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Multimodal Prediction of Favorable Outcome After Cardiac Arrest: A Cohort Study*

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OBJECTIVES: Prognostic guidelines after cardiac arrest (CA) focus on unfavorable outcome prediction; favorable outcome prognostication received less attention. Our aim was to identify favorable outcome predictors and combine them into a multimodal model.

DESIGN: Retrospective analysis of prospectively collected data (January 2016 to June 2021).

SETTING: Two academic hospitals (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Brigham and Women's Hospital, Boston, MA).

PATIENTS: Four hundred ninety-nine consecutive comatose adults admitted after CA.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: CA variables (initial rhythm, time to return of spontaneous circulation), clinical examination (Full Outline of UnResponsiveness [FOUR] score at 72 hr, early myoclonus), electroencephalography (EEG) (reactivity, continuity, epileptiform features, and prespecified highly malignant patterns), somatosensory-evoked potentials, quantified pupillometry, and serum neuron-specific enolase (NSE) were retrieved. Neurologic outcome was assessed at 3 months using Cerebral Performance Category (CPC); 1 and 2 were considered as favorable outcome. Predictive performance of each variable toward favorable outcomes were calculated, and most discriminant items were combined to obtain a multimodal prognostic score, using multivariable ordinal logistic regression, receiving operator characteristic curves, and cross-validation. Our analysis identified a prognostic score including six modalities (1 point each): 1) early (12–36 hr) EEG not highly malignant, 2) early EEG background reactivity, 3) late (36–72 hr) EEG background reactivity and 4) continuity, 5) peak serum NSE within 48 hours less than or equal to 41 µg/L, and 6) FOUR score greater than or equal to 5 at 72 hours. At greater than or equal to 4 out of 6 points, sensitivity for CPC 1–2 was 97.5% (95% CI, 92.9–99.5%) and accuracy was 77.5% (95% CI, 72.7–81.8%); area under the curve was 0.88 (95% CI, 0.85–0.91). The score showed similar performances in the validation cohort.

CONCLUSIONS: This study describes and externally validates a multimodal score, including clinical, EEG and biological items available within 72 hours, showing a high performance in identifying early comatose CA survivors who will reach functional independence at 3 months.

KEY WORDS: biomarkers; brain hypoxia-ischemia; electroencephalography; neurologic examination; prognosis

Hypoxic-ischemic brain injury after cardiac arrest (CA) is related to considerable morbidity and mortality (1); death occurs mostly following withdrawal of life-sustaining therapy (WLST) (2, 3). Accurate prognostication is essential, and recent recommendations, such as those of the European Society of Intensive Care Medicine (4), propose a multimodal

*See also p. 829.

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KEY POINTS

Question: Can a multimodal prognostic model reliably identify patients with favorable neurologic outcome after cardiac arrest?

Findings: We created and externally validated a multimodal prognostic score identifying within the first 72 hours most patients reaching functional independence at 3 months (sensitivity of 97.5%, accuracy of 77.5%, area under the curve of 0.88), using routinely available tools (four electroencephalographic features, one serological, one clinical).

Meaning: Our study addresses an important and understudied issue with a potential to influence current practice, namely focusing on favorable (as opposed to the currently used unfavorable) outcome in patients after cardiac arrest.

approach combining clinical examination, electrophysiology, brain imaging, and serological biomarkers.

However, existing guidelines essentially focus on prediction of unfavorable outcome, thereby leaving many patients in an intermediate prognosis (5, 6). Furthermore, because of confounders, or when some patients require longer recovery, a subset of patients might be at risk of premature WLST (2, 7). There is therefore a crucial need to reliably identify patients with good recovery chances (8), not only to reduce prognostication uncertainty, but also to reassure families and direct resources from caregivers.

Several indicators of good outcome have already been identified (8–14): continuous, reactive electroencephalography (EEG) without epileptiform features, absence of diffusion-weighted changes on brain MRI, a Glasgow Coma Scale (GCS) motor score greater than or equal to 3, or normal values of serum neuron-specific enolase (NSE). However, these variables have been mostly described separately, and their sensitivity toward a favorable outcome appears often suboptimal when the test is considered alone. As opposed to prediction of unfavorable prognosis (which aims at a maximum specificity to avoid false positivity with potential catastrophic consequences), prediction of favorable outcome ideally needs high sensitivity to avoid missing patients with a potential for good recovery (15). Indeed, most predictive modalities are dichotomous, but forecast of favorable outcome is not always efficiently achieved by simply inverting sensitivity and specificity of poor outcome predictors, since their sensitivity toward good prognosis may result too low (8, 15). Additionally, some predictors are continuous or ordinal variables and require a threshold identification, which will differ depending on the outcome considered.

A multimodal strategy for good prognosis seems reasonable to increase prognostic accuracy but has surprisingly received little attention so far. The aim of this study was to identify and combine predictors of favorable outcome into a multimodal prognostication model. We also hypothesized that a different cutoff of the model could identify different favorable outcomes.

MATERIAL AND METHODS

Design and Patients

We analyzed data from a prospective registry of consecutive comatose adults treated following CA at the Centre Hospitalier Universitaire Vaudois (CHUV) between January 1, 2016, and June 7, 2021. Patients dying within 24 hours of admission are not included in the registry. The study was Institutional Review Board (IRB) approved (Commission éthique de la recherche-VD, protocol 116-13; 2013); consent waived as there was no intervention; data analyzed in anonymous form; patients who objected to the use of their data for general research were excluded according to the Swiss Law). The study was in accordance with the ethical standards of the institutional IRB and the Helsinki Declaration of 1975. Further details have been published (10, 16).

Management and Variables

According to recommendations during recruitment (17), patients received targeted temperature management (TTM) at 36°C for 24 hours with external cooling devices. Propofol (2–3 mg/kg/hr) or midazolam (0.1 mg/kg/hr) were given for 24–36 hours; fentanyl and curare were administered as needed; for details, see (16). Patients with myoclonus or EEG seizures were treated with levetiracetam and valproate and, individually, with other anticonvulsants including propofol (18).

Patients underwent repetitive routine (20 min) or continuous video-EEGs with 21 electrodes (international 10–20 system). A first EEG (EEG1) was performed during TTM (12–36 hr), and a second EEG (EEG2) in normothermic conditions off-sedation (36–72 hr), except for those who died or awoke before 72 hours. EEGs were interpreted at the same recording day by clinical neurophysiologists (J.N., A.O.R.) regarding background continuity, reactivity, and epileptiform activity, according to the American Clinical Neurophysiology Standardized Terminology (19); continuous recordings were assessed at the same time points (relative to CA onset) as routine EEGs. The presence of sedative and antiseizure medication during EEG was recorded. Additionally, EEGs were categorized on the recording day into (20): highly malignant (suppression or burst-suppression, with or without periodic discharges), malignant (periodic or rhythmic patterns, abnormal or nonreactive background), and benign (absence of all malignant features).

Between 60 and 84 hours, when normothermic and off sedation, patients were repetitively examined (the best examination was kept in the registry) by certified neurologists noting the Full Outline of UnResponsiveness (FOUR, whose verbal score, as opposed to the GCS, is not limited by intubation) (21) and the presence of early (within 72 hr) myoclonus. Somatosensory-evoked potentials (SSEPs) after 24 hours and serum NSE (at 24 and 48 hr, measured through automated immunofluorescent assay; Thermo Scientific Brahms NSE Kryptor, Waltham, MA) were also collected. The highest NSE value was used for this analysis (22). In 110 patients, automated quantitative pupillometry (the percentage of pupillary light response [PLR]) was recorded; details can be found elsewhere (23); for this analysis, we considered the lowest and the highest values within 48 hours.

This battery of tests was used for multimodal prognostication (17). The decision of WLST was made by interdisciplinary consensus under systematic and close involvement of the patients' proxies on occurrence of at least two elements among: absence of brainstem reflexes at 72 hours, presence of repetitive epileptiform EEG features or seizures/myoclonus resistant to treatment, highly malignant EEG with lack of reactivity at 72 hours, and bilateral lack of cortical SSEP (10, 16).

Data Collection and Outcome Assessment

Demographic and clinical parameters were collected prospectively following Utstein's recommendations (24); CA etiology was dichotomized as cardiac versus noncardiac, and initial cardiac rhythm as shockable versus nonshockable. Time to return of spontaneous circulation (ROSC) was estimated upon admission. The best neurologic outcome at 3 months was assessed through semi-structured phone interviews, as per usual ICU practice for clinical follow-up care, using Cerebral Performance Categories (CPCs) (25). We considered CPC 1–2 (functional independence) as favorable outcome.

External Validation

This was performed on a registry of comatose adults treated following CA at the Brigham and Women's Hospital, Boston, MA (BWH cohort, January 2015 to December 2020; the study was IRB approved; consent waived as there was no study intervention). Sedation protocols were similar to the CHUV. Data were retrieved for early and late EEG from continuous recordings (in analogy with the CHUV cohort, also scored according to [19, 20] by J.W.L. or H.E.), FOUR score, NSE, and CPC at 3 months (as part of clinical information). One patient was removed (suicide attempt with barbiturate intoxication, biasing EEG for several days). Patients were treated with mild therapeutic hypothermia, primarily to 33°C (26), with sedation given in analogy with the CHUV. Decisions regarding WLST were taken similarly to the CHUV (**eTable 1**, http://links.lww.com/CCM/H311).

Statistics

Contingency tables were assessed by chi-square or two-sided Fisher exact tests, and normally distributed variables by two-sample Student *t* tests, as needed. Continuous variables (time to ROSC, FOUR score at 72 hr, peak NSE on 48 hr, maximum and minimum PLR within 48 hr) were categorized using thresholds identified through receiver operating characteristic (ROC) curve analyses, a priori targeting sensitivity greater than or equal to 90% and specificity greater than or equal to 50% toward CPC 1–2. We assessed for each variable predictive performances toward CPC 1–2. The most discriminating items were combined

to obtain a prognostic score, optimized by stepwise multivariable logistic regression and least absolute shrinkage and selection operator (LASSO) statistics. Discrimination was assessed with a ROC curve also allowing identification of the threshold with best performances for CPC 1–2; we then assessed the score performance using 10-fold cross-validation, and calibration through linear fitting, on CHUV patients. The prognostic score retained in the derivation cohort was then applied to identify survival (CPC 1–3) in the CHUV and to both outcomes (CPC 1–2 and CPC 1–3) in the validation cohort. In the derivation cohort, we calculated as a sensitivity analysis the score performance in patients sedated with propofol or midazolam only. Calculations were performed with STATA software, Version 17 (StataCorp, College Station, TX) and MedCalc, Version 19.4 (MedCalc Software, Ostend, Belgium).

RESULTS

Five hundred thirty-one CA episodes were in the CHUV registry; five were admitted twice: only the last time was considered. Before or after CA, 27 patients declined participation in research (10 died); therefore, 499 patients were included; 191 (38.3%) reached functional independence (CPC 1–2) at 3 months, and 63 (12.1%) survived with CPC 3; 3 (0.6%) were in a vegetative state (CPC 4); 242 died (48.5%) (CPC 5). **eTable 2** (http://links.lww.com/CCM/H311) shows their demographic and clinical characteristics. Patients with a favorable outcome had a shorter time to ROSC, were more likely to have cardiac etiology and an initial shockable rhythm; more often had preserved brainstem reflexes, FOUR score greater than or equal to 5, motor GCS greater than or equal to 3, absence of myoclonus, presence of SSEPs, benign EEG features (reactive, continuous, and nonirritative), higher quantitative-PLR values and lower NSE. EEG recording latencies were comparable among groups but more missing values for EEG2 were noted in those with favorable outcomes. Among patients with data for both EEG recordings (401/499), 17 of 243 (7.0 %) with EEG1 reactivity lost it on EEG2.

eTable 3 (http://links.lww.com/CCM/H311) summarizes favorable outcome predictors and their prognostic performances. For continuous variables, ideal thresholds (sensitivity ≥ 90% with the best specificity) were identified using ROC curves. The following variables were most informative (sensitivity ≥ 90%, specificity ≥ 50%): not highly malignant EEG1, EEG1 background reactivity, EEG2 background reactivity and continuity, presence of all brainstem reflexes, FOUR score greater than or equal to 5, and peak NSE less than or equal to 41 µg/L. Several other items showed a high sensitivity in identifying good outcomes, but with specificities less than 50%, and were therefore not considered: quantitative pupillometry (all thresholds on ROC curve analysis with sensitivity ≥ 90% had low specificity), nonepileptiform EEG 1 and 2, not highly malignant EEG2, brainstem reflexes taken individually, absence of myoclonus, and cortical SSEP presence. Furthermore, 80.0% of patients with NSE less than 17 µg/L reached CPC 1–2 (very high positive predictive value [PPV]), albeit with very low sensitivity (29.6%), confirming a recent study (9).

Multimodal Score to Identify Patients With Good Neurologic Outcome

After multivariable logistic regression, we retained six variables: not highly malignant EEG1, EEG1 background reactivity, EEG2 background reactivity and continuity, NSE less than or equal to 41 µg/L, and FOUR score greater than or equal to 5 at 72 hours. Among the 499 patients in the registry, 346 (69%) had data for each of these six variables: we restricted the score analysis on them, assigning 1 point to each (score from 0 to 6; **Table 1**). There were more favorable outcomes in the subgroup of patients in whom one or more score items were missing, compared with the subgroup of 346 with a full score (46.4% vs 34.7%; $p = 0.013$). Among the latter, 195 (56%) had a score of 4–6 and 118 (34%) had CPC 1–2 at 3 months (115 were identified by the score). On the ROC curve (**Fig. 1** and **Table 2**), at cutoff greater than or equal to 4, the score showed a sensitivity of 97.5% (95% CI, 92.9–99.5%) and specificity of 65.0% (95% CI, 58.4–71.3%) for CPC 1–2, classifying patients correctly in 77.5% (95% CI, 72.7–81.8%). The LASSO function showed similar results for the seven items (lambda 0.0015, R^2 0.383, Bayes information criterion [BIC], 328.31) and the six items (lambda 0.0115, R^2 0.380, Bayesian information criterion–BIC 326.79) score obtained after omitting brainstem reflexes (clinical redundancy with the FOUR score). The area under the curve (AUC) was 0.88 (95% CI, 0.85–0.91); 10-fold cross-validation showed an

TABLE 1.
Multimodal Score (Full Outline of UnResponsiveness Score ≥ 5 at 72 hr) to Predict Favorable Outcome in Comatose Patients After Cardiac Arrest

Eponym	Clinical Variable	Score
No	EEG 12–36 hr not "highly malignant"	1 point
2R	EEG 12–36 hr with reactive background	1 point
	EEG 36–72 hr with reactive background	1 point
Co	EEG 36–72 hr with continuous background	1 point
N	Peak neuron-specific enolase within 48 hr ≤ 41 µg/L	1 point
4	Full Outline of UnResponsiveness score within 72 hr ≥ 5/16	1 point

EEG = electroencephalography.

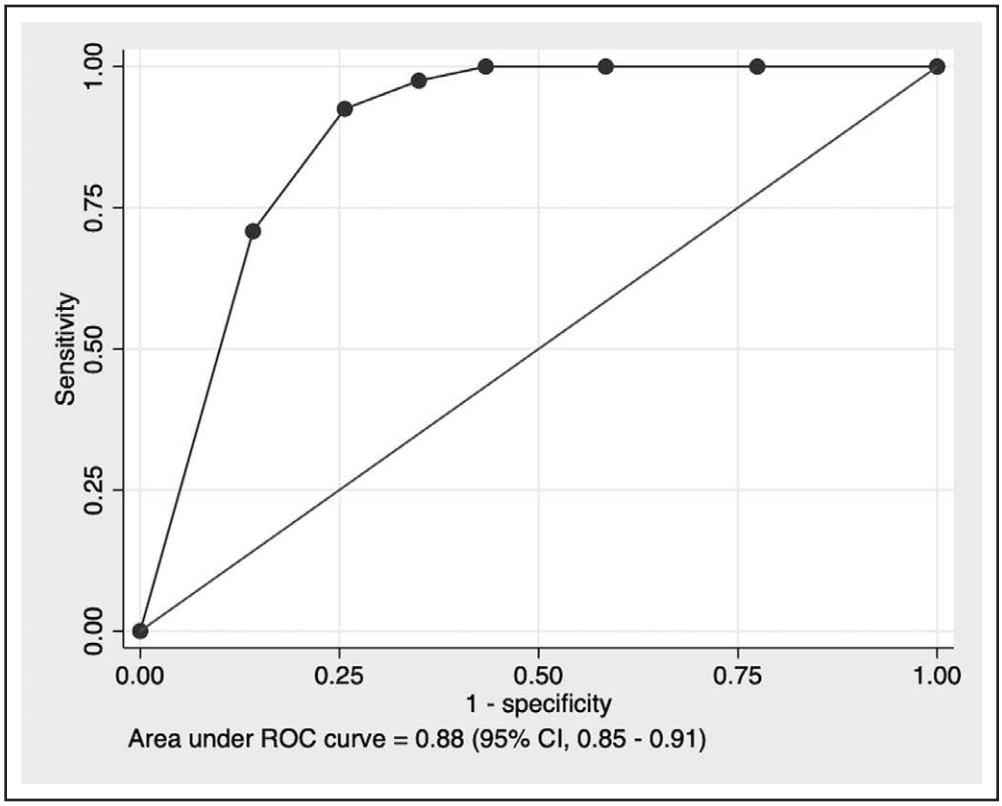

Figure 1. Prognostic performance of the multimodal score in the Centre Hospitalier Universitaire Vaudois cohort to predict good neurologic outcome (Cerebral Performance Categories 1–2) at 3 mo, assessed using receiver operating characteristic (ROC) curve analysis.

excellent performance (AUC, 0.88; corrected 95% CI, 0.81–0.89). The calibration of the score performance to identify patients with CPC 1–2 on CHUV patients with all available data showed a weighted calibration error of 7.8% (**Fig. 2**). **eTable 4*A*** (http://links.lww.com/CCM/H311) shows performances toward CPC 1–3 at cutoff greater than or equal to 3 (AUC, 0.92; 95% CI, 0.88–0.95). At the same cutoff, for midazolam-only sedated subjects (83 patients) score sensitivity and accuracy were 95.7% (95% CI, 78.1–99.9%), and 73.5% (95% CI, 62.7–82.6%), while for propofol-only sedation (137 patients) they were 98.0% (95% CI, 89.6–100.0%), and 74.5% (95% CI, 66.3–81.5%) (**eTable 5**, http://links.lww.com/CCM/H311). Although some relatively minor differences exist at the cutoff of four out of six, the 95% CI appear comparable with that of the whole cohort.

External Validation

We applied the score to the BWH cohort. Thirty-six of the 50 patients had data for all score items. Compared with the derivation cohort, age distribution (mean 58.5 vs 62.3 yr; $p = 0.0944$) was similar; however, there were less shockable rhythms (ventricular fibrillation or tachycardia) (28.6% vs 47.9%; $p = 0.010$) and a lower proportion of favorable outcomes (10.0% vs 38.3% CPC 1–2; $p < 0.001$). On the ROC curve (**Fig. 3** and Table 2), at a cutoff of greater than or equal to 4, the score showed a sensitivity of 100.0% (95% CI, 47.8–100.0%) and a specificity of 80.7% (95% CI, 62.5–92.6%) for identifying favorable outcomes, classifying patients correctly in 82.6% (95% CI, 66.3–93.1%). **eTable 4*B*** (http://links.lww.com/CCM/H311) shows predictive performances

TABLE 2.

Performance of the Multimodal Score to Predict Favorable Neurologic Outcome (Cerebral Performance Categories 1–2) at 3 Months (Centre Hospitalier Universitaire Vaudois Cohort [*n* = 346] and Brigham and Women's Hospital Cohort [*n* = 36])

Centre Hospitalier Universitaire Vaudois	Good Outcome CPC 1–2		
Score	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
≥ 1/6	100.00 (96.97–100.00)	22.57 (17.29–28.58)	52.21 (46.80–57.58)
≥ 2/6	100.00 (96.97–100.00)	41.59 (35.09–48.32)	63.95 (58.64–69.02)
≥ 3/6	100.00 (96.97–100.00)	56.64 (49.90–63.19)	73.24 (68.24–77.83)
≥ 4/6	**97.50 (92.87–99.48)**	**65.04 (58.44–71.25)**	**77.47 (72.70–81.76)**
≥ 5/6	92.50 (86.24–96.51)	74.34 (68.12–79.90)	81.29 (76.77–85.26)
6/6	70.83 (61.84–78.77)	85.84 (80.60–90.11)	80.10 (75.49–84.17)
Brigham and Women's Hospital	**Good Outcome CPC 1–2**		
Score	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Accuracy (95% CI)**
≥ 1/6	100.00 (47.82–100)	16.13 (5.45–33.73)	24.52 (11.77–41.68)
≥ 2/6	100.00 (47.82–100.00)	51.61 (33.06–69.85)	56.45 (38.95–72.85)
≥ 3/6	100.00 (47.82–100.00)	70.97 (51.96–85.78)	73.87 (56.58–87.04)
≥ 4/6	**100.00 (47.82–100.00)**	**80.65 (62.53–92.55)**	**82.58 (66.31–93.14)**
≥ 5/6	60. 00 (14.66–94.73)	87.10 (70.17–96.37)	84.39 (68.43–94.29)
6/6	20.00 (0.51–71.64)	93.55 (78.58–99.21)	86.19 (70.60–95.38)

CPC = Cerebral Performance Category.

Three hundred forty-six of 499 patients in Centre Hospitalier Universitaire Vaudois (CHUV) registry (and 36/50 patients in Brigham and Women's Hospital [BWH] registry) had data for each of the 6 score items. Score performance analysis on CHUV registry (up) and its external validation on BWH registry (down). Best score cutoffs are given in boldface font.

Score made with six variables: not highly malignant Westhall category electroencephalography (EEG) 1, EEG1 reactivity; EEG2 reactivity; EEG2 continuity; Full Outline of UnResponsiveness score ≥ 5; peak neuron-specific enolase on 48 hr ≤ 41 μg/L. Patients received 1 point for each positive element. Please see *Text* for selection criteria of score items.

toward CPC 1–3 at cutoff greater than or equal to 3 (AUC, 0.92; 95% CI, 0.83–1.00).

DISCUSSION

This analysis describes several prognosticators with high performance for good outcome after CA, whose combination (six items, available within 72 hr) identifies patients at different cutoffs reaching good outcome (CPC 1–2) or survival (CPC 1–3) after 3 months, with high sensitivities and accuracies above 70%. Internal calibration and external validation showed highly comparable results. While most of the proposed items have been described in isolation for the identification of good prognosis (8), this multimodal approach scores better than any single predictor, particularly by improving specificity, in analogy to multimodal approaches to identify poor outcome patients, where the use of single items may lead to falsely pessimistic forecasts (27).

The reliability of some EEG items to detect good outcomes varies with time. Some parameters from early EEGs (12–36 hr, during TTM and sedation) were more discriminating than later (36–72 hr). Early EEG reliability has already been described (10, 14, 28) and may reflect a less confounded situation in the early post-CA setting. However, early EEG continuity was less sensitive than later: soon after CA, EEG may show some suppression, subsequently returning to continuity in most good outcome patients (4). The EEG predictive performance regarding good outcome appears otherwise broadly in line with previous descriptions (8, 10, 14, 18, 20, 28).

Although a recent study suggests that quantitative SSEP analysis may be able to track brain recovery and predict favorable outcome (29, 30), our results confirm

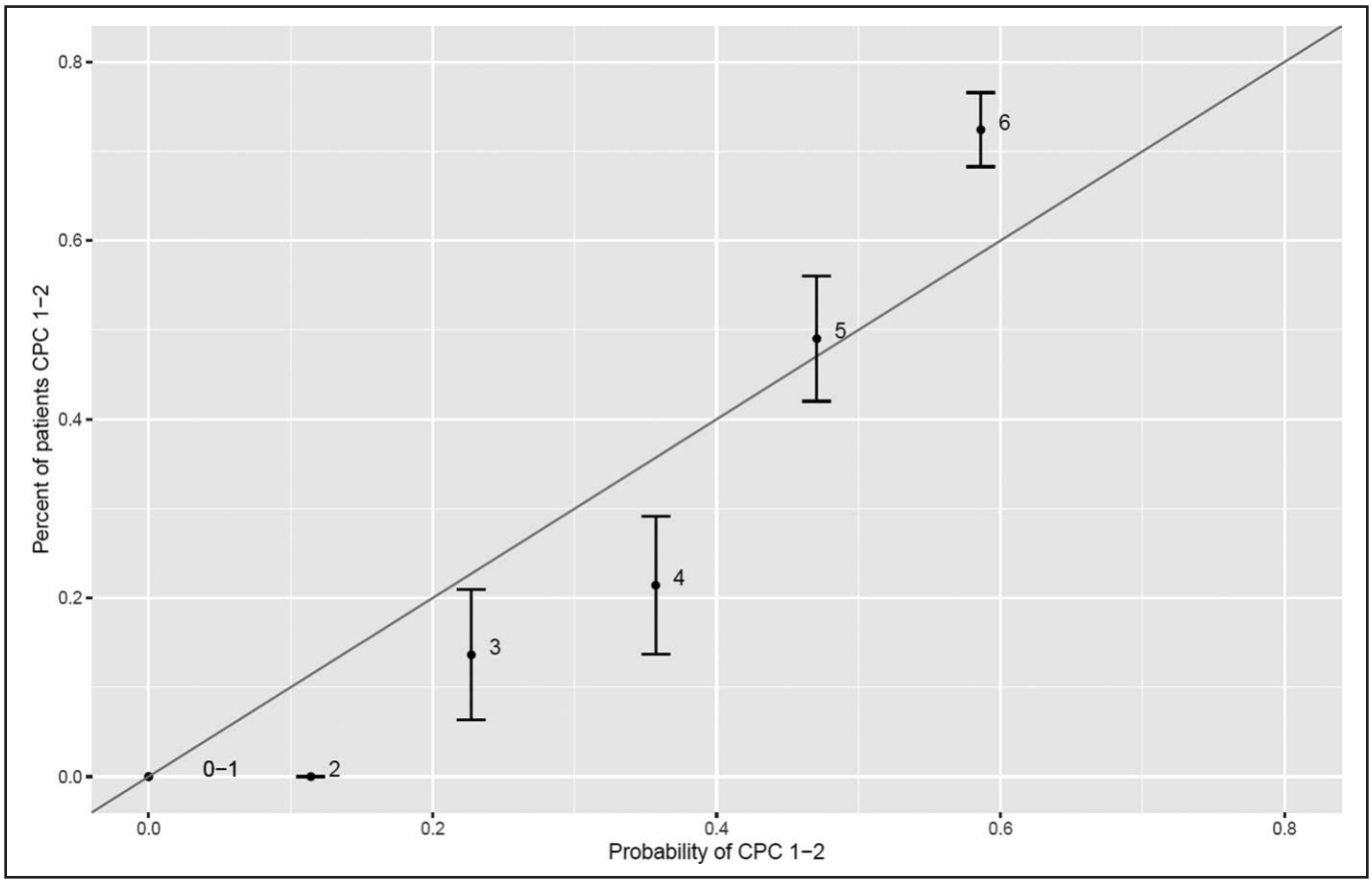

Figure 2. Linear curve fitting on 349 patients with all data. The numbers in the graph correspond to score points. The global calibration error is 7.8%. CPC = Cerebral Performance Category.

that the mere presence of cortical SSEPs (conventional analysis) is inadequate to forecast good outcome (10, 15), contrasting to bilateral absence of N20 response for poor prognosis (15, 17, 31). Auditory event-related potentials, still unfrequently used in clinical practice, may assess the presence of higher cortical processing and predict good outcome with high PPV but low sensitivity (30, 32, 33).

Few studies have investigated the importance of clinical examination in predicting good outcome (8, 34); none focused on the FOUR score at 72 hours, for which a discriminant threshold of greater than or equal to 5 seems reasonable. For dichotomous clinical variables (e.g., presence or absence of corneal reflex), the accuracy in predicting favorable outcome corresponds to the inverse of accuracy for poor outcome; our results confirm this (31); however, sensitivities are too low. We found a discriminant threshold of less than or equal to 41 μg/L NSE toward CPC 1–2, considerably higher than less than 17 μg/L (8, 9, 35), but clearly more sensitive. Finally, while quantitative pupillometry is a strong indicator of poor neurologic outcome (23), our results suggest that it has limited utility for good prognosis.

A systematic review on good outcome prediction was recently published (8): motor GCS 4–5, normal (< 17 μg/L) NSE, N20 amplitude greater than 4 μV, continuous EEG background, and absent diffusion restriction on MRI are especially mentioned; however, multimodality was not assessed (i.e., the review focuses only on single predictors), and emphasis was set on specificity (> 80%), rather than sensitivity. One of the few studies using a multimodal approach on 99 post-CA patients proposed EEG reactivity, SSEP amplitude, and gray-white matter ratio on CT to detect patients with CPC 1–2 at 6 months (36). This 3 items model had an AUC of 0.920, very close to ours, but was conducted on a much smaller sample, was not externally validated, and included quantitative CT measures that are not routinely performed. Two recent studies from our groups focused on good outcomes detection but were limited to patients with myoclonus (37) or epileptiform EEG (18).

We included only prognosticators offering high sensitivity with specificity greater than 50%, necessarily at the expense of lower PPV. As mentioned

above, some studies on good prognostic factors have preferred targeting high specificity, but this will result in lower sensitivity: many patients with good outcomes will be missed (8, 9, 38). We feel that proposing a model detecting most patients who will recover is more relevant for clinical practice to avoid missing patients with potential recovery. Furthermore, by combining different prognosticators, we increased the model's specificity (65% for CPC 1–2, 71% for CPC 1–3). Specificities above 70–80% seem nevertheless difficult to obtain, given, for example, that deaths from non-neurologic causes represent a confounder (39). Of note, we identified 56% of the CHUV cohort with a good outcome score; on the CHUV historical cohort (on a different timespan), at least two poor outcome items (similar but not identical to the current approach) were present in 35 out of 134 (26% of patients [16]). This would leave about 20% of patients in the prognostic undetermined zone.

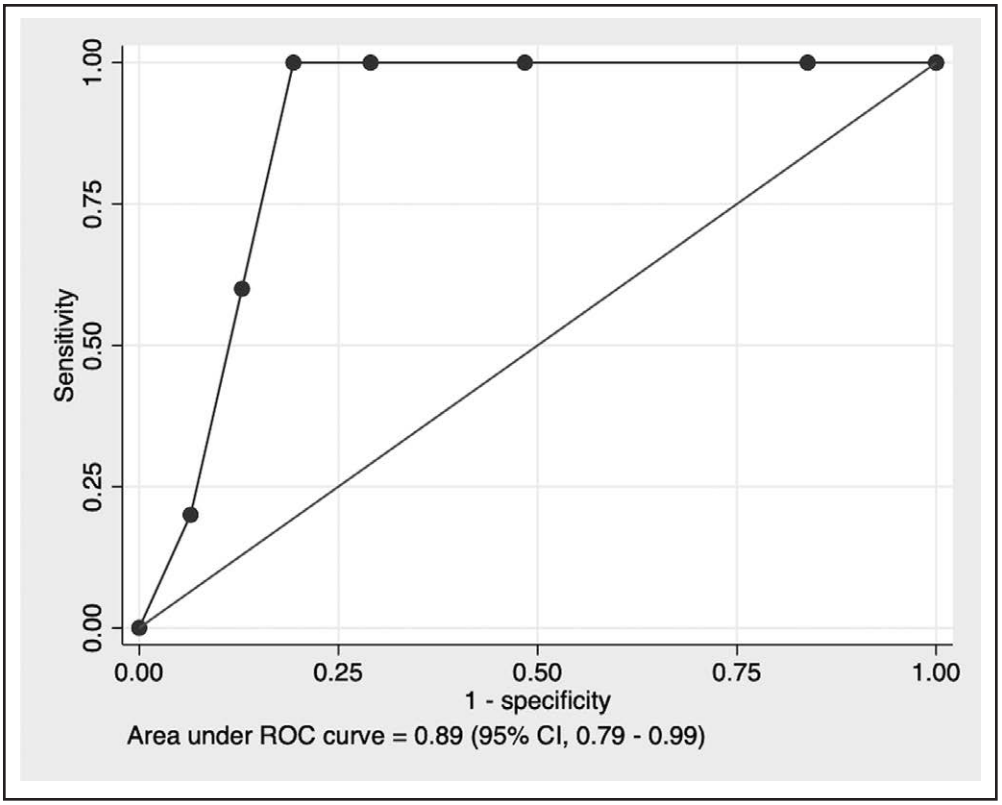

Figure 3. Prognostic performance of the multimodal score in the Brigham and Women's Hospital cohort (external validation) to predict good neurologic outcome (Cerebral Performance Categories 1–2) at 3 mo, assessed using receiver operating characteristic (ROC) curve analysis.

The main strengths of the present study are the large size of the derivation cohort, strict WLST criteria (15), and early application to patients still comatose at 72 hours. Furthermore, the prognostic score uses six readily available items. Another advantage is the external validation, despite a limited number of subjects and the lower proportion of good outcomes (SSEP and NSE not drawn regularly). Despite being somewhat different in terms of clinical variables and TTM strategy, the cohorts showed similar predictive performances (especially regarding sensitivity and accuracy, somewhat less for specificity), supporting reasonable generalizability of the results. Standardized EEG interpretation following predefined criteria (19, 20) across the two centers supports internal validity.

Our analysis has limitations, some of which are common to other CA prognostication studies. WLST can bias outcome, and causes of death were not documented. Even if almost all assessments on prognostication after CA use CPC, this may suffer from some subjectivity and the fact that it does not necessarily correlate with quality of life (4, 40, 41). Particularly, CPC 3 is heterogeneous, including a wide range of situations, from a minimally conscious state to dependent, albeit conscious and interactive. We therefore also present analyses toward survival (CPC 1–3). We selected for the score sensitive (≥ 90%) variables offering a specificity greater than or equal to 50%, discarding those with lower specificity; we cannot rule out that including one of these variables may have changed the score. The score is multimodal but strongly relies on EEG (4/6 items). Even though we confirm that EEG is an excellent tool for good outcome forecast (10, 14), imperfect inter-rater reliability, especially for background reactivity, should be acknowledged (42–44). Centers using markedly different (and higher) sedation protocols should interpret these results with caution. The model's similar

performance across two different cohorts may, however, hamper this concern; in this regard, quantitative EEG analysis, not currently used in clinical practice, is promising (33). The calibration curve appears to somewhat overestimate the probability of good outcome patients groups with lower scores and underestimate it in those with high scores. While mild hypothermia does not have major effects on EEG (45), this may be affected by sedation (4, 15, 46, 47). However, sedation administered in our cohorts probably did not influence the score performance (14, 30). A specific caveat applies to drug-overdoses CA, where EEG can be confounded by extremely high doses of opioids, benzodiazepines, or barbiturates. The use of mild hypothermia has been questioned by recent large trials (48, 49); our results seem to consistently apply to the CHUV (using mainly 36°C) and the BWH (using mainly 33°C) cohorts; however, their validity in patients not undergoing TTM remains unstudied. Most EEGs were routine recordings in the derivation and continuous in the validation cohorts; however, the prognostic information seems comparable, and outcome seems unaffected by these modalities (50, 51). The lower late EEG number, especially in patients with good outcome, reflects awakening or dying in the interval, but taking into account the two time points allows concentrating on those patients that are still unconscious. FOUR score may be high (≥ 5) in patients starting to awaken relatively early, adding the possibility of a circular prophecy. However, timing of awakening after CA has been shown to correlate with long-term prognosis (52), and the cutoff we identified is relatively low. Brain imaging was not routinely used before awakening for patients with convergent signs of poor outcome (or, conversely, "benign" EEGs and low NSE), preventing its inclusion in the model; recent studies show interesting results, especially in quantitative aspects (8, 36); however, these require selective expertise for assessment. Finally, as mentioned earlier, we applied SSEP as a dichotomous variable without amplitude analysis (8).

CONCLUSIONS

Our study proposes a multimodal prognostic score detecting most patients who will reach functional independence (CPC 1–2) or survive (CPC 1–3) at 3 months, using routinely available tools (four EEG features, one serological, one clinical). The model may represent an improvement to existing prognostication methods, giving families and caregivers, within 72 hours of CA, reliable information on chances of favorable outcome. Further emphasis on multimodal prognostic scores in large cohorts is indicated.

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