RESUSCITATION 179 (2022) 259–266

Available online at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Neurological pupil index and its association with other prognostic tools after cardiac arrest: A *post hoc* analysis

Lorenzo Peluso[a,b,c,*], *Mauro Oddo*[d], *Andrea Minini*[c], *Giuseppe Citerio*[e], *Janneke Horn*[f,g], *Eugenio Di Bernardini*[c], *Malin Rundgren*[h], *Alain Cariou*[i,j], *Jean-Francois Payen*[k], *Christian Storm*[l], *Pascal Stammet*[m,n], *Claudio Sandroni*[o], *Fabio Silvio Taccone*[c]

Abstract

Introduction: We evaluated the concordance of the Neurological pupil Index (NPi) with other predictors of outcome after cardiac arrest (CA).

Methods: *Post hoc* analysis of a prospective, international, multicenter study including adult CA patients. Predictors of unfavorable outcome (UO, Cerebral Performance Category of 3–5 at 3 months) included: a) worst NPi $\leq$ 2; b) presence of discontinuous encephalography (EEG) background; c) bilateral absence of N20 waves on somatosensory evoked potentials ($N20_{ABS}$); d) peak neuron-specific enolase (NSE) blood levels > 60 mcg/L; e) myoclonus, which were all tested in a subset of patients who underwent complete multimodal assessment (MMM).

Results: A total of 269/456 (59 %) patients had UO and 186 (41 %) underwent MMM. The presence of myoclonus was assessed in all patients, EEG in 358 (78 %), N20 in 186 (41 %) and NSE measurement in 228 (50 %). Patients with discontinuous EEG, $N20_{ABS}$ or high NSE had a higher proportion of worst NPi $\leq$ 2. The accuracy for NPi to predict a discontinuous EEG, $N20_{ABS}$, high NSE and the presence of myoclonus was moderate. Concordance with NPi $\leq$ 2 was high for NSE, and moderate for discontinuous EEG and $N20_{ABS}$. Also, the higher the number of concordant predictors of poor outcome, the lower the observed NPi.

Conclusions: In this study, NPi $\leq$ 2 had moderate to high concordance with other unfavorable outcome prognosticators of hypoxic-ischemic brain injury. This indicates that NPi measurement could be considered as a valid tool for coma prognostication after cardiac arrest.

Keywords: Prognosis, Automated pupillometer, Heart arrest, Concordance, Automated pupillometry, Brain injury

Introduction

Prognostication of neurological outcomes in comatose cardiac arrest (CA) patients plays a pivotal role, to minimize improper therapies in patients with irreversible brain injury, improving the quality of care in patients with a good chance of survival and the communication with the relatives to avoid false expectations.[1] The 2021 European Resuscitation Council (ERC)/ European Society of Intensive Care Medicine (ESICM) guidelines for post-resuscitation care[2] suggested a multimodal prognostic algorithm in this setting. According to this algorithm, an unfavorable neurological outcome is likely in the presence of two or more of the following: a) highly malignant patterns at electroencephalography (EEG); b) neuron-specific enolase (NSE) > 60 mcg/L at 48–72 hours from the return of spontaneous circulation (ROSC); c) bilateral absence of cortical response of short-latency somatosensory evoked potentials (SSEPs) at more than 24 hours from ROSC; d) presence of status myoclonus $\leq$ 72 hours from ROSC; e) extensive hypoxic-ischemic brain injury on brain imaging; f) bilateral absence of pupillary and corneal reflex at $\geq$ 72 hours from ROSC. The assessment of pupillary reactivity with automated pupillometry (AP) may improve outcome prediction and reduce the bias of standard manual evaluation.[3] In a multicenter study,[3] which aimed to compare prognostic performance of standard vs quantitative assessment of PLR, a neurological pupil index (NPi) $\leq$ 2 at 24–72 h from

* Corresponding author at: Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy.
E-mail address: lorenzopeluso80@gmail.com (L. Peluso).

https://doi.org/10.1016/j.resuscitation.2022.07.030
Received 30 May 2022; Received in Revised form 18 July 2022; Accepted 23 July 2022

ROSC had 100 % specificity and 32 % sensitivity for unfavorable outcome in this setting.

Compared to the 2015 guidelines, the updated 2021 guidelines introduced the principle of concordance among test results. In case of discordance between those tests, a prognostic reassessment is recommended to avoid misclassification and false-positive predictions. As available tools evaluate different cerebral areas and pathways with variable sensitivity to the anoxic injury, more analyses on concordance among different predictors are necessary. In this setting, no data evaluating NPi with other recommended prognostic factors are available.

The aim of this study was therefore to assess the concordance of NPi with other prognostication tools in unconscious patients suffering from post-anoxic brain injury.

Methods

Study design

This is a *post hoc* analysis of a prospective, multicentric international prognostic study involving 10 European intensive care units and enrolling 456 comatose patients following CA.[3] The different centers were selected, through the ESICM Neuro-Intensive Care Section, based on their experience with neuro-prognostication of CA patients. The study protocol was approved by the Ethics Committee of each institution, and informed consent to participate in the study was obtained from the patients' next of kin or their legal tutors, following local ethical recommendations. The accuracy of the data collected was monitored by the various researchers. The design and methodology of the study are in accordance with the STARD guidelines regarding the diagnostic accuracy of the reported data[4] and the Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest issued by the American Heart Association.[5]

Patients

Patients were unconscious (Glasgow Coma Score $\leq$ 6) adults (>18 years) who were admitted to an Intensive Care Unit from January 2015 to March 2017, following resuscitation from cardiac arrest from all rhythms. Patients were treated according to the 2015 ERC/ESICM guidelines for post-resuscitation care, including targeted temperature management (TTM, i.e., 33° or 36° C, according to local practices), sedation (midazolam or propofol) and analgesia (morphine, fentanyl and remifentanil).

Demographic and clinical variables

Demographic and clinical variables included age, gender, initial arrest rhythm [categorized as shockable (ventricular fibrillation or pulseless ventricular tachycardia) or non-shockable (asystole or pulseless electrical activity, PEA)], time to ROSC, the dose of noradrenaline on admission, body temperature on admission, temperature target for TTM (categorized in TTM 33 °C or TTM 36 °C), duration of TTM and administration of sedatives, analgesics, and noradrenaline.

Intervention

Quantitative pupillometry was performed using the NPI-200 pupillometer (Neuroptics Inc, Irvine, CA, USA). The pupillometer uses an infrared camera and through calibrated light stimulations of fixed intensity (1000 Lux) and fixed duration (3.2 s) ensures fast and accurate measurement of pupil diameter and sampling of other dynamic variables of the pupils. The instrument-specific algorithm is based on diameter, constriction and latency percentage, constriction rate and pupil dilation rate. As such, the NPi is provided, using a scale from 0 to 5, combining the results from the above variables and those collected in healthy individuals, through an algorithm developed by the company. The pupillometry data were acquired on each eye from admission to day 3 after the CA; an NPi $\leq$ 2 occurring anytime between day 1 to day 3 was identified as the best cut-off to predict UO with a specificity of 100 %.[3]

The ICU doctors or nurses who used the pupillometer were not directly involved in patient care and those who verified the outcome were blinded to quantitative pupillometry data. Decisions on treatment intensity and withdrawal of life-sustaining therapies (WLST) were based on local prognosis algorithms used in this category of patients and did not include pupillometry data.

Neurological monitoring and assessment

Neurological monitoring was instituted according to local protocols and not standardized in participating centers. For EEG monitoring, it was requested whether a "discontinuous" EEG background (i.e., less than 50 % of the monitored time with a suppressed background) was present, regardless of the use of an intermittent or continuous recording. The highest NSE value within the first 72 hours after arrest was also recorded. If SSEPs were performed, the bilateral absence of N20 waves ($N20_{ABS}$) within 48–72 hours from arrest was recorded. The presence of myoclonus, regardless if subtle presentation or status myoclonus, was recorded daily within the first 72 hours from arrest.

Neurological outcome was assessed 3 months after the arrest, using the Cerebral Performance Categories (CPC).[6] A favorable outcome (FO) was defined as CPC 1 (=full recovery) or 2 (=moderate disability, return to home). An unfavorable outcome (UO) was defined as CPC 3 (=severe disability, at the rehabilitation facility), 4 (=vegetative state) or 5 (=death).

Study endpoints

The primary aim of this analysis was to assess the concordance between the NPi and the other prognostic tests that were performed over the study period. The working hypothesis is that an NPi $\leq$ 2 would be more frequently observed in patients with additional features of brain injury (i.e., "discontinuous" EEG pattern, bilateral absence of cortical SSEP N20 wave, $N20_{ABS}$; blood levels of NSE above 60 mcg/L; myoclonus), which would confirm its accuracy to detect severe hypoxic-ischemic brain injury. To evaluate this hypothesis, the worst NPi value over the first 3 days and the worst result from each predictor (if assessed repeatedly) were used.

Secondary outcomes included the concordance between NPI $\leq$ 2 with other predictors of poor outcome; for this analysis, only patients having all available prognostic tools (defined as the multimodal monitoring (MMM) group) were considered.

Statistical analysis

Data are presented as counts (percentages) or medians [interquartile range]. Descriptive statistics were calculated for all study variables and the normal distribution was evaluated using the Kolmogorov-Smirnov test. The differences between the two groups were compared using Student T-Test or Mann-Whitney U test for continuous variables and Chi-Square test or Fisher Exact test for categorical variables, as appropriate. The differences within three groups or

more were tested using the One-Way ANOVA Test or Kruskal-Wallis Test, as appropriate. Pairwise *post hoc* comparisons were made using Bonferroni correction. The correlation between continuous variables was calculated with Pearson Test or Spearman Test, as appropriate. The performance of each predictor was analyzed by calculating the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV). The false-positive rate (FPR) for each tool was calculated as the rate of false-positive divided by the number of patients with FO. A receiver operating characteristics (ROC) curve was also computed to identify the NPi cut-off values resulting in a specificity of at least 95 % to predict a discontinuous EEG, $N20_{ABS}$, NSE > 60 mcg/L or the presence of myoclonus. The concordance between the different indices for predicting UO was defined as the presence of two or more indices suggesting UO and expressed as a percentage. As described in a previous study, we arbitrarily considered a > 75 % concordance between two or more predictors as "high"; a 50–74 % concordance as "moderate" and a < 50 % concordance was defined as "weak".[7] The statistical analysis was performed using IBM SPSS Statistics for Macintosh 25 (Armonk, NY, USA) and GraphPad Prism 9 (San Diego, CA, USA). Statistical significance was considered with a $p < 0.05$.

Results

Patients' characteristics

A total of 456 patients were enrolled in the study; of those, 186 (41 %) were included in the MMM group for concordance analysis. The characteristics of the study population are presented in Table 1. A total of 269 patients (59 %) had UO. Patients in the MMM group were less frequently of male gender and had higher temperature during TTM compared to patients without MMM; patients in the MMM group also presented more frequently with $N20_{ABS}$, discontinuous EEG and myoclonus than others, and had a higher occurrence of UO (70 % vs 51 %) and higher mortality (62 % vs 47 %).

Performance of poor neurological outcome predictors

Myoclonus was assessed in all patients, EEG was assessed in 358 (78 %) patients, 228 (50 %) patients had at least one NSE measurement and 186 (41 %) SSEPs were recorded. Specificity and sensitivity for each predictor for UO are reported in Table 2. $N20_{ABS}$ showed

Table 1 – Characteristics of the study population, according to the presence of multimodal monitoring.

	Overall (n = 456)	MMM (n = 186)	No MMM (n = 270)	*p values*
Age, years	62 [51–72]	63 [53–72]	62 [50–73]	0.96
Male gender, n (%)	357 (78)	137 (74)	220 (81)	0.04
Cardiac arrest characteristics				
Time to ROSC, min	22 [15–36]	22 [16–35]	20 [13–36]	0.14
Non-shockable rhythm, n (%)	196 (43)	84 (45)	112 (41)	0.61
Non-cardiac cause, n (%)	170 (37)	73 (39)	97 (36)	0.49
Cooling methods, n (%) *Intra-vascular* *Surface*	123 (27)333 (73)	49 (26)137 (74)	74 (27)196 (73)	0.83
TTM target temperature, °C	36 [33–36]	36 [33–36]	35 [33–36]	0.03
Temperature on admission °C	35.2 [34.5–36.0]	35.2 [34.5–36.0]	35.2 [34.3–36.0]	0.41
Vasopressors on admission, n (%)	188 (58)	80 (60)	108 (57)	0.65
Neuro-prognostication				
Worst NPi	3.7 [3.1–4.2]	3.5 [3.1–4.0]	3.9 [3.1–4.3]	< 0.01
NPi ≤ 2, n (%)	87 (19)	32 (17)	55 (20)	0.47
Discontinuous EEG, n (%)	137/358 (38)	80/166 (48)	57/192 (30)	< 0.01
$N20_{ABS}$, n (%)	63/186 (34)	63/186 (34)	-	< 0.01
Peak NSE, μg/L	43 [25–120]	45 [27–120]	39 [25–119]	0.54
NSE > 60 μg/L, n (%)	92/228 (40)	51/125 (41)	41/103 (40)	0.89
Myoclonus at any time, n (%)	92 (20)	52 (28)	40 (15)	< 0.01
Therapies				
Vasopressors on admission, n (%)	188/322 (58)	80/133 (60)	108/189 (57)	0.65
Vasopressors on day 1, n (%)	209/343 (61)	87/151 (58)	122/192 (64)	0.27
Vasopressors on day 2, n (%)	132 /293 (45)	73/150 (49)	59/143 (41)	0.24
Opioids on admission, n (%)	106/198 (54)	41/72 (57)	65/126 (52)	0.55
Opioids on day 1, n (%)	143/231 (62)	62/93 (67)	81/138 (59)	0.27
Opioids on day 2, n (%)	76/246 (31)	39/117 (33)	37/129 (29)	0.49
Outcomes				
UO at 3 months, n (%)	269 (59)	131 (70)	138 (51)	< 0.01
3-month mortality, n (%)	243 (53)	115 (62)	128 (47)	< 0.01

NPi = neurologic pupil index; ROSC = return of spontaneous circulation; TTM = targeted temperature management; EEG = electroencephalography; $N20_{ABS}$ =-bilaterally absent N20 cortical potentials; NSE = neuron specific enolase; UO = unfavorable neurological outcome.

Table 2 – Different prognostic tools according to neurological outcome.

	UO (n = 269)	FO (n = 187)	*p values*	Sensitivity [95 % CI] Specificity [95 % CI]	PPV [95 % CI] NPV [95 % CI]	FPR
Worst NPi	3.4 [0.0–3.9]	4.1 [3.7–4.0]	< 0.01	-	-	-
NPi $\leq$ 2	87 (33)	-	< 0.01	32 [27–38]% 100 [98–100]%	100 [100–100]% 51 [49–53]%	0 [0–2]%
Discontinuous EEG	111/210 (53)	26/148 (18)	< 0.01	53 [46–60]% 82 [75–88]%	81 [75–86]% 55 [51–59]%	18 [12–25]%
$N20_{ABS}$	63/131 (48)	0/55 (0)	< 0.01	48 [39–57]% 100 [94–100]%	100 [100–100]% 45 [41–49]%	0 [0–6]%
NSE > 60 mcg/L	86/141 (61)	6/87 (7)	< 0.01	61 [52–69]% 93 [86–97]%	93 [87–97]% 60 [55–65]%	7 [3–14]%
Myoclonus	80 (30)	12 (6)	< 0.01	30 [34–36]% 94 [89–97]%	87 [79–92]% 48 [46–50]%	6 [3–11]%

UO = Unfavorable Outcome; FO = Favorable Outcome; NPi = Neurological Pupil index; EEG = electroencephalography; $N20_{ABS}$ = bilaterally absent N20 cortical potentials; NSE = neuron specific enolase; PPV = Positive Predictive Value; NPV = Negative Predictive Value; FPR = False Positive Rate.

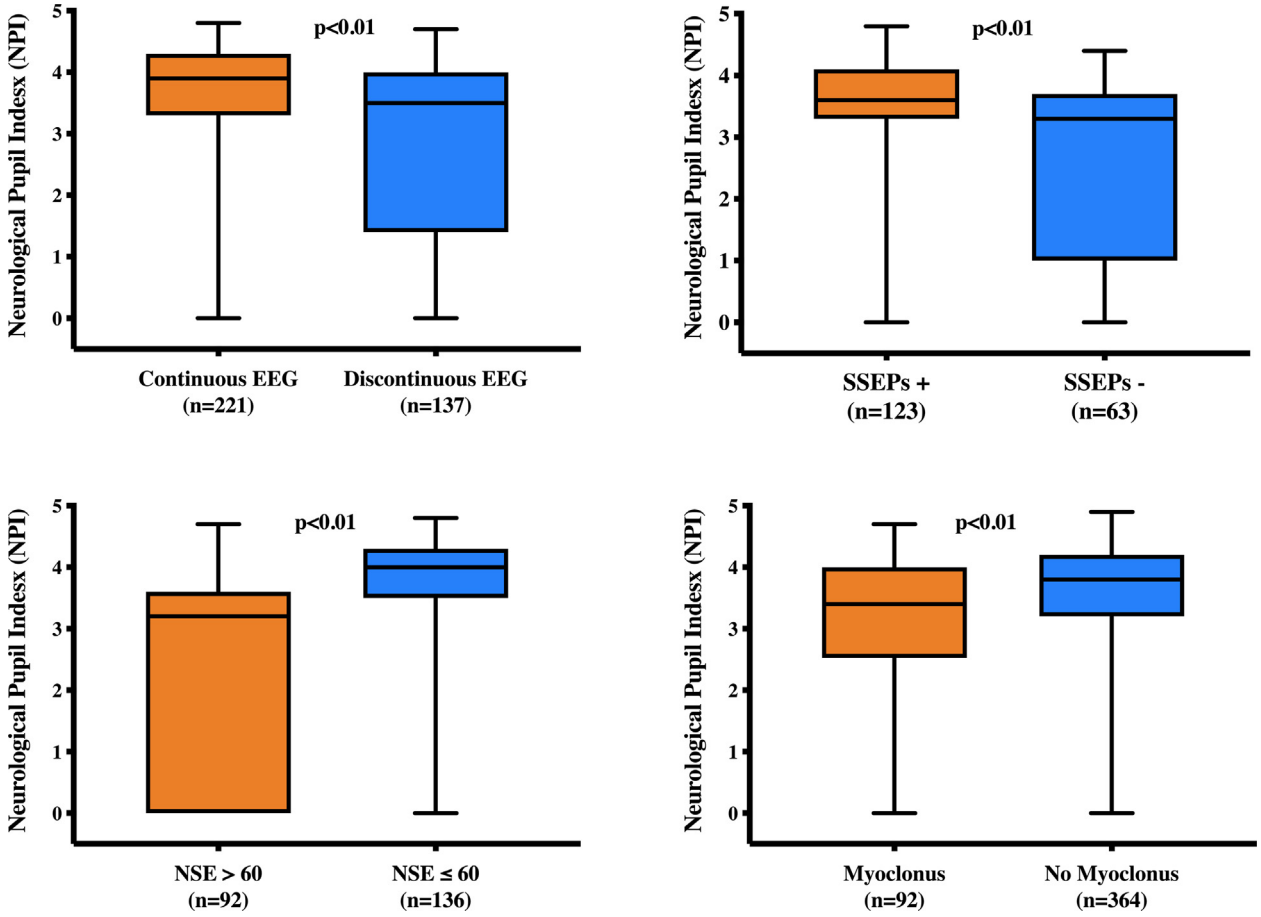

Fig. 1 – The difference in NPi values between patients with continuous and discontinuous EEG, with bilaterally absent N20 (SSEPs -) or others (SSEPs +), between high NSE or other values, between those with and without myoclonus.

a specificity of 100 % [95 % CI 94 %-100 %]; NSE levels above 60 mcg/L and myoclonus showed similar predictive values, both with a specificity of 93 % [95 % CI 86 %-97 %] and 94 % [95 % CI 89–97 %] and with a FPR of 7 % [95 % CI 3 %-14 %] and 6 % [95 % CI 3 %-11 %], respectively.

Correlation of NPi with other predictors of unfavorable outcome

Patients with discontinuous EEG, $N20_{ABS}$, NSE > 60 mcg/L, or myoclonus had a lower worst NPi value as compared to those in whom these predictors of unfavorable outcome were absent (Fig. 1 and Table 3). Also, patients with discontinuous EEG, $N20_{ABS}$ or high NSE had a higher proportion of worst NPi values ≤ 2 (Fig. 2). Moreover, the worst NPi value was inversely correlated with NSE values ($R^2 = 0.28$; $p < 0.001$; Supplemental Fig. 1); in addition, median NSE values were significantly higher in patients with NPi ≤ 2 (152 [117–400] mcg/L) than in those with higher NPi values (88 [43–169] mcg/L) for NPi between 2.1 and 2.9; 42 [27–119] mcg/L for NPi 3.0–3.9; 31 [18–46] mcg/L for NPi ≥ 4; $p < 0.01$ – Supplemental Fig. 1).

The AUCs for NPi to predict a discontinuous EEG, $N20_{ABS}$, NSE > 60 mcg/L and the presence of myoclonus were 0.63 (95 % CI 0.58–0.70), 0.68 (95 % CI 0.61–0.76), 0.79 (95 % CI 0.73–0.85) and 0.60 (95 % CI 0.54–0.66), respectively. The NPi cut-off values to predict with a specificity of at least 95 % was < 2.25 for NSE > 60 mcg/L (with a sensitivity of 39 %). For other predictors, NPi cut-offs could not provide the same specificity (<0.25 for discontinuous EEG, with specificity of 92 % and sensitivity of 21 %; <0.4 for $N20_{ABS}$ with specificity of 92 % and sensitivity of 24 %; <0.25 for the presence of myoclonus, with specificity 85 % and sensitivity 17 %).

Concordance of different prognostic tools to predict unfavorable outcome

The concordance among different prognostic tools in the MMM group is reported in Table 4. Regarding concordance between two predictors, NPi ≤ 2 was highly concordant with the presence of high NSE, while the concordance was moderate with discontinuous EEG and $N20_{ABS}$ and it was weak with myoclonus. Moreover, high NSE levels and $N20_{ABS}$ were moderately concordant with a discontinuous EEG pattern.

A moderate to high concordance was also observed for the presence of at least 3 concordant predictors; also the higher the number of concordant predictors of poor outcome, the lower the observed NPi (Supplemental Table 1). The proportion of patients with UO significantly increased with the number of concomitant predictors of unfavorable neurological outcome (i.e. 100 % [95 % CI 87 %-100 %] if at least 3 were present).

Discussion

In this study, we observed that in unconscious adult patients after resuscitation from cardiac arrest: a) NPi values were significantly lower among patients with myoclonus, abnormal EEG or SSEPs findings and high NSE levels; b) NPi values ≤ 2 had a good concordance with other predictors of UO, such as high NSE levels, discontinuous EEG or $N20_{ABS}$; c) the higher the number of concordant predictors of UO in the same patient the higher was the rate of UO.

Our multicenter study showed a good concordance between NPi and NSE. This result is in line with a single-center study[7] and suggests that low NPi values indicate the presence of an extensive hypoxic-ischemic brain injury after cardiac arrest.[8] NSE correlates with other test results suggesting severe cortical damage, such as $N20_{ABS}$ and large infarcted areas on MRI.[9] We found a moderate concordance between NPi and EEG findings. However, the only EEG predictor that was collected in this cohort was the presence of a discontinuous background. Discontinuous EEG is a pattern of moderate severity compared with highly malignant patterns, such as burst suppression or persistent suppressed background, that have been identified as strong predictors of UO.[1,10–13] Moreover,

Table 3 – Worst neurological pupil index (NPi) value and proportion of NPi ≤ 2 according to the results of other predictors of poor outcome.

	Discontinuous EEG	Continuous EEG	*p values*
	(*n* = 137)	(*n* = 221)	
Worst NPi	3.5 [1.6–4.0]	3.9 [3.3–4.3]	<0.01
NPi ≤ 2, n (%)	35 (26)	24 (11)	<0.01
	$N20_{ABS}$	Other SSEP findings	
	(*n* = 63)	(*n* = 123)	
Worst NPi	3.3 [1.1–3.7]	3.6 [3.3–4.1]	<0.01
NPi ≤ 2, n (%)	17 (27)	15 (12)	0.01
	NSE > 60	NSE $\leq$ 60	
	(*n* = 92)	(*n* = 136)	
Worst NPi	3.2 [0.0–3.6]	4.0 [3.5–4.3]	<0.01
NPi ≤ 2, n (%)	33 (36)	4 (3)	<0.01
	Myoclonus present	Myoclonus Absent	
	(*n* = 92)	(*n* = 364)	
Worst NPi	3.4 [2.6–4.0]	3.8 [3.2–4.2]	<0.01
NPi ≤ 2, n (%)	19 (21)	68 (19)	0.66

NPi = Neurological Pupil index; EEG = electroencephalography; $N20_{ABS}$ = bilaterally absent N20 cortical potentials; SSEP = Somatosensory Evoked Potential; NSE = Neuron Specific Enolase.

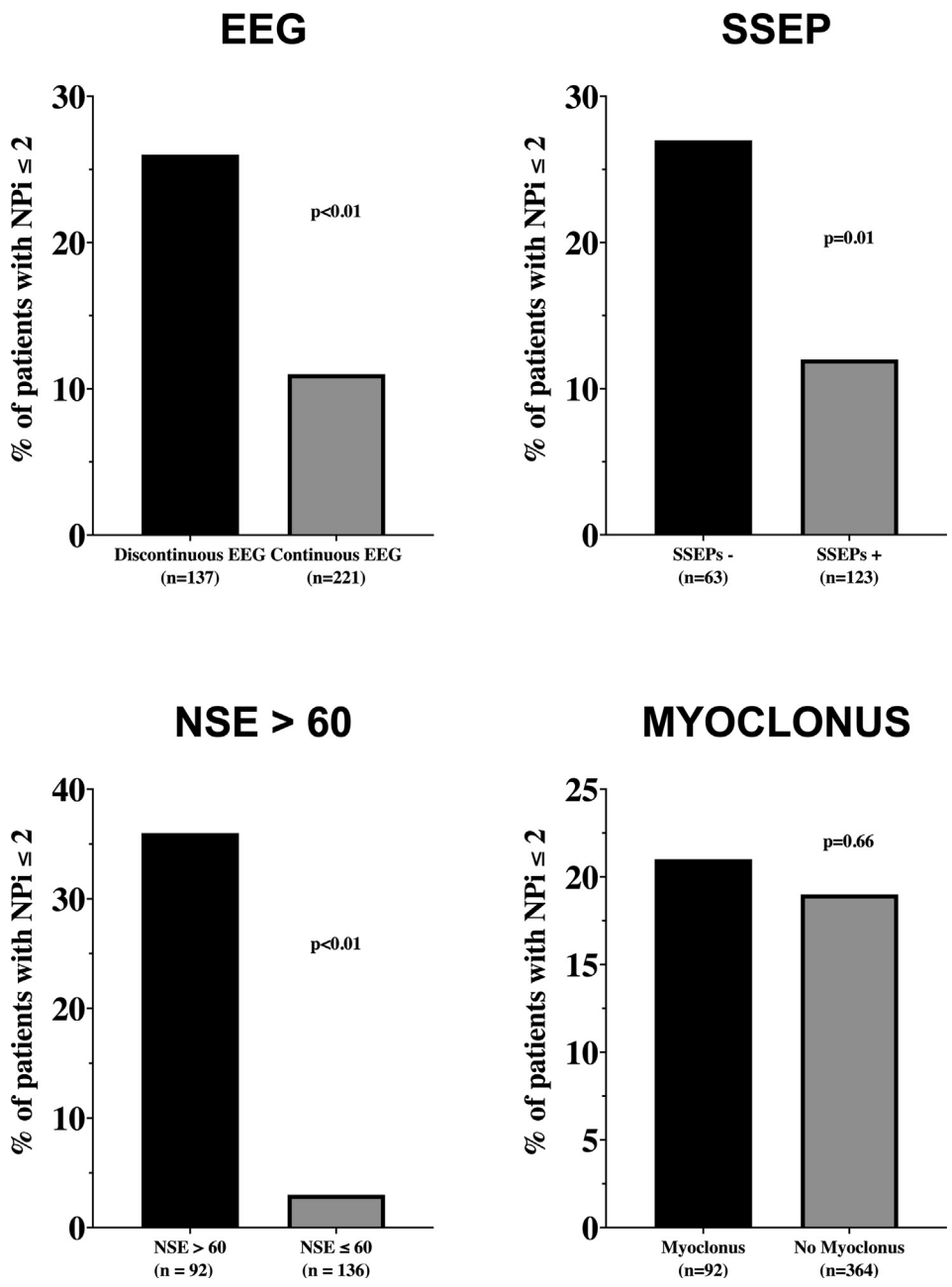

Fig. 2 – The difference in the number of patients with continuous and discontinuous EEG (a), with N20 absent (SSEPs -) and present (SSEPs +) (b), NSE < or > 60, presence of myoclonus.

the American Clinical Neurophysiology Society (ACNS) recently published guidelines precisely defining a standardized nomenclature, to avoid misinterpretation and overestimation of highly malignant patterns.[14] Pending further confirmation in other studies, these results have important clinical implications, as automated pupillometry is easily available, less costly than other prognostic tools, and easy to use or implement in clinical practice.

Our analysis could not provide additional information on the best combination of different predictors of UO. However, we observed that the higher the number of concomitant predictors of severe neurological injury was, the highest was the proportion of patients with UO. In a limited subgroup, we had a 100 % of probability of UO when at least 3 concomitant predictors were present. In another study, the combination of SSEPs, brain CT and EEG also increased the sensitivity of UO prediction from 30–54 % to 61 %.[15] In one retrospective study, a prognostic model including brain CT-scan, NSE, EEG, SSEPs, and PLR also predicted UO with a 0 % FPR,[16] significantly higher than each prognostic modality alone. Also, a combination of clinical examination, EEG reactivity, and NSE yielded the best predictive accuracy to predict UO in this setting.[17] Taking together these findings and the data from our study, the concomitant use of at least three different prognostic tools with concordant findings, has the potential to accurately predict UO, as suggested by guidelines.[2] Importantly, although most of these prognostic tools might also provide "redundant" information (i.e., adding more predictors would marginally increase the overall predictive value of one or two strong

Table 4 – Concordance among different predictors for poor outcomes in the multimodal monitoring group.

	NPi ≤ 2 (*n* = 32)	Discontinuous EEG (*n* = 80)	NSE > 60 (*n* = 51)	$N20_{ABS}$ (*n* = 63)	Myoclonus (*n* = 52)	2 Predictors (*n* = 36)	3 Predictors (*n* = 26)	4 Predictors (*n* = 13)
NPi ≤ 2 (*n* = 32)	-	16/80 (20)	13/51 (26)	17/63 (27)	12/52 (23)	9/36 (25)	9/26 (35)	2/13 (15)
Discontinuous EEG (*n* = 80)	16/26 (62)	-	32/45 (71)	41/55 (75)	33/48 (69)	19/29 (66)	24/26 (92)	13/13 (100)
High NSE (*n* = 51)	13/17 (77)	32/61 (53)	-	36/43 (84)	21/32 (66)	16/26 (62)	17/18 (94)	13/13 (100)
$N20_{ABS}$ (*n* = 63)	17/32 (53)	41/80 (51)	36/51 (71)	-	29/52 (56)	21/36 (58)	23/26 (89)	13/13 (100)
Myoclonus (*n* = 52)	12/32 (38)	33/80 (41)	21/51 (41)	29/63 (46)	-	16/36 (44)	14/26 (54)	13/13 (100)

NPi = Neurological Pupil index; EEG = electroencephalography; $N20_{ABS}$ = bilaterally absent N20 cortical potentials; SSEP = Somatosensory Evoked Potential; NSE = neuron specific enolase.

predictors), a multimodal assessment in this setting remains clinically relevant, as each isolated predictor may be biased by confounders. For instance, NPi showed an excellent specificity in the prediction of unfavorable outcomes; nevertheless, NPi ≤ 2 in the absence of severe post-anoxic brain damage has also been reported in association with sevoflurane and ketamine therapy.[18]

The clinical implications of our study are multiple. First, low NPi is a robust predictor of post-anoxic brain injury and could be adequately implemented in clinical practice to assess neurological prognosis in these patients. Although a previous study already addressed this issue,[3] in the present analysis we provided additional evidence to support the role of low NPi values as robust and quantitative markers of extended brain injury. Second, despite a good concordance with other predictors, NPi is complementary to available prognostic tools and should not be used to replace them. Indeed, only the association of several predictors increases the sensitivity of the multimodal approach to discriminate neurological outcome in CA patients. Moreover, low NPi have limited value (i.e. AUC 0.60–0.80) and clinical relevance (i.e. large confidence intervals) to predict the presence of discontinuous EEG, $N20_{ABS}$ or myoclonus, even when very low values were used. Third, in the setting where not all predictors are available (i.e. SSEPs require skills and expertise in recording and interpretation; brain imaging might not be feasible in unstable patients), NPi is a valuable, bedside available and easy-to-implement prognostic tools to increase the reliability of the predictive algorithm.

The study has several limitations. The first is the *post hoc* nature of the analysis, therefore a formal sample size calculation for the primary endpoint of the study was not performed. Second, the EEG patterns were not re-evaluated by a neurophysiologist and the discontinuous pattern rather than the highly malignant pattern, as recommended in the guidelines, was reported. As previously specified, this aspect may have biased the role of EEG in the analysis. Also, myoclonus was reported without details on its characteristics (i.e., status myoclonus or not). Third, the multimodal prognostic algorithms were not standardized in the study, which accounted for several missing pieces of information for each patient. Fourth, as for all the prognostication studies in this field, the risk of self-fulfilling prophecy may have influenced some results. Fifth, in the assessment of concordance, we considered only patients with MMM; this cohort was composed of sicker patients (i.e., highest mortality and unfavorable outcome), in whom additional prognostication parameters are more frequently used, and therefore may not be representative of all our cohort (i.e. selection bias) or a more heterogeneous populations of CA patients. Sixth, we could not further detail the reasons of death (i.e. severe post-anoxic encephalopathy vs other causes), as we expect neurological predictors to be more accurate in patients dying from neurological reasons than from others. Finally, no data on brain imaging (i.e., MRI and/or CT scans) and clinical examination were available and no associations with potential structural cerebral lesions were possible.

Conclusions

In our study, an abnormal NPi was associated with other important signs of hypoxic-ischemic brain injury, supporting its value as a predictor of UO after cardiac arrest.

Ethics approval and consent to participate

The original study protocol was approved by the ethics committees and the informed written consent was waived for the post-hoc design of the study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

No funding was obtained to this study.

Authors' contributions

LP, CS and FST conceived the study; LP, AM and FST selected the population; LP, AM and FST conducted the statistical analysis and wrote the first draft of the paper; all the other authors revised the text for intellectual content.

Conflict of interest

We declare FST, GC and MO as scientific advisors for NeurOptics Inc. The other authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2022.07.030.

Author details

[a]*Department of Biomedical Sciences, Humanitas Huniversity, Pieve Emanuele, Milan, Italy* [b]*Department of Anaestesiology and Intensive Care, Humanitas Gavazzeni, Bergamo, Italy* [c]*Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium* [d]*Medical Directorate for Research, Education, Innovation, Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne, Lausanne, Switzerland*[e]*School of Medicine and Surgery, University Milano Bicocca, Neuro-intensive Care Unit, San Gerardo Hospital, ASST-Monza, Monza, Italy* [f]*Department of Intensive Care, Amsterdam University Medical Centers, Amsterdam, the Netherlands* [g]*Amsterdam Neurosciences, Amsterdam University Medical Centers, Amsterdam, the Netherlands* [h]*Department of Clinical Sciences, Anesthesiology and Intensive Care Medicine, Skåne University Hospital, Lund University, Lund, Sweden* [i]*Intensive Care Unit, Hopital Cochin, Paris, France* [j]*Paris Descartes University, Paris, France*[k]*Department of Anesthesia and Critical Care, Grenoble Alpes University Hospital, Grenoble, France* [l]*Department of Internal Medicine, Nephrology and Intensive Care, Charité-University, Berlin, Germany* [m]*Department of Intensive Care Medicine, Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg* [n]*Department of Life Sciences and Medicine, Faculty of Science, Technology and Medicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg* [o]*Department of Intensive Care Emergency Medicine and Anaesthesiology, Fondazione Policlinico Universitario A. Gemelli-IRCCS, Rome, Italy*

REFERENCES

1 Sandroni C, D'Arrigo S, Cacciola S, et al. Prediction of poor neurological outcome in comatose survivors of cardiac arrest: a systematic review. Intensive Care Med 2020;46:1803–51.
2 Nolan JP, Sandroni C, Bottiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care. Resuscitation 2021;161:220–69.
3 Oddo M, Sandroni C, Citerio G, et al. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. Intensive Care Med 2018;44.
4 Cohen JF, Korevaar DA, Altman DG, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open 2016;6:e012799.
5 Geocadin RG, Callaway CW, Fink EL, et al. American Heart Association Emergency Cardiovascular Care C: Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation 2019;140:e517–42.
6 Brain Resuscitation Clinical Trial I Study Group. A randomized clinical study of cardiopulmonary-cerebral resuscitation: design, methods, and patient characteristics. Am J Emerg Med 1986;4(1):72–86.
7 Peluso L, Boisdenghien T, Attanasio L, et al. Multimodal Approach to Predict Neurological Outcome after Cardiac Arrest: A Single-Center Experience. Brain Sciences 2021;11(7):888.
8 Stammet P, Collignon O, Hassager C, et al. Neuron-Specific Enolase as a Predictor of Death or Poor Neurological Outcome After Out-of-Hospital Cardiac Arrest and Targeted Temperature Management at 33°C and 36°C. J Am Coll Cardiol 2015;65(19):2104–14.
9 Cronberg T, Rundgren M, Westhall E, et al. Neuron-specific enolase correlates with other prognostic markers after cardiac arrest. Neurology 2011;77(7):623–30.
10 Backman S, Cronberg T, Friberg H, et al. Highly malignant routine EEG predicts poor prognosis after cardiac arrest in the Target Temperature Management trial. Resuscitation 2018;131:24–8.
11 Amorim E, Rittenberger JC, Baldwin ME, Callaway CW, Popescu A. Post Cardiac Arrest S: Malignant EEG patterns in cardiac arrest patients treated with targeted temperature management who survive to hospital discharge. Resuscitation 2015;90:127–32.
12 Sondag L, Ruijter BJ, Tjepkema-Cloostermans MC, et al. Early EEG for outcome prediction of postanoxic coma: a prospective cohort study with cost-minimization analysis. Crit Care 2017;21:111.
13 Sandroni C, Cronberg T, Sekhon M. Brain injury after cardiac arrest: pathophysiology, treatment, and prognosis. Intensive Care Med 2021;47:1393–414.
14 Hirsch LJ, Fong MWK, Leitinger M, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. J Clin Neurophysiol 2021;38:1–29.
15 Scarpino M, Lolli F, Lanzo G, et al. Does a combination of ≥2 abnormal tests vs. the ERC-ESICM stepwise algorithm improve prediction of poor neurological outcome after cardiac arrest? A post-hoc analysis of the ProNeCA multicentre study. Resuscitation 2021;160:158–67.
16 Kim JH, Kim MJ, You JS, et al. Multimodal approach for neurologic prognostication of out-of-hospital cardiac arrest patients undergoing targeted temperature management. Resuscitation 2019;134:33–40.
17 Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med 2014;42:1340–7.
18 Peluso L, Legros B, Caroyer S, Taccone FS, Gaspard N. Falsely predictive EEG and clinical signs after post-anoxic brain injury under sevoflurane anesthesia. Clin Neurophysiol 2021;132:1080–2.