless, the aim of this analysis was to explore correlations between EEG activity and NSE, and not neurologic outcomes. Even more importantly, EEG was interpreted before peak NSE was available. Furthermore, as stated above, sedation might influence EEG interpretation by facilitating early background burst-suppression. However, it has been shown that EEG retains high prediction performances in the first 24 hours (Ruijter et al., 2019a,b). Moreover, in our study, the number of subjects undergoing sedation during the second EEG recording was markedly decreased, and the relationship between EEG features, peak NSE and clinical outcome remained unchanged after restricting analyses to patients off sedation in normothermia. Finally, NSE was not measured twice in each patient.

5. Conclusion

This study outlines the complex relationship between neuronal injury (which is assumed to be reflected by serum NSE) and several EEG features: neuronal damage correlates with increasing background discontinuity (also paralleled by the Westhall classification), lack of its reactivity, and presence of repetitive epileptiform discharges. While in patients with increasing EEG background continuity (particularly in early recordings) higher NSE occurs with epileptiform discharges, in those with suppressed background (especially in late recordings) lower NSE is seen with epileptiform discharges. This shows that the interplay between epileptiform activity and neuronal injury is strongly influenced by the underlying EEG background, and that in patients with suppressed background, which portends a poor prognosis, some residual neuronal preservation seems necessary to generate epileptiform activity.

Conflict of Interest

None of the authors have potential conflicts of interest to be disclosed.

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