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# **Performance of the ERC/ESICM-recommendations for neuroprognostication after cardiac arrest: Insights from a prospective multicenter cohort**

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**Keywords:**

Cardiac arrest; Coma; Electroencephalogram (EEG); Neuron-Specific Enolase (NSE); Prognosis; Short-latency Somatosensory Evoked Potentials (SSEPs).

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# Abstract

## **Aim:**

To investigate the performance of the 2021 ERC/ESICM-recommended algorithm for predicting poor outcome after cardiac arrest (CA) and potential tools for predicting neurological recovery in patients with indeterminate outcome.

## **Methods:**

Prospective, multicenter study on out-of-hospital CA survivors from 28 ICUs of the AfterROSC network. In patients comatose with a Glasgow Coma Scale motor score  $\leq 3$  at  $\geq 72$  h after resuscitation, we measured: (1) the accuracy of neurological examination, biomarkers (neuron-specific enolase, NSE), electrophysiology (EEG and SSEP) and neuroimaging (brain CT and MRI) for predicting poor outcome (modified Rankin scale score  $\geq 4$  at 90 days), and (2) the ability of low or decreasing NSE levels and benign EEG to predict good outcome in patients whose prognosis remained indeterminate.

## **Results:**

Among 337 included patients, the ERC-ESICM algorithm predicted poor neurological outcome in 175 patients, and the positive predictive value for an unfavourable outcome was 100% [98-100]%. The specificity of individual predictors ranged from 90% for EEG to 100% for clinical examination and SSEP. Among the remaining 162 patients with indeterminate outcome, a combination of 2 favourable signs predicted good outcome with 99[96-100]% specificity and 23[11-38]% sensitivity.

## **Conclusion:**

All comatose resuscitated patients who fulfilled the ERC-ESICM criteria for poor outcome after CA had poor outcome at three months, even if a self-fulfilling prophecy cannot be completely excluded. In patients with indeterminate outcome (half of the population), favourable signs predicted neurological recovery, reducing prognostic uncertainty.

# Introduction

Out-of-hospital cardiac arrest (OHCA) accounts for over 300,000 deaths per year in Europe,<sup>1</sup> with a mortality rate exceeding 90%.<sup>2</sup> Among OHCA patients admitted to the intensive care unit (ICU) in a coma after the return of spontaneous circulation (ROSC), two-thirds will die before discharge, primarily after withdrawal of life sustaining therapy (WLST) because of predicted poor neurological outcome due to severe hypoxic-ischemic brain injury (HIBI).<sup>3–5</sup> Accurate neuroprognostication in these patients is crucial to prevent inappropriate WLST on the one hand and unnecessary and prolonged treatment on the other hand.<sup>5,6</sup>

To maximise neuroprognostication accuracy in patients who are comatose after OHCA, the 2021 guidelines issued by the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM)<sup>5</sup> recommend that, in patients who are comatose at  $\geq 72$  h from ROSC after major confounders have been excluded, poor neurological outcome is predicted when at least two concordant signs indicating poor outcome are present. In a Korean retrospective study, the ERC-ESICM algorithm predicted poor neurological outcome after OHCA with high specificity.<sup>7</sup> However, the feasibility and performance of this prognostic strategy have not yet been assessed in Europe, where the post-arrest management and the availability of the clinical tests recommended by these guidelines might differ.<sup>8</sup> Another knowledge gap is represented by patients lacking two unfavourable signs, whose prognosis remains indeterminate. These patients may represent a remarkable fraction of those assessed for neuroprognostication<sup>9</sup> and many of them achieve neurological recovery.<sup>10</sup> Identifying signs of good outcome could reduce prognostic uncertainty in these patients. However, no consensus exists on the best strategy for good outcome prediction in HIBI.<sup>11</sup>

We conducted this study in a European multicenter ICU patient cohort to assess the accuracy for poor outcome prediction of the prognostic tests recommended by the ERC-ESICM post-resuscitation guidelines<sup>5</sup> and to investigate whether neurological recovery could be predicted in patients with indeterminate outcome using recently identified good outcome predictors.

## Methods

This study is reported according to the Strengthening The Reporting of OBservational studies in Epidemiology guidelines<sup>12</sup> and was registered on ClinicalTrial.gov before enrolling the first patient (Cohorts AfterROSC-1, NCT04167891, AfterROSC-2, NCT05606809).

### Ethical approval and consent

Information was provided to the relatives of each patient. In cases where relatives were unavailable, emergency inclusion was permitted by French law. In the latter case, patients were informed of their participation in the study when they regained their decision-making capacity, and their consent was requested. If they refused, their data was deleted. The research protocol was approved by the ethical committees (2019-A01378-49, CPP-SMIV-190901; 2022-A01811- 42; CPP-Ile-de-France-I) and the French data protection authorities, in accordance with the Declaration of Helsinki.

## Study setting and population

The After ROSC Network includes 28 ICUs in public or private university- or non-university hospitals in France and Belgium. After- ROSC prospectively collects all data from adult OHCA patients admitted to the network's ICUs starting August 1, 2020.<sup>13,14</sup> The inclusion period for this study was from registry inception to December 2022. We screened for inclusion all patients admitted in a coma (Glasgow Coma Scale [GCS] score  $\leq 8$ ) to the participating ICUs, eligible for neuroprognostication based on the ERC-ESICM guidelines, i.e., those who were still comatose at 72 h or later from ROSC with a motor GCS score  $\leq 3$  after suspension of sedation (including dexmedetomidine) and exclusion of confounders.<sup>5,15</sup> We excluded patients who died or recovered consciousness before the prognostication time point (i.e., 72 h after ICU admission) and those who awakened less than 24 h after sedation discontinuation.

## Data collection

All data were collected by study investigators in each center. The following variables were recorded: baseline characteristics, comorbidities using Charlson scale,<sup>16</sup> OHCA characteristics according to the Utstein style,<sup>17</sup> clinical characteristics upon ICU admission, treatments in the ICU, daily neurological assessments, sedation and opioids given, vital and neurological status at hospital discharge, and day 90 after ROSC. For each deceased patient, we classified the cause of death according to Witten<sup>18</sup>: refractory hemodynamic shock, recurrent cardiac arrest, respiratory failure, WLST warranted by presumed severe HIBI, and WLST warranted by comorbidities.

## Neuroprognostication

### *Prediction of poor neurological outcome*

Based on the ERC-ESICM guidelines, poor neurological outcome was considered likely if at least two unfavourable predictors were present among:<sup>5</sup>

- bilaterally absent standard (visually-assessed) pupillary and corneal reflex 72 h or later after ROSC;
- status myoclonus, defined as continuous and generalized myoclonus for more than 30 min in the first 72 h after ROSC;<sup>5</sup>
- bilaterally absent N20 wave on somatosensory evoked potentials (SSEPs);
- highly malignant EEG patterns (HMEP; defined as suppressed background ( $<10$  mV the entirety of the record) with or without superimposed periodic discharges or burst-suppression patterns (EEG bursts alternating with suppression periods constituting 50% of the recording). The definitions were based on the 2021 American Clinical Neurophysiology Society (ACNS) terminology<sup>19</sup> and Westhall et al.<sup>20</sup> Staff electrophysiologists or intensivists with dedicated training identified the HMEPs at participating centers. No automated EEG device was used. The EEG interpretation was performed locally without centralized adjudication, using local equipment) recorded 24 h or later after ROSC;
- blood levels of neuron-specific enolase (NSE) above 60 mg/L at 48 or 72 h after ROSC (using Roche or Thermo-Fisher platforms);
- signs of diffuse and extensive anoxic injury on brain CT or MRI 24 h or later after ROSC, visually assessed by the local radiologist

WLST was performed in each participating ICU according to local policy.

### ***Prediction of good neurological outcome***

Based on a recent review,<sup>11</sup> a favourable neurological outcome was considered likely when at least one of the following favourable predictors was present:

- benign EEG pattern, defined as a continuous, normal voltage, reactive EEG without malignant or highly malignant criteria<sup>19</sup> at 24 h or later after ROSC;<sup>11</sup>
- normal ( $\leq 17$  mg/L) blood levels of NSE at 48 or 72 h after ROSC;<sup>11,21,22</sup>
- a consistent decrease in blood levels of NSE (whatever the initial level) from 24 to 72h after ROSC, considering that changes in NSE could be as useful as absolute levels for predicting outcome.<sup>23,24</sup>

### ***Outcome assessment***

Poor outcome was defined as a modified Rankin Scale (mRS) score of 4–6 (moderate-severe disability, severe disability, or death).<sup>25,26</sup> The outcome was assessed at 90 days from ROSC by unblinded local investigators via a structured telephone interview.<sup>5,27,28</sup>

### ***Statistical analysis***

Continuous data were described as mean  $\pm$  SD or median [interquartile range], depending on their distribution. Categorical data were described as number (percentage). Continuous variables were compared using the Student's t-test, or the Mann-Whitney test as appropriate. Categorical variables were compared using the chi-square test. To ensure representativeness, we included consecutively all patients with OHCA recorded in this registry. No specific sample size calculation was conducted (unselected convenience sample). Net reclassification index (NRI) <sup>29, 30</sup> was used as a numeric assessment of accuracy improvement of a classification model. We assessed the use of each prognostication tool and measured the percentage of patients for whom the local team collected the neuroprognostic test.

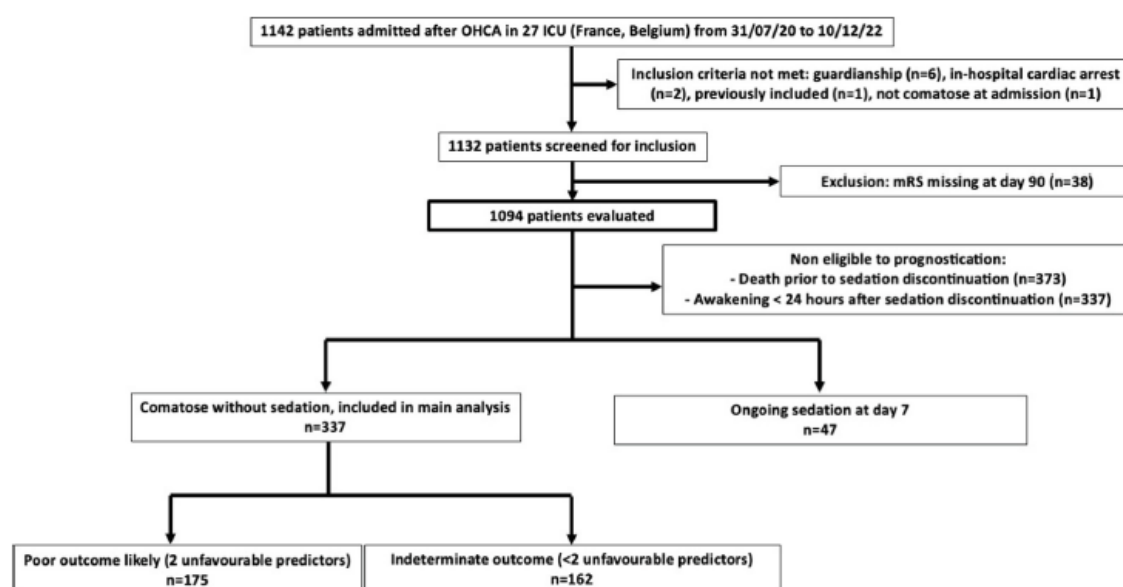
Firstly, we assessed the performance of each tool suggested in the ERC-ESICM algorithm<sup>5</sup> in predicting poor outcome, considering sensitivity, specificity, positive predictive value (PPV), and false positive rate (FPR), with their corresponding 95% confidence intervals ([95% CIs]). NRI was calculated as the additional predictive power versus the universally available clinical examination (i.e., absent corneal and pupillary reflexes and status myoclonus), used as the benchmark. Secondly, we focused on patients with indeterminate outcome (i.e., without two unfavourable test results) after applying the ERC-ESICM algorithm.<sup>5</sup> In this population, we assessed the performance of potentially favourable prognostic signs, isolated and in combination, in predicting good outcomes.

All tests were two-sided with a p-value  $<0.05$  considered significant. Analyses were performed using STATA/SE 15.1 (Lakeway Drive, TX, USA).



## Results

From August 2020 to December 2022, a total of 1094 patients were assessed for eligibility (Fig. 1). Among these, we excluded individuals who died before sedation discontinuation ( $n = 373$ ), those who regained consciousness within the initial 24 h following sedation discontinuation ( $n = 337$ ), and those who remained under sedation for more than seven days ( $n = 47$ ). The remaining 337 patients (31%) who remained comatose for  $>24$  h following sedation discontinuation were included in the analysis. Their characteristics are reported in Table 1. Median age was 64 (53–73) years, and 217 patients (64%) were male. No significant disability (mRS = 0–1) before OHCA was reported in 275 patients (82%). Most patients had no reported comorbidities (median Charlson score = 0). The main cause of OHCA was ST-elevation myocardial infarction (77/337 patients, 23%).



**Fig. 1 – Flow chart of the study population.**

A total of 286 patients (85%) died in the ICU, of whom 240 (84%) died after WLST based on neurological criteria. ESM Table 1 reports the modes of death. The median time to death was 7 (5–9) days after OHCA. Forty-seven patients (14%) survived hospital discharge, and 31 (9%) achieved neurological recovery. At 90 days, 40/337 patients (12%) were alive with good neurological outcome (ESM Table 2).

### *Performance of the ERC-ESICM algorithm*

The use of the ERC/ESICM-recommended predictors ranged from 25% of the population for SSEPs (available in only 11 ICUs) to 99% for status myoclonus, with a median of 4 (3–5) prognostic indices per patient. Their accuracies are reported in Table 2. Specificity ranged from 90% for the EEG to 100% for corneal and pupillary reflexes, SSEPs and status myoclonus. Compared with status myoclonus, NRI was higher than 0 for all tools, with NRINSE reaching 0.59 [95%CI 0.43–0.74];  $p < 0.01$ . Compared with corneal and pupillary reflexes, the NRI was significantly higher than 0 for SSEPs and NSE. Overall, 175/337 patients (52%) had two unfavourable predictors (Fig. 2). All these patients had poor neurological outcome (PPV 100[98–100%]%; FPR 0[0–9%]).

**Table 1 – Characteristics of the study population (n = 337).**

Variable	
Male sex	217 (64%)
Age	64 (53–73)
Occurrence at home	215 (64%)
Bystander	275 (82%)
Bystander CPR	221 (66%)
Collapse to CPR, minutes	5 (0–10)
CPR to ROSC, minutes	24 (15–30)
Shockable rhythm	124 (39%)
Cumulative epinephrine dose, mg	2 (1–4)
Stable ROSC	319 (97%)
Arterial pH at admission	7.26 (7.15–7.34)
Arterial lactate at admission, mmol/l	4.5 (2.6–7.3)
Target temperature management	305 (91%)

Values are reported as number (percentage) or median (interquartile range); CPR: Cardiopulmonary resuscitation; ROSC: Return Of Spontaneous Circulation. Stable ROSC was defined as the return of spontaneous circulation for at least 20 min.

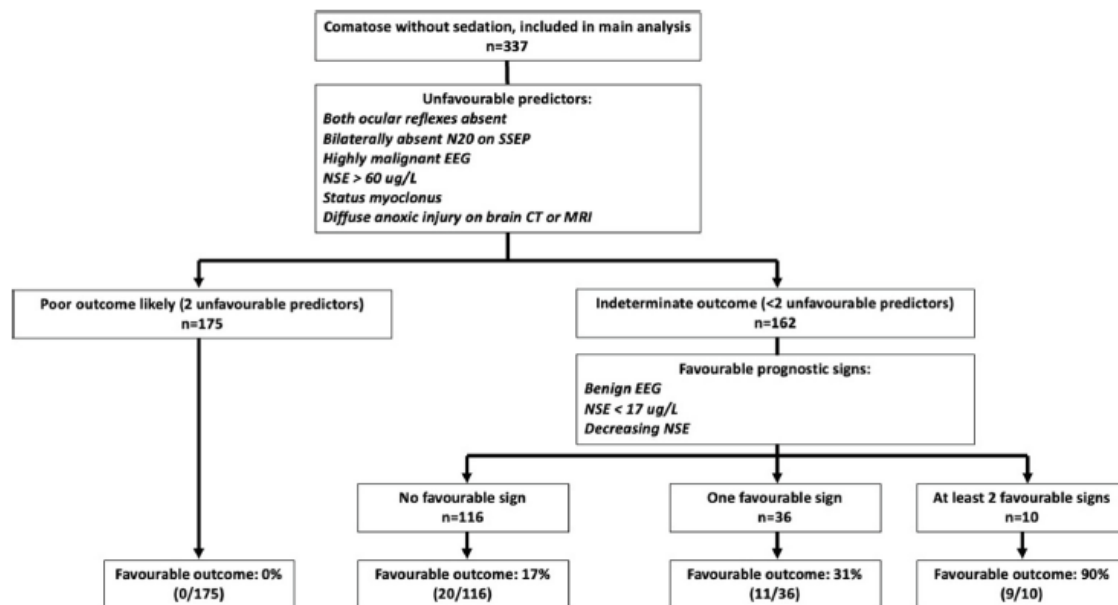
### *Prognostication in patients with indeterminate outcome*

After applying the ERC-ESICM algorithm, the outcome remained indeterminate in 162 patients (48%), of whom 113 (70%) died in the ICU after a median time of 7(4–10) days. The main causes of death were WLST for neurological reasons (82/113, 73%), WLST for comorbidities (12/113, 11%) and brain death (8/113, 7%). Of the remaining 49 patients, 40 (82%) were alive with good neurological outcome at 90 days. No favourable prognostic signs were found in 116/162 patients (Fig. 2), of whom 20 (17%) recovered. We found one favorable prognostic sign in 36 patients, of whom 11 (31%) recovered. Finally, 10 patients had two concordant signs of good neurological outcome. Of these, nine (90%) recovered. The specificity for good outcome prediction of combining two concordant favourable signs was 99[96–100]%. The complete combination of prognostic signs in patients with indeterminate outcome is shown in ESM Fig. 1. Neurological recovery was significantly more common in patients with no unfavourable signs (36/84 (43%)) than in those who had one unfavourable sign (4/78 (5%)),  $p < 0.001$ . In 19 patients, we found discordant prognostic signs, i.e., one sign suggesting an unfavourable outcome with another suggesting a favourable outcome. Of these, 2/19 (11%) had good neurological outcome at 90 days. Among favourable signs, normal NSE blood levels had the highest specificity (96[88–99]%) for good outcome and decreasing NSE had the lowest one (37[19–58]%; ESM Table 3).

**Table 2 – Accuracy of individual tests for predicting poor outcome.**

Prognostic sign	Availability	PPV	Sensitivity	Specificity	Net Reclassification Index (NRI) of each factor			
					Compared with status myoclonus	P	Compared with absent pupillary and corneal reflexes	P
No pupillary and corneal reflexes at >72 h	79%	100%	48% [41–54%]	100% [88–100%]	0.31 [0.22–0.39]	<0.01	NA	NA
Bilaterally absent N20 on SSEP	25%	100%	53% [41–65%]	100% [66–100%]	0.36 [0.20–0.51]	<0.01	0.14 [0.01–0.27]	0.03
Highly malignant EEG >24 h	79%	99%	69% [62–75%]	90% [70–99%]	0.42 [0.25–0.59]	<0.01	0.14 [–0.005–0.28]	0.06
NSE level >60 µg/L at 48 or 72 h	63%	99%	80% [74–86%]	95% [76–99.9%]	0.59 [0.43–0.74]	<0.01	0.27 [0.12–0.42]	0.0004
Status myoclonus <72 h	99%	100%	15% [11–20%]	100% [91–100%]	Reference	–	–0.31 [–0.39, –0.22]	<0.01
Diffuse anoxic injury on brain CT or MRI	49%	99%	47% [38–55%]	94% [70–99.8%]	0.26 [0.10–0.43]	0.002	–0.09 [–0.33, 0.16]	0.50
Two or more concordant signs	100%	100%	59% [53–65%]	100% [91–100%]	0.44 [0.36–0.52]	<0.01	0.16 [0.10–0.23]	<0.01

All values are reported as point estimates [95% CIs]; NSE: Neuron-Specific Enolase; SSEP: Short-latency Somatosensory Evoked Potentials.



**Fig. 2 – 90-day outcome based on the results of prognostic tests.**

## Discussion

In this prospective multicenter European study, the ERC/ESICM algorithm predicted poor neurological outcome with a 100% positive predictive value and 0% false-positive rate in patients who were comatose with two unfavourable signs at >72 h after OHCA. However, the prognosis remained indeterminate in almost half of patients, one-quarter of whom ultimately recovered, including some without favourable signs.

Because WLST due to neurological reasons is the leading cause of mortality following OHCA, 3, 31–33 ensuring 100% specificity in predicting poor outcomes is essential, even at the cost of reducing sensitivity, since a falsely pessimistic prediction in patients destined for a favourable prognosis could result in inappropriate WLST and potentially avoidable harm. In our study, all patients who fulfilled the criteria for unfavourable outcome recommended in the ERC-ESICM Guidelines died or survived with severe neurological disability. This finding does not completely rule out the risk of a self-fulfilling prophecy since, in our study, the treating teams were not blinded to the prognostic tests' results, which may have influenced their decisions. However, another validation study conducted in a country where WLST was not permitted, 34 confirmed the 100% specificity of the ERCESICM algorithm we found.<sup>7</sup>

Although all patients were assessed with a minimum of two tests (median 4) in our study, the utilisation rate of these tests ranged from 25% to 99%, which reflects the limited availability of some tests – especially SSEPs – in several ICUs. This could lead to inequality across healthcare systems, depending on where patients are treated. This issue may be addressed by implementing a centralized reading system for neuroprognostic tests. For tests based on electrophysiology, this can be implemented by transmitting the raw data for remote reading on a standard mobile network, a solution that is applicable even in low-income countries.<sup>35</sup> In addition to favouring their deployment, a centralized reading of neuroprognostic tests might also improve their accuracy. Recent evidence shows that while HMEPs on EEG at ≥24 h after ROSC predicted poor outcome with 100% specificity in studies where EEG reading was

centralised or conducted by experts,<sup>20,36</sup> they may yield false positive results when the EEG is interpreted by local neurologists, even if guidance on ACNS terminology had been provided.<sup>37</sup> Our study, which was also based on local test interpretation, confirmed these results and suggests that large-scale implementation of prognostic tests might lead to inaccuracy.

As in previous studies,<sup>7, 38</sup> in our study the specificity of a combination of two or more predictors was higher than that of some individually taken. Indeed, the FPR of high NSE levels, diffuse HIBI signs on brain imaging, and HMEP were 5%, 6%, and 10%, respectively.

This underlines the need to use a combination of predictors to achieve maximal specificity. The difficulty in obtaining a consistent threshold for 100% specificity with biomarkers is well-known,<sup>6</sup> due to their nature of continuous variables and the presence of outliers.<sup>22</sup> However, in our study, NSE reached the higher NRI, indicating a greater improvement in prognostic assessment compared to clinical parameters. Concerning brain CT, the results of our study and previous studies<sup>7, 39</sup> showed that visual assessment of post-anoxic brain oedema, not based on the grey matter/white matter density ratio thresholds, can give falsely pessimistic predictions. Although one study suggested that inaccuracy of CT-based neuroprognostication may be due to a too-early assessment (<24 h),<sup>39</sup> this does not seem to be the case in our study, where we considered only CTs performed after 24 h from ROSC.

Among instrumental prognostic tests, SSEPs were the most specific in our cohort, where a bilaterally absent N20 wave had 0% FPR for predicting poor outcome. However, SSEPs also showed low sensitivity. Strategies to increase SSEP sensitivity while maintaining 100% specificity have been investigated and may include recording mid-latency N70 SEP<sup>40</sup> or using a low-amplitude threshold – instead of the absence – for the N20 SSEP wave.<sup>38,41</sup> Concerning biomarkers, serum neurofilament light chain has shown higher accuracy than NSE.<sup>11,21</sup> However, its availability is still limited.

In this prospective multicenter European study, the prognosis remained indeterminate in nearly half of the patients after we applied the ERC-ESICM algorithm. A quarter of these patients recovered, highlighting the crucial need for a cautious approach to observation and reassessment when multiple concordant signs of poor outcome are lacking.

In particular, neurological recovery occurred in 31% and 90% of patients with one and two signs of good outcome, such as normal NSE levels and benign EEG patterns, respectively. These signs indicate that HIBI could be reversible and should encourage intensivists to continue aggressive life support in these patients. Neurological recovery still occurred in 20/116 (17%) patients with no signs of good outcome. However, almost all these recoveries occurred when no sign suggesting poor outcome was present either. Instead, when one unfavourable prognostic sign was observed without any discordant sign of potential recovery, poor outcome occurred in 97% of cases.

The ERC-ESICM guidelines recommend caution and prolonged observation in patients with discordant prognostic signs (one favourable and one unfavourable predictor). In our study, 11% of patients showing this pattern had favourable outcome, confirming the recommendation. The progression of good or poor neurological outcomes in our population according to the different proportions and concordance of good or poor signs suggests the ERC-ESICM prognostic model is consistent and provides further investigation insights.

We acknowledge some limitations of our study. Firstly, the treating physicians were not blinded to the results of prognostic tests, and the WLST policy was not standardised. This may have caused a self-fulfilling prophecy bias, which often represents a significant concern in intensive care studies, particularly those focused on acute brain injury.<sup>42, 43</sup> Various strategies can mitigate this bias, including standardized neuroprognostication protocols, especially regarding decisions on WLST, and blinding of prognostic tests. However, blinding is not always possible in post-resuscitation care. Namely, predictors like the EEG cannot be concealed from the treating team because they are essential for clinical management (e.g., to detect and treat non-convulsive seizures).<sup>5</sup> Other limitations of our study are the non-uniform availability of prognostic tests across participating centers and the lack of centralized interpretation. Notably, NSE decrease was reported only in 23% of patients with indeterminate outcome, scarcity largely attributable to local practices with several participating centers conducting only one NSE assessment. However, although these characteristics may have reduced the reliability of some prognostication tools, they closely reflect the current prognostication practices within our ICU network. Finally, some patients were included during the COVID surges, and we cannot completely exclude that resource allocation limitations may have occurred during this period and led to modifications in WLST.<sup>44</sup>

## Conclusion

Our prospective multicenter study demonstrated that in adults who remain comatose following OHCA, the combination of two or more unfavorable signs among those recommended by the ERC-ESICM 2021 guidelines exhibited greater specificity than most individual tests conducted independently. Although all centres used at least two tests to prognosticate, not all tests were available at every site. After applying the ERC-ESICM algorithm, the prognosis remained indeterminate in almost half of patients, one-quarter of whom ultimately recovered, including some without favourable signs. This underscores the importance of a cautious approach of observation and reassessment in this subgroup. In this population, normal NSE levels and benign EEG predict good neurological outcome and could help reduce prognostic uncertainty.

## Disclosures

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## CRedit authorship contribution statement

Wulfran Bougouin: Writing – original draft, Formal analysis, Data curation, Conceptualization. Jean-Baptiste Lascarrou: Writing – original draft, Funding acquisition. Jonathan Chelly: Writing – review & editing, Resources, Investigation. Sarah Benghanem: Writing – review & editing, Resources, Investigation. Guillaume Geri: Writing – review & editing, Resources, Investigation. Julien Maizel: Writing – review & editing, Resources, Investigation. Nicolas Fage: Writing – review & editing, Resources, Investigation. Ghada Sboui: Writing – review & editing, Resources, Investigation. Nicolas Pichon: Writing –



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### **Declaration of competing interest**

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: “Jean Baptiste Lascarrou reports financial support was provided by BD. Jean Baptiste Lascarrou reports financial support was provided by Masimo Corporation. Guillaume Geri reports financial support was provided by BD. Guillaume Geri reports financial support was provided by Bard. Claudio Sandroni and Alain Cariou are Associate Editor of Resuscitation If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper”.

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