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Neuron-Specific Enolase Levels in Adults Under Venoarterial Extracorporeal Membrane Oxygenation

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Objectives: We aimed to determine if elevations in serum neuron-specific enolase are associated with brain injury and outcomes in adults who require venoarterial extracorporeal membrane oxygenation.
Design: Prospective observational study.
Setting: Two ICUs of a university hospital, Paris, France.
Patients: Consecutive adult patients treated with venoarterial extracorporeal membrane oxygenation for refractory cardiogenic shock or in-hospital refractory cardiac arrest.
Interventions: None.
Measurements and Main Results: Serum sampled 1, 3, and 7 days after venoarterial extracorporeal membrane oxygenation cannulation was stored at −80°C and neuron-specific enolase concentrations were measured in batches at the end of the study. The association between neuron-specific enolase concentrations and outcomes (28-d mortality and poor outcome, defined by a score of 4–6 on the modified Rankin scale at 90 d) were explored by multivariable logistic regression, with neuron-specific enolase concentrations dichotomized according to median values. One-hundred three patients were included, of whom 26 (25%) received preextracorporeal membrane oxygenation cardiopulmonary resuscitation. Median (interquartile range) day-1, day-3, and day-7 neuron-specific enolase serum concentrations were 37 µg/L (26–51 µg/L), 25 µg/L (19–37) µg/L, and 22 µg/L (17–31 µg/L). After adjustment for Simplified Acute Physiology Score II, preextracorporeal membrane oxygenation cardiopulmonary resuscitation, and Sepsis Organ Failure Assessment score at time of cannulation, a day-3 neuron-specific enolase greater than 25 µg/L remained independently associated with 28-day mortality (adjusted odds ratio, 4.98; 95% CI, 1.86–13.32) and poor outcome at 90 days (adjusted odds ratio, 4.63; 95% CI, 1.81–11.84). A day-3 neuron-specific enolase threshold greater than 80 µg/L had a 100% specificity for prediction of both mortality (95% CI, 92–100%) and poor functional outcome (95% CI, 89–100%). In a subset of patients who underwent brain CT, neuron-specific enolase concentrations were significantly higher in patients diagnosed with stroke, as compared with those without stroke.
Conclusions: In adult patients under venoarterial extracorporeal membrane oxygenation, day-3 serum neuron-specific enolase concentrations are independently associated with short-term mortality and poor

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Information was given to next-of-kin's participants, followed, whenever possible, by patient information.

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functional outcomes. These findings deserve validation in a multicenter setting.

Key Words: extracorporeal membrane oxygenation; neuron-specific enolase; outcome; stroke

Venoarterial extracorporeal membrane oxygenation (ECMO) is an effective technique to provide emergency mechanical support for patients with refractory cardiogenic shock, with hospital discharge survival rates of 40% (1). In patients requiring ECMO during extracardiopulmonary resuscitation (ECPR), survival with satisfactory neurologic outcome is observed in less than 35% of cases (2–4). Neurologic complications during venoarterial ECMO are reported in 15% of adult patients and are associated with morbidity and mortality (5–7). In the Extracorporeal Life Support Organization registry, main neurologic complications were brain death (7.9%), cerebral infarction (3.6%), seizures (1.8%), and cerebral hemorrhage (1.8%) (5). In ECPR patients, 25% patients developed brain injury, mainly of hypoxic-ischemic origin (8). The pathophysiology of neurologic complications during venoarterial ECMO is not yet fully understood, but cerebral hypoxia, cerebral blood flow alterations, as well as abrupt $Paco_2$ changes may play a role (9). Risk factors for neurologic complications include age, pre-ECMO cardiac arrest, hypoglycemia, and administration of inotropes (6).

Detection of brain injury in venoarterial ECMO patients may significantly influence therapeutic plans, including decisions to withhold or withdraw life support. Furthermore, brain injury associated with venoarterial ECMO may represent a determinant of cognitive outcomes and quality of life in survivors (10).

Neurologic assessment in patients receiving venoarterial ECMO is difficult, as most patients are comatose and/or receive sedative infusion at the early phase. Furthermore, intra-hospital transport under mechanical support to perform brain imaging is challenging and MRI studies are not feasible.

Neuron-specific enolase (NSE), a serum biomarker of neuronal injury, is recommended as part of a bundle for prognostication after cardiac arrest (11). In two studies, NSE was investigated in patients treated with venoarterial ECMO for refractory cardiac arrest (12, 13). Whether serial NSE measurements are informative regarding neurologic outcomes of refractory cardiogenic shock patients, who are requiring venoarterial ECMO support, is unknown. In the present study, we aimed to investigate the association between early serum NSE measurements and outcomes of adult patients requiring venoarterial ECMO.

MATERIALS AND METHODS

Patients

This single-center prospective cohort study was conducted between June 2015 and November 2017 in the medical and surgical ICUs of the Bichat-Claude Bernard University Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France. All patients admitted to the unit and requiring venoarterial ECMO were screened for inclusion. Inclusion criteria were: 1) initiation of venoarterial ECMO for refractory cardiogenic shock and/or in-hospital refractory cardiac arrest and 2) age superior or equal to 18 years. The main exclusion criteria were: 1) moribund patients (i.e., unstable patients with a life expectancy of < 24 hr) and 2) an inability to assess clinical neurologic status at venoarterial ECMO initiation.

Clinical Parameters

Data recorded at inclusion were age, gender, Charlson comorbidity index, body mass index, history of brain injury, Simplified Acute Physiology Score (SAPS) II (14), and reason for ICU admission (i.e., postcardiac surgery or a cardiogenic shock of medical origin). Data recorded at ECMO initiation included pre-ECMO cardiopulmonary resuscitation, Sepsis-related Organ Failure Assessment (SOFA) (15), site of venoarterial ECMO cannulation, use of catecholamines, renal replacement therapy, and invasive mechanical ventilation. A standardized neurologic evaluation was performed by one of the investigators at venoarterial ECMO initiation and included the presence of ongoing sedation, Glasgow Coma Scale (GCS) score (16), and Richmond Agitation-Sedation Scale (RASS) score (17).

Neuroimaging

The decision to perform a brain CT during the 28 days following venoarterial ECMO cannulation was triggered by the attending physician's clinical suspicion of neurologic complications or by the need to perform a body CT in a pretransplant setting.

Neuron-Specific Enolase Measurements

Blood samples were collected at days 1, 3, and 7 after venoarterial ECMO initiation and allowed to clot 30 minutes at room temperature before being centrifugated at 3,000 revolutions per minute at 20°C and stored in aliquots at –80°C until assayed. NSE concentrations in sera were measured in batches at the end of the study and were therefore not used for prognostication during hospitalization. Samples presenting visible hemolysis were excluded. Quantitative assessment of NSE concentrations was obtained using time-resolved amplified cryptate emission technology on a Kryptor KC+ analyzer (BRAHMS, Hennigsdorf, Germany), as recommended by the manufacturer.

Outcome Variables

The primary endpoint was 28-day mortality. Secondary endpoint were poor functional outcome (severe disability or death) at 90 days, defined by a score of 4 to 6 on the modified Rankin scale (mRS), and stroke diagnosed on neuroimaging among patients who underwent brain CT within 28 days following venoarterial ECMO cannulation. Functional outcomes measured on the mRS were assessed during a telephone interview performed by a trained physician using the simplified mRS questionnaire (18).

Ethics

Ethical approval was obtained from our institutional Ethics Committee (IRB 00006477, study number 14-050). Next-of-kin information was given to all participants, followed, whenever possible, by patient information.

Statistical Analysis

Qualitative and quantitative data are provided as counts (percent) or medians (interquartile range), respectively. The association between NSE concentrations and outcome was explored by logistic regression analysis with NSE concentrations being dichotomized according to median values measured at day 1 and day 3. Sensitivity, specificity, negative predictive value, and positive predictive value and their 95% CI were calculated for NSE thresholds defined at days 1 and 3, respectively. Clinically relevant variables associated with outcome ($p < 0.2$) in univariate analysis (i.e., cardiopulmonary resuscitation [CPR] before ECMO cannulation, SAPS II at ICU admission, and SOFA at time of ECMO cannulation) were entered in the multivariable analysis. Two-by-two interactions and collinearity between selected variables were tested. Post hoc analyses were conducted in noncardiac arrest patients and cardiac arrest patients, respectively. Missing values were imputed to the median or mode for quantitative and qualitative variables, respectively. A p value of less than 0.05 was considered significant. Statistics were performed using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Patients

A study flowchart is provided in **ESM 1** (Supplemental Digital Content, http://links.lww.com/CCX/A378). Overall, 103 patients (age: 58 yr [46–64 yr], predominantly males) were included (**Table 1**). SAPS II and SOFA scores at ICU admission were 57 (41–68) and 11 (8–14), respectively. Venoarterial ECMO was initiated following surgery in 41 patients (40%) and for refractory cardiogenic shock of medical origin in 62 patients (60%). Patients were mainly cannulated in the operating room ($n = 72$, 70%) and cannulation was performed in the femoro-axillar position in most cases ($n = 62$, 60%). Overall, pre-ECMO CPR was performed in

TABLE 1. Characteristics of Patients

Variable	All Patients, $n = 103$	Alive, Day 28, $n = 54$	Dead, Day 28, $n = 49$	p	mRS < 4, Day 90, $n = 36$	mRS ≥ 4, Day 90, $n = 67$	p
At ICU admission							
Age, yr	58 (46–64)	56 (43–62)	60 (50–67)	0.01	53 (44–62)	59 (49–66)	0.11
Male sex	66 (64)	32 (59)	34 (69)	0.29	21 (58)	45 (67)	0.37
Charlson comorbidity index	1 (1–3)	1 (0–3)	2 (1–3)	0.47	1 (0–2)	2 (1–3)	0.19
Body mass index	26 (23–30)	26 (24–31)	25 (23–29)	0.44	26 (24–30)	26 (23–30)	0.56
History of brain injury	18 (18)	8 (15)	10 (20)	0.46	5 (14)	13 (19)	0.48
Simplified Acute Physiology Score II	57 (41–68)	52 (34–64)	60 (45–78)	0.01	49 (33–63)	60 (45–70)	0.03
Medical admission (vs postoperative)	66 (64)	31 (57)	35 (71)	0.14	18 (50)	19 (28)	0.03
Cardiopulmonary resuscitation before ECMO cannulation	26 (25)	10 (19)	16 (33)	0.10	6 (17)	20 (30)	0.15
At ECMO initiation							
Time between ICU admission and venoarterial ECMO initiation, d	1 (1–2)	1 (1–2)	1 (1–2)	0.46	1 (1–2)	1 (1–2)	0.61
Sepsis-related Organ Failure Assessment score	12 (9–15)	11 (8–13)	12 (11–15)	< 0.01	12 (9–13)	12 (10–15)	0.06
Abnormal pupillary reactivity	11 (11)	6 (12)	5 (11)	0.69	5 (18)	6 (10)	0.31
Glasgow Coma Scale							
Score	3 (3–6)	3 (3–6)	3 (3–4)	0.16	4 (3–8)	3 (3–4)	0.01
Motor response	1 (1–1)	1 (1–4)	1 (1–1)	0.26	1 (1–4)	1 (1–1)	0.03
Motor response 1 or 2	79 (78)	39 (72)	40 (82)	0.26	23 (64)	56 (84)	0.03
Richmond Agitation-Sedation Scale score	−5 (−5 to −4)	−5 (−5 to −4)	− 5 (−5 to −4)	0.09	−5 (−5 to −4)	−5 (−5 to −4)	0.06
Sedation-analgesia	93 (90)	47 (87)	46 (94)	0.25	31 (86)	62 (93)	0.30
Midazolam dose, mg/hr	4 (0–5)	4 (0–5)	5 (2–5)	0.63	2 (0–5)	5 (2–5)	0.13
Morphine dose, mg/hr	4 (0–5)	3 (0–5)	4 (0–5)	0.59	1 (0–4)	4 (0–5)	0.03

ECMO = extracorporeal membrane oxygenation, mRS = modified Rankin Scale.
Data are n (%) or median (interquartile range).

26 patients (25%) (postcardiac arrest shock, n = 19; ECPR, n = 7), with a no-flow of 0 minutes (0–0 min) and a low-flow of 15 minutes (3–38 min).

At the time of venoarterial ECMO cannulation, all patients were invasively mechanically ventilated, unresponsive to verbal commands (RASS –5 [–5 to –4], GCS score of 3 [3–6]), with a SOFA score of 12 (9–15). Ninety-three patients (90%) received a continuous infusion of sedative drugs and 94 (91%) received vasopressors.

NSE Values and Study Endpoints

Day-1, day-3, and day-7 NSE serum concentrations were 37 µg/L (26–51 µg/L) (n = 94 patients), 25 µg/L (19–37 µg/L) (n = 73 patients), and 22 µg/L (17–31 µg/L) (n = 34 patients). Day-3 NSE serum levels were associated with both 28-day mortality and poor functional outcome at 90 days (**Fig. 1**), whereas day-1 and day-7 levels were not.

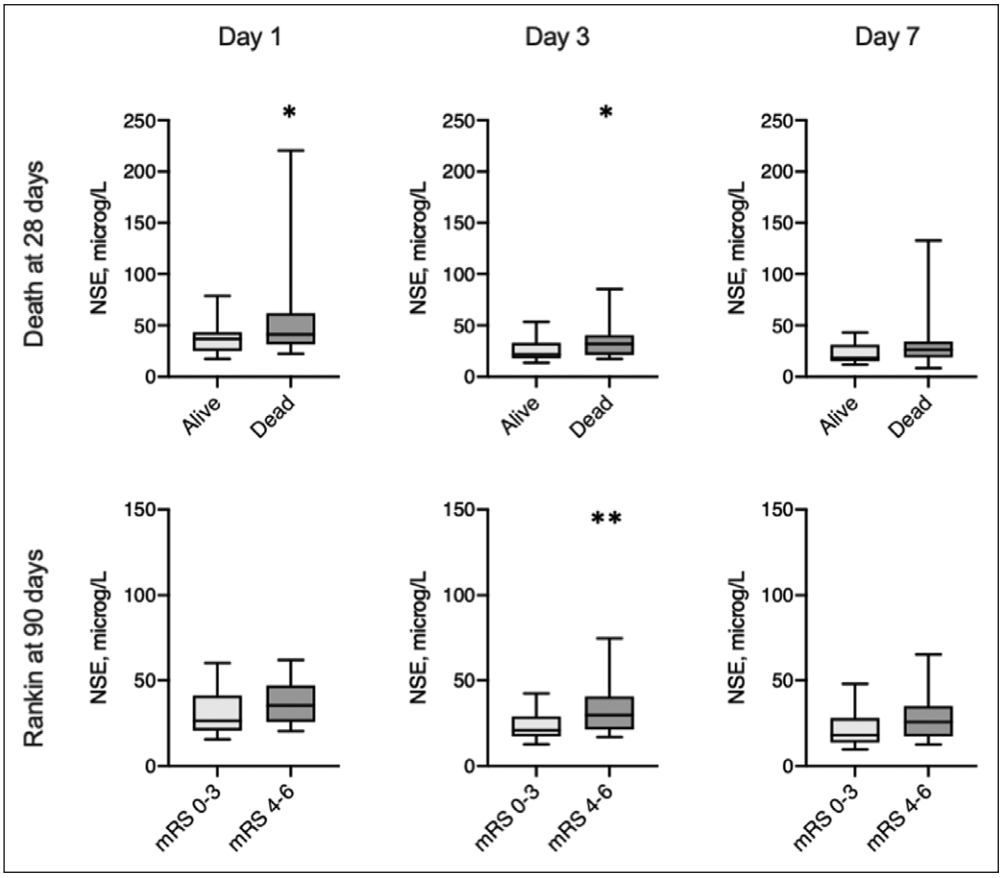

Figure 1. Serum neuron-specific enolase (NSE) serum values at day 1, day 3, and day 7 after venoarterial extracorporeal membrane oxygenation cannulation. *Box plots* are presented according to survival status at 28 d and functional outcome at 90 d, with the *central line* indicating the median, the *box* indicating the interquartile range, and the *whiskers* indicating the 10th and 90th percentiles. A score on the modified Rankin scale (mRS) of 4–6 indicates severe disability or death. $^{*}p < 0.05$; $^{**}p < 0.01$.

At 28 days, 49 patients (48%) had died. A poor functional outcome at 90 days was observed in 67 patients (65%), including 58 deaths. Measures of diagnostic accuracy (**Table 2**) revealed that the a priori defined day-3 NSE threshold greater than 25 µg/L had a sensitivity of 71% and 65% and a specificity of 62% and 67% for prediction of mortality at 28 days and poor functional outcome at 90 days, respectively. Of note, a threshold greater than 80 µg/L had a 100% specificity for prediction of both mortality (95% CI, 92–100%) and poor functional outcome at 90 days (95% CI, 89–100%).

Multivariable analyses are presented in **Figure 2**. After adjustment for SAPS II at admission, pre-ECMO CPR and SOFA score a time of cannulation, a day-3 NSE greater than 25 µg/L remained independently associated with 28-day mortality (adjusted odds ratio [aOR], 4.98; 95% CI, 1.86–13.32) and poor functional outcome at 90 days (aOR, 4.63; 95% CI, 1.81–11.84), whereas no such association was observed at day 1. The distribution of the mRS scores at 90 days differed according to NSE concentrations measured on day 3 (p = 0.02) (**Fig. 3**). In a subset of 43 patients who underwent brain CT within 28 days following venoarterial ECMO initiation, median day-1 (49 vs 35 µg/L; p = 0.005), day-3 (40 vs 24 µg/L; p = 0.026), and day-7 (36 vs 18 µg/L; p = 0.03) NSE concentrations were higher in patients with stroke, as compared with patients without stroke, respectively (**ESM 2**, Supplemental Digital Content, http://links.lww.com/CCX/A378).

TABLE 2. Measures of Diagnostic Accuracy of Different Neuron-Specific Enolase Concentration Thresholds at Day 3 for Prediction of Mortality at 28 Days and Poor Functional Outcome at 90 Days

Variable	Sensitivity % (95% CI)	Specificity % (95% CI)
Mortality at day 28, µg/L		
NSE > 25	71 (53–85)	62 (48–75)
NSE > 50	14 (6–31)	89 (77–95)
NSE > 75	11 (4–27)	98 (88–100)
NSE > 80	10 (4–27)	100 (92–100)
Modified Rankin scale ≥ 4 at 90 d, µg/L		
NSE > 25	65 (51–79)	67 (50–84)
NSE > 50	19 (10–33)	93 (79–99)
NSE > 75	9 (4–22)	100 (89–100)
NSE > 80	7 (2–19)	100 (89–100)

NSE = neuron-specific enolase.

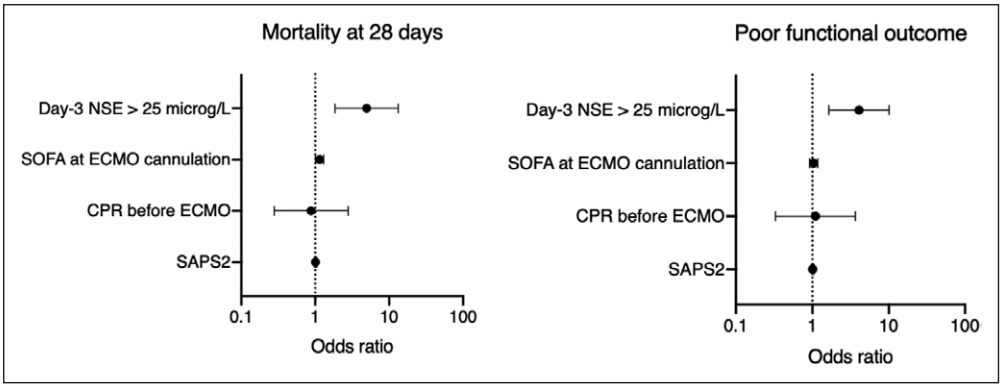

Figure 2. Predictors of outcomes, multivariable logistic regression analysis. The analysis was conducted on 99 patients (Three patients died before day 3, and one patient was weaned from extracorporeal membrane oxygenation [ECMO] before day 3). Area under the curve (AUC) = 0.739 for mortality; AUC = 0.714 for poor functional outcome. A poor functional outcome was defined as a score of 4 to 6 on the modifed Rankin scale at 90 d. CPR = cardiopulmonary resuscitation, NSE = neuron-specific enolase, SAPS = Simplified Acute Physiology Score, SOFA = Sepsis-related Organ Failure Assessment.

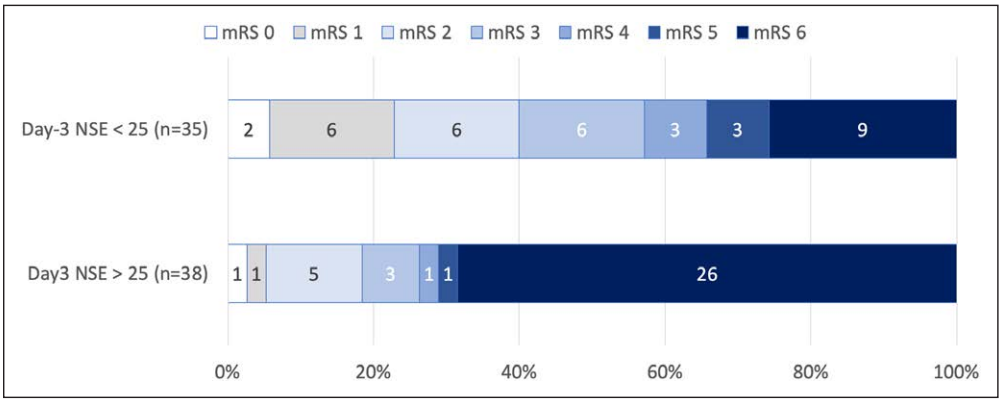

Figure 3. Distribution of the modified Rankin Scale (mRS) scores at 90 d. Scores range from mRS 0 to mRS 6, with mRS 0 indicating no neurologic deficit; mRS 1, no clinically significant disability (return to usual activities); mRS 2, slight disability; mRS 3, moderate disability requiring some help; mRS 4, moderately severe disability; mRS 5, severe disability; and mRS 6, death. NSE = neuron-specific enolase.

Post hoc analyses for the primary endpoint are presented in **ESM 3** (Supplemental Digital Content, http://links.lww.com/CCX/A378) and **ESM 4** (Supplemental Digital Content, http://links.lww.com/CCX/A378). We observed no significant differences at any time point in noncardiac arrest patients and cardiac arrest patients, respectively. We observed no significant interaction between day-3 NSE greater than 25 µg/L and pre-ECMO CPR in the main multivariable analysis.

DISCUSSION

In this prospective single-center cohort study conducted in consecutive adult patients treated with venoarterial ECMO in two ICUs of a university hospital, we found that elevated NSE concentrations were associated with poor outcomes. Specifically, a priori defined day-3 NSE threshold of 25 µg/L remained independently associated with mortality at 28 days and poor functional outcome at 90 days, after adjustment for pre-ECMO characteristics. Furthermore, in a subset of patients who underwent brain CT within 28 days following venoarterial ECMO initiation, day-1, day-3, and day-7 NSE concentrations were significantly higher in patients diagnosed with stroke on neuroimaging, as compared with patients without stroke.

The use of venoarterial ECMO to treat refractory cardiogenic shock is associated with brain injury in 15% of cases (5, 6). In a retrospective analysis of the Extracorporeal Life Support Organization registry, main neurologic complications included brain death (7.9%), cerebral infarction (3.6%), seizures (1.8%), and cerebral hemorrhage (1.8%) (5). Hospital mortality was 89% in patients diagnosed with neurologic complications, compared with 57% in patients without. In cardiac arrest patients treated with ECPR, one in four patients developed brain injury and the most common type was hypoxic-ischemic brain injury (8). In those patients, survival with acceptable neurologic outcome is observed in less than 35% of cases (2–4).

Neuromonitoring of ECMO patients is a complex process requiring clinical examination, electroencephalography (EEG), and neuroimaging to orient clinicians for decisions and level of care (19). It is a difficult task, as neurologic examination at ECMO initiation may be confounded by sedative drugs and neuromuscular blockers. Brain neuroimaging may be informative, but MRI studies are not feasible during ECMO support. Previous EEG studies reported an association between unreactive and/or discontinuous EEG background and neurologic outcomes (20–22). Elevated serum biomarkers of brain injury (i.e., glial fibrillary acidic protein, monocyte chemoattractant protein 1/chemokine ligand 2, NSE, and S100B) during ECMO were associated with unfavorable outcome and/or the presence of neuroimaging abnormalities in pediatric patients (23). However, serum biomarkers were scantly assessed in the noncardiac arrest adult patients. A previous single-center study suggested that serum S100B could be useful in deeply sedated patients to detect cerebral complications associated with ECMO (24).

Serum NSE has been used as a serum marker of neuronal injury for a long time. Elevated serum NSE concentrations are associated with poor neurologic outcome in brain-injured patients, such as those remaining comatose after cardiac arrest, traumatic brain injury, or stroke. Recently, it has been recommended as part of a bundle for prognostication after cardiac arrest (11). Serum NSE was previously investigated in adult cardiac arrest patients treated with venoarterial ECMO (12, 13). In these studies, serum NSE reliably indicated relevant cerebral injury in patients on extracorporeal support after cardiopulmonary resuscitation, and serum NSE measurement after 48 hours showed the best discrimination for poor neurologic outcome.

Our study differed from previous studies conducted in ECMO patients for several reasons. First, we included mainly noncardiac arrest patients. Cardiac arrest patients accounted for only 25% of the cohort and the proportion of cardiac arrest patients treated with ECPR, who are likely to have a poor neurologic outcome (3), was low (7/103 patients, 7%). Second, contrary to previous studies that focused on hospital discharge outcomes, we used clinically relevant study endpoints, including short-term mortality, functional outcomes at 90 days, and stroke events diagnosed on neuroimaging (25). Our post hoc analyses revealed no significant interaction between NSE levels and pre-ECMO CPR. The absence of significant difference in small subgroup analyses is likely explained by a lack of statistical power. However, the magnitude of effect of pre-ECMO CPR on NSE levels and outcomes may be lower than expected, as the proportion of ECPR patients in our cohort was low.

Our study has several strengths, including a large number of serial measurements in a cohort of consecutive adult patients treated with venoarterial ECMO. Serum was sampled at predefined time points, and NSE concentrations were analyzed in batches at the end of the study. Therefore, serum NSE was not used for prognostication during hospitalization, reducing the risk of self-fulfilling prophecy.

Our study also has limitations, including a single-center design and a lack of validation in an independent cohort of patients. Also, our cohort included consecutive patients with various venoarterial ECMO indications. However, our multivariable analyses were adjusted for pre-ECMO characteristics, including pre-ECMO cardiac arrest. Choice of the site for ECMO cannulation site was left to the surgeons' discretion, resulting in a high percentage of axillary artery—femoral vein configurations, which may not reflect clinical practice in other centers. NSE is not brain-specific and is also found in other cell types, that is, erythrocytes and platelets. Thus, hemolysis, which is frequently observed in venoarterial ECMO patients, may result in slightly increased serum NSE concentrations, even in the absence of neuronal damage. Another limitation is the absence of systematic brain imaging studies in our patients.

As for most other prognostic tools, our study suggested that a poor neurologic outcome could not be perfectly predicted by NSE concentrations alone, as most serum biomarkers have imperfect sensitivity and specificity. Early serum NSE measurements could be included in a multimodal noninvasive neuromonitoring protocol, including other prognostic tools such as clinical examination, electroencephalography, or brain imaging. The ability of such a multimodal evaluation to predict outcome in venoarterial ECMO patients deserves further investigation.

CONCLUSIONS

In adult patients under venoarterial ECMO, day-3 serum NSE concentrations are independently associated with short-term mortality and poor functional outcomes. These findings deserve validation in a multicenter setting.

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Ethical approval was obtained from our institutional Ethics Committee (Institutional Review Board 00006477, study number 14-050).

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

Drs. Reuter, Peoc'h, Bouadma, Timsit, and Sonneville designed the work. Drs. Chicha-Cattoir, Faille, Bourrienne, Dupuis, Magalhaes, Tanaka, Vinclair, and Sonneville collected the data. Drs. Ruckly, de Montmollin, and Sonneville carried out the statistical analysis. Drs. Reuter, Ruckly, Timsit, and Sonneville analyzed and interpreted the patient data. Drs. Reuter, Peoc'h, and Sonneville wrote the article. Drs. Mazighi, Para, Braham, Pisani, Ajzenberg, and Timsit revised the article. All authors have read and approved the final article.

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