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ORIGINAL COMMUNICATION

Clinico-biological markers for the prognosis of status epilepticus in adults

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Abstract

Prediction of mortality, functional outcome and recovery after status epilepticus (SE) is a challenge. Biological and clinical markers have been proposed to reflect the brain injury or to monitor critical ill patients' severity. The aim of this study was to characterize short-term and long-term prognostic factors for SE patients hospitalized in intensive care unit. Patient's outcome was assessed using the modified Rankin Scale at discharge and after 6–12 months. We first assessed the univariate prognosis significance of 51 clinical, demographic or biochemical markers. Next, we built multivariate clinico-biological models by combining most important factors. Statistical models' performances were compared to those of two previous published scales STESS and mSTESS. Eighty-one patients were enrolled. Thirty-five patients showed a steady state while 46 patients clinically worsened at discharge: 14 died, 14 had persistent disability at 6–12 months and 18 recovered. Logistic regression analysis revealed that clinical markers (SE refractoriness, SE duration, de novo SE) were significant independent predictors of worsening while lipids markers and progranulin better predicted mortality. The association of clinico-biological variables allowed to accurately predict worsening at discharge (AUC > 0.72), mortality at discharge (AUC 0.83) and recovery at long-term (AUC 0.89). Previous scales provided lower prediction for worsening (AUC 0.63, STESS; 0.53, mSTESS) and mortality (AUC 0.56, STESS; 0.62, mSTESS) ($p < 0.001$). We proposed new clinico-biological models with a strong discrimination power for prediction of short- and long-term outcome of hospitalized status epilepticus patients. Their implementation in electronic devices may enhance their clinical liability.

Keywords Status epilepticus · Prognosis · Recovery · Clinico-biological scores

Abbreviations

AUC	Area under the receiver operating characteristic curve
CSF	Cerebrospinal fluid
FC	Free cholesterol
ICU	Intensive care unit
ML	Machine learning
mRS	Modified Rankin score
NORSE	New-onset refractory status epilepticus
NPV	Negative predictive value
PPV	Positive predictive value
RSE	Refractory status epilepticus
S100B	S100-beta protein
SE	Status epilepticus
SVM	Support vector machine

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Introduction

Status epilepticus (SE) is a life-threatening prolonged epileptic seizure [1, 2]. The reported SE mortality ranges from 5 to 46% [2, 3]. Survivors of severe SE—, resistant to drugs, managed in intensive care unit—frequently show impairment of their functional outcome at discharge, with inconsistent recovery after several months [2, 4].

The identification of valuable prognostic biomarkers is challenging due to the heterogeneity of SE etiology and clinical presentation. To help clinicians, various markers (demographic, clinical, biochemical, electrophysiological, brain imaging) and four scales (STESS, EMSE, mSTESS,

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END-IT) have been proposed to predict SE outcome [5–10]. The STESS, EMSE and mSTESS scales were built to assess the risk of mortality at discharge. Only STESS and mSTESS scales, based on pre-hospitalized clinical data (i.e. seizure type, consciousness level, age, previous history of epilepsy; and functional state before SE for mSTESS), can be applied to all patients. Indeed, the EMSE scale, a clinical-electrophysiological tool, is only available for specific etiologies. Moreover, while EEG findings have a certain significance to predict the outcome of SE patients, EEG findings may rapidly change over time. Therefore, only a quantification of the findings obtained by a continuous EEG monitoring could participate to patients' outcome. Nonetheless, continuous EEG monitoring is not available in every country for every SE patient and quantification of its features is not simply available.

Despite its key role for treatment decisions, the END-IT scale is the only one developed to assess the functional outcome at 3 months post discharge. Nevertheless, the END-IT scale requires brain MRI, which is not always performed in SE management and rarely in the same timeframe across patients. Thereafter, STESS and EMSE scales were further evaluated to assess the functional outcome [11–14]. Nevertheless, their performances are inconsistent and these scales are not able to predict the degree of worsening, precluding their utilization to accurately assess the functional outcome [11–14].

Here, we wondered if demographic, clinical and biochemical markers, available for all hospitalized SE patients, could efficiently assess the SE outcome and if these variables could be combined to improve the prediction of short-term and long-term SE outcome. Statistical models obtained by machine learning (ML) methods allow the integration of complex and heterogeneous data into personalized medicine systems. Although statistical algorithms have been successfully used in the neurocritical care setting [15] (e.g. for the assessment of consciousness, intracranial pressure and hemorrhages, or seizure detection), they have never been applied to predict SE outcome.

Here, we assessed, in 81 patients, the prognosis value of 51 demographic, clinical or biochemical markers and we applied statistical analysis to build new multivariate clinico-biological models, to predict mortality, functional outcome (i.e., worsening of clinical condition and its degree) at discharge and recovery after 6–12 months.

Methods

Study design, setting and participants

We prospectively enrolled adult patients admitted in the neurological intensive care unit (ICU), the medical ICU or the neurological continuing care unit of the Pitié-Salpêtrière Hospital, from February 2013 to June 2020. Patients were either initially managed at Pitié-Salpêtrière Hospital or transferred from another ICU due to an uncontrolled SE.

Eligible SE patients were patients aged at least 18 years, with an ongoing SE, either a generalized convulsive SE, or a focal convulsive or non-convulsive SE diagnosed according to the International League Against Epilepsy criteria. None of the patients had a generalized non-convulsive SE. Physicians from ICU excluded: patients with a subtle SE defined by minor and erratic myoclonic movements in patients with severely impaired consciousness; patients with post-anoxic SE; patients whose SE was linked to a pathological condition, such as trauma or subarachnoid aneurysmal hemorrhage, who needed immediate surgery and for whom the outcome could be impaired by the underlying disease. Patients for whose parent, guardian or other reliable person refused permission or patients who refused themselves permission were also excluded.

Standard protocol approvals, registrations, and patient consents

This study received approval from the University Ethic Committee (2012, CPP Paris-VI). All patients or relatives were informed and provided their consent. The study design and report are in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines [16].

Variables selection

We evaluated the prognosis significance of 51 features which have been selected according to previous studies (see details in Table1) [5, 6, 8, 17–21].

First, we looked for demographic marker (age) as it was reported that younger patients have a better outcome than older patients [2, 12, 22]. We did not look for the impact of gender because it did not seem to impact the SE outcome [22].

Second, we focused on clinical markers previously found to be involved in SE severity: previous history of epilepsy, SE etiology (classified into four groups [acute, remote, progressive, or unknown] according to the previous history epilepsy and how the SE appeared [20]), SE refractoriness (defined as a failure of at least two appropriately selected and dosed parenteral medications including a benzodiazepine; super-refractory SE and prolonged super-refractory SE were defined respectively as a refractory SE that persists for at least 24 h and 7 days, including ongoing need for anesthetics [21]), SE duration (the SE end was defined as the absence of seizures after the anesthetics withdrawal), and consciousness at admission evaluated by the Glasgow Coma Scale and

Table 1 Demographic, clinical and biochemical markers

Demographic marker (1)	Age
Clinical markers (12)	
SE subtype (3)	Refractory SE, super-refractory SE, prolonged-super-refractory SE
SE etiology (4)	Acute, remote, progressive, unknown
Others clinical markers (5)	Previous history of epilepsy, SE duration[a], mRS baseline, GCS score at enrollment, FOUR score at enrollment
Biochemical markers (38)	
Routine laboratory blood measures (14)	Sodium, potassium, chloride, urea, creatinine, aspartate aminotransferase, alanine aminotransferase, gamma gt, lactates, bilirubin, hemoglobin, platelet count, white blood cell count, neutrophil/lymphocyte ratio
Brain injury biomarkers in blood (3)	Neuron specific enolase, S100-beta protein, progranulin
Brain injury biomarkers in CSF (3)	Neuron specific enolase, S100-beta protein, progranulin
Routine blood lipid biomarkers (17)	Total cholesterol (TC), triglycerides, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), TC/HDL-C, apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), ApoA1/HDL-C, ApoB/LDL-C, lipoprotein(a), apolipoprotein E, lipoprotein-associated phospholipase A2, free cholesterol, esterified cholesterol (EC), cholesterol esterification ratio (EC/TC), phospholipids (PL), TC/PL
Routine CSF lipid biomarkers (1)	Apolipoprotein E

CSF Cerebrospinal fluid, *FOUR score* Full Outline of UnResponsiveness score, *GCS* Glasgow Coma Scale, *mRS* modified Rankin score, *SE* status epilepticus

[a]The SE end was defined as the absence of seizures after the anesthetic's withdrawal

the Full Outline of UnResponsiveness score. We did not look for the impact of individual anti-seizure medications as we previously observed that anti-seizure medications did not modify biochemical markers levels [19, 23, 24].

Third, as SE is associated with molecular and cellular changes that may induce brain injury and subsequent neurologic sequelae, we looked for biochemical markers able to reflect the SE consequences [25]. Protein markers were proposed to assess the brain injury (e.g. Neuron Specific Enolase, S100beta protein, progranulin) [17, 18, 26–30]. Moreover, we have highlighted the role of lipid metabolism in SE excitotoxicity, suggesting the usefulness of lipid biomarkers as SE outcome biomarkers [19, 31, 32]. In addition, we looked for routine laboratory markers (ion count, liver and kidney markers) and other biological variables (white blood cell count, platelet count, bilirubin, hemoglobin) previously found to be useful to monitor the critical ill patients' severity or potential complications of treatment [33–37]. Despite their interest, we did not consider albumin and C-reactive protein because they had been measured for a too small proportion of our patients [11, 38].

We did not look for brain imaging biomarkers and electrophysiological (EEG) variables because MRI and EEG were not performed for all SE patients in our cohort.

Biochemical analyses and data extraction

The clinical data and routine laboratory measures were extracted from medical records. The biochemical markers were assessed upon admission in Pitié-Salpêtrière hospital. All patients presented with an ongoing SE during the blood and CSF samples collection.

Neuron Specific Enolase (NSE) and S100beta protein (S100B) assays were performed using immunofluorimetric assays and electrochemiluminometric sandwich immunoassays (Kryptor®, Brahms and Modular®E170, Roche Diagnostics), respectively. Progranulin measurements were obtained, in duplicated, using the progranulin-human-ELISA kit (Adipogen).

Total cholesterol (TC), triglycerides, HDL-cholesterol were analyzed by enzymatic methods; and apolipoprotein A1 and apolipoprotein B100 by immunoturbidimetric method on Cobas analyzer (Roche). Phospholipids and free cholesterol (FC) were analyzed by colorimetric method on Konelab analyzer (Thermo Fisher Scientific). Esterified cholesterol (EC) was calculated by difference (EC = TC-FC). Lipoprotein(a) and apolipoprotein E were measured by immunonephelemetric method on BNII analyzer (Siemens).

Outcome assessment

The global outcome was assessed from medical records, or by in-person or telephone structured interview at discharge (called *discharge)* and at 6–12 months (called *follow-up*) using the 7-point version of the modified Rankin Scale (mRS), rated from death (6) to symptom-free full recovery (0) [39]. The same scale was used to assess the functional state before SE (called *baseline*). If patients had several follow-up evaluations, we considered the last evaluation as the $mRS_{follow\text{-}up}$. The physicians were not informed on the results

of the measurements before managing patients or assessing the mRS scores.

We performed four analyses: (1) prediction of poor outcome at discharge (i.e. mortality or worsening of clinical conditions; $mRS_{discharge} > mRS_{baseline}$); (2) prediction of the degree of worsening at discharge (i.e. $1 \leq mRS_{discharge}\text{-}mRS_{baseline} \leq 6$); (3) mortality prediction at discharge (i.e. $mRS_{discharge} = 6$); and (4) prediction of recovery at 6–12 months (i.e. $mRS_{follow\text{-}up} < mRS_{discharge}$). We only focused on surviving patients with poor outcome at discharge to identify biomarkers able to predict the recovery at 6–12 months.

Statistical analyses

Univariate analyses

We first performed univariate logistic regression analyses to identify markers able to predict SE outcome. The Benjamini–Hochberg procedure was used to correct for multiple comparisons. We used the boostrap method to estimate the standard errors of R^2 ($n = 1000$).

Levels of correlation between quantitative variables and the degree of worsening at discharge (defined as $mRS_{discharge} - mRS_{baseline}$) were obtained with Spearman correlation analysis. We performed Fisher tests to assess whether the frequency distribution of categorical data differed between groups.

Selection of variables in multivariate analyses

To design multivariate models able to predict SE outcome for all patients, we selected only variables that were available for all patients. First, we excluded the CSF measures as lumbar puncture is not systematically performed in SE management (4 variables). Then, we discarded variables with more than 10% of missing data (6 variables), and interrelated variables (9 variables, defined as Spearman's ρ above 0.80). Our multivariate analyses were conducted on 32 variables (26 non-binary and 6 binary variables). These variables are either routinely measured in all hospitalized units (e.g. ion count, white blood cell count, platelet count, liver and kidney markers, routine lipid biomarkers) or not looked for in daily practice but easy to implement in all biochemical departments (e.g. NSE, S100B, progranulin, esterified cholesterol, free cholesterol, apolipoproteins). Five patients had missing data on some of these 32 variables and were not considered for multivariate ML analysis.

Multivariate analyses

We applied a data-driven approach using statistical machine learning (ML) models (support vector machine and logistic regression) to identify markers predictive of SE outcome. The maximum number of variables to combine was defined according to statistical rules.

Support vector machine (SVM) The SVM classifiers are known to be robust to overfitting and work well with complex and high-dimensional datasets (i.e. they allow to combine more than 30 variables whatever the size of the study cohort) [15]. They used a kernel transformation to project input data in a higher dimensional space: input data that cannot be distinguished in the original space may become separable after transformation (Fig. 1a) [40]. Although there are some kernels proposed for binary variables, most of SVM classifiers are optimized for non-binary variables. For this reason, here we only evaluated the prognosis value of our 26 non-binary variables. There were two stages in building the prediction model (Fig. 1b): a training phase, in which a binary classifier (poor or good outcome, death or survival, recovery or non-recovery) used 70% of observations to learn the model; and then a testing phase, in which the remaining 30% of data were used to evaluate its prediction performance. A cross-validation procedure was used with 1000 folds. We also controlled classifiers' performance using permutation tests ($n = 1000$) where class labels are randomly re-assigned [41].

We next selected the most relevant variables. The most "non-significant" variables were removed one by one by a pruning procedure (Fig. 1c): (1) the area under the receiver operating curve (AUC) values were obtained by cross-validation, after removal of each variable; (2) the variable without which the model had the highest AUC was removed; and (3) the procedure was repeated with the remaining variables. We could thus identify a set of variables that improves the classification after their removal. If the removal procedure further continued, the classification performance decreased. The most relevant variables were selected for each analysis separately (i.e. poor outcome; mortality and recovery). Therefore, we identified a different set of variables to assess the poor outcome at discharge, the mortality at discharge and the recovery at long-term.

Logistic and linear regression models Logistic regression analysis is currently used to assess relationships between one dependent binary variable and one or more continuous or binary variables. It allows us to construct an index (score) that combined the most important markers. In contrast to SVM, logistic regression models are very sensitive to overfitting. For this reason, we retained only one feature per 10 patients. We therefore did not use logistic regression to predict SE mortality and recovery because we had less than 20 patients in both groups. Therefore, we only used it to predict the poor outcome at discharge (as 35

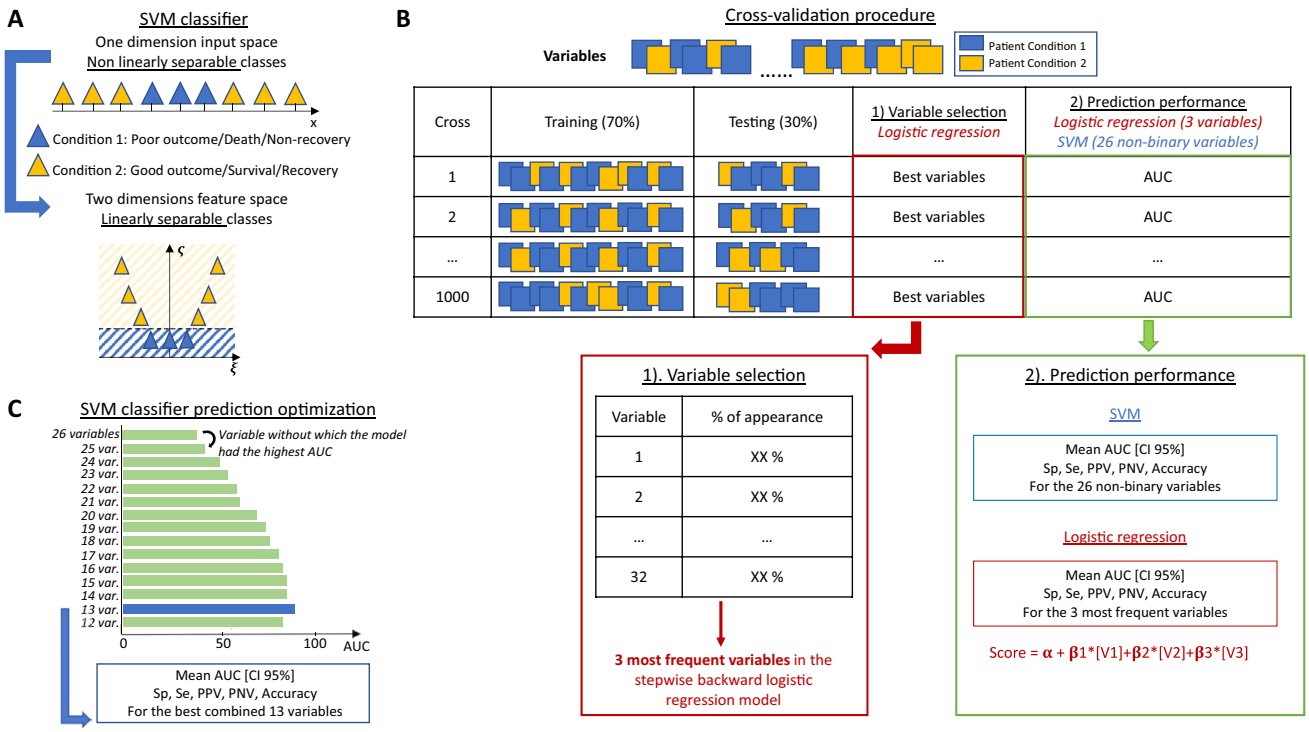

Fig. 1 General scheme of the prediction method. **a** Nonlinear transformation of non-separable data in the original input space: input data are mapped into a higher dimensional feature space (from 1 to 2-dimensional space in this example) where data become separable. **b** Scheme of the cross-validation procedure. The ML classifiers used 70% of the observations to train the model; and then the remaining 30% of data were used to test the prediction performance. A first step of variable selection was performed for logistic regression: the 3 most frequently found variables were retained for the prediction performance. A cross-validation procedure was used with 1000 folds. **c** The SVM classifier prediction performances were optimized by selecting the most relevant variables. The "non-significant" variables were removed one by one by a pruning procedure: (i) The area under the receiver operating curve (AUC) values were obtained by cross-validation, after removal of each variable; (ii) the variable without which the model had the highest AUC was removed; and (iii) the procedure was repeated with the remaining variables

patients presented a good outcome and 46 a poor outcome, we were able to combine a maximum of 3 variables).

To identify the most significant variables to assess the poor outcome at discharge, we first split our population into two sets: a training set (70% of observations) and a testing one (the remaining 30% of data) (Fig. 1b). We performed a backward stepwise regression procedure with a 1000-fold cross-validation procedure. At each fold, we obtained the most significant variables and we selected the three most frequently found variables. We further used these variables, to build the prediction model (Fig. 1b). Again, a cross-validation procedure (70% of observations were used for the training phase and the remaining 30% for testing) was used with 1000 folds [41].

Here, we also used a linear regression model to identify variables able to predict the degree of worsening at discharge. Validation and reliability of the prediction system were assessed with Bland–Altman method and Spearman correlation coefficient.

Comparison with previous scales

Except END-IT, previous scales mostly assessed short-term mortality [5–8]. We did not compare our scores to END-IT because this scale required MRI data for all patients. We compared our prediction performances, using Wilcoxon-test, for poor outcome and mortality at discharge to both STESS and mSTESS scales using the better cut-off reported, 3 for STESS score and 4 for mSTESS score, respectively [6, 10, 14]. We did not use EMSE scale, as some of our patients had SE etiologies, such as auto-immune encephalitis, not covered by this algorithm.

Data availability

Anonymized data will be made available by request from any qualified investigator.

Results

Study participants

We included 81 patients with SE (49 men and 32 women, mean age: 50 (± 19) years) (Fig. 2). Fifty-six patients (69%) were initially managed at Pitié-Salpêtrière Hospital while 25 patients (31%) were transferred from another hospital due to uncontrolled SE. At admission, patients had in average 3 antiepileptic drug (minimum = 1, maximum = 7), 1 anesthetic (minimum = 0, maximum = 4) and an average Glasgow Coma Score of 7 (± 4). At admission, 33 patients (41%) were treated by propofol, 30 patients (37%) by midazolam, 11 patients (14%) by pentothal and 9 patients (11%) by ketamine. Fifty-seven patients (70%) presented with refractory SE (RSE); among them, 44 patients (77%) presented with super-refractory SE and 29 (51%) with prolonged super-refractory SE. The SE etiologies were categorized into four subgroups: acute (29 patients, 36%), remote (24 patients, 30%), progressive (19 patients, 23%), and SE of unknown etiology (9 patients, 11%). The SE etiologies are detailed in Supplementary Table 1. Thirty-eight patients (47%) had previously been diagnosed with epilepsy. Thirty-eight patients (47%) had no previous neurological disability ($mRS_{baseline} = 0$), while 15 patients (19%) were already dependent before SE ($mRS_{baseline}$ ranging from 3 to 5). All blood and CSF samples were collected at Pitié-Salpêtrière hospital admission, in average 8 (± 15) days after the ongoing SE onset.

Outcome prediction at discharge

Prediction of poor outcome at discharge

Forty-six patients (57%) had a higher $mRS_{discharge}$ score (i.e. poor outcome), when compared with their $mRS_{baseline}$ score (Fig. 2). Forty of the 57 patients with RSE (70%) presented with poor outcome after SE compared to only 6 of the 24 patients with non-refractory SE (25%; $p = 0.049$). Patients who had previously been diagnosed with epilepsy had a lower risk to present poor outcome (15 of the 38 patients, 39%) when compared with the other patients (31 of the 43 patients, 72%; $p = 0.045$).

Five clinical markers were found to be significantly different between the 46 patients with poor outcome and the 35 patients for whom SE had no effect on their functional outcome at discharge in the univariate analyses (Table2): previous history of epilepsy, SE duration, refractory SE, super-refractory SE and prolonged super-refractory SE. Nevertheless, none of these biomarkers yielded a sufficient R^2 value to be used alone to predict the risk to present poor outcome after SE. Therefore, we looked for combined clinico-biological markers that optimally predicted the poor outcome.

The SVM analysis revealed that the association of all the 26 non-binary variables retained for multivariate analyses failed in most cases (AUC = 0.46 [0.27–0.67]) to predict the poor outcome. The prediction performance was, however, improved using the following 10 most relevant markers identified after the pruning procedure (AUC = 0.72 [0.54–0.88], $p = 0.003$): phospholipids, serum NSE, gamma GT, sodium,

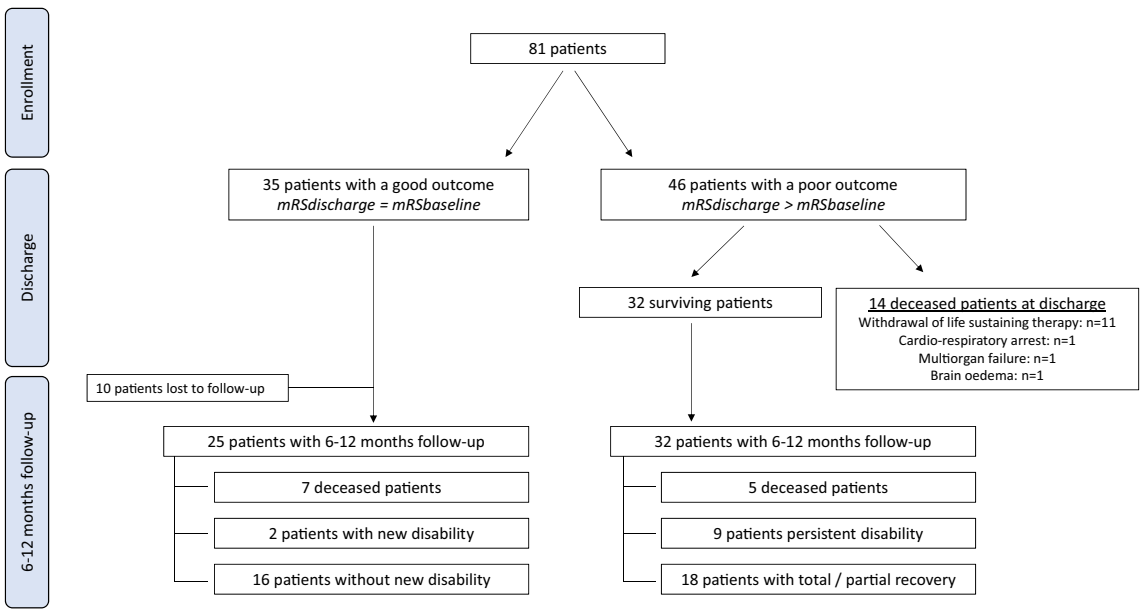

Fig. 2 Flow chart of the study population

Table 2 Prognosis value of selected markers in predicting poor outcome and mortality at discharge

Markers	**Mean values for good outcome patients**	**Mean values for poor outcome patients**	Mean R^2	p value	Markers	**Mean value for surviving patients**	**Mean value for died patients**	Mean R^2	p value
Age (years)	47	52	0.019	0.51	Age (years)	49	53	0.009	0.82
Total cholesterol (g/L)	1.53	1.59	0.003	0.75	Total cholesterol (g/L)	1.61	1.34	0.047	0.28
Triglycerides (g/L)	1.61	1.80	0.003	0.75	Triglycerides (g/L)	1.67	1.95	0.009	0.82
HDL-cholesterol (g/L)	0.41	0.34	0.035	0.36	HDL-cholesterol (g/L)	0.40	0.25	0.091	0.09
Apolipoprotein B (g/L)	0.79	0.99	0.084	0.15	Apolipoprotein B (g/L)	0.90	0.90	0.001	0.98
Lipoprotein(a) (g/L)	0.28	0.41	0.025	0.39	Lipoprotein(a) (g/L)	0.38	0.21	0.013	0.47
Apolipoprotein E (mg/dL)	5.16	5.67	0.014	0.65	Apolipoprotein E (mg/dL)	5.39	5.73	0.003	0.85
Free cholesterol (g/L)	0.53	0.62	0.039	0.32	Free cholesterol (g/L)	0.57	0.63	0.012	0.78
Esterified cholesterol (g/L)	1.01	0.98	0.000	0.87	Esterified cholesterol (g/L)	**1.05**	**0.71**	**0.123**	**0.044**
Phospholipids (g/L)	2.13	2.25	0.010	0.64	Phospholipids (g/L)	2.19	2.24	0.002	0.88
NSE (ng/mL)	20.4	18.9	0.007	0.75	NSE (ng/mL)	19.1	22.0	0.017	0.77
S100-beta (ng/mL)	0.11	0.24	0.024	0.39	S100-beta (ng/mL)	0.13	0.46	0.090	0.10
Progranulin (ng/mL)	120.7	154.4	0.051	0.31	Progranulin (ng/mL)	**129.1**	**191.1**	**0.124**	**0.044**
AST (UI/L)	409.1	74.8	0.009	0.51	AST (UI/L)	254.7	49.5	-0.007	0.83
ALT (UI/L)	97.0	77.7	0.002	0.83	ALT (UI/L)	95.8	39.6	-0.003	0.78
γGT (UI/L)	198.3	170.6	0.002	0.83	γGT (UI/L)	176.6	211.2	0.008	0.85
Sodium (mmol/L)	139.4	140.2	0.008	0.65	Sodium (mmol/L)	140.2	138.4	0.026	0.47
Potassium (mmol/L)	3.81	3.81	0.001	0.98	Potassium (mmol/L)	3.79	3.91	0.010	0.80
Chlorine (mmol/L)	102.9	103.6	0.004	0.75	Chlorine (mmol/L)	103.3	103.5	0.003	0.89
Urea (mmol/L)	5.21	5.44	0.010	0.87	Urea (mmol/L)	5.38	5.16	0.001	0.88
Creatinine (µmol/L)	86.1	61.9	0.050	0.31	Creatinine (µmol/L)	77.2	50.6	0.037	0.43
Platelet count (G/L)	228.7	277.0	0.020	0.39	Platelet count (G/L)	261.1	231.2	0.005	0.82
Hemoglobin (g/dL)	11.7	10.7	0.048	0.31	Hemoglobin (g/dL)	11.3	10.3	0.036	0.47
White blood cell count (G/L)	10.0	10.5	0.002	0.81	White blood cell count (G/L)	10.2	10.6	0.005	0.88
Previous epilepsy (%)	**60.5**	**39.5**	**0.136**	**0.048**	Previous epilepsy (%)	86.8	13.2	0.011	0.75
SE acute (%)	24.1	75.9	0.095	0.11	SE acute (%)	75.9	24.1	0.011	0.55
SE remote (%)	58.3	41.7	0.046	0.32	SE remote (%)	91.7	8.33	0.020	0.47
SE progressive (%)	52.6	47.4	0.012	0.59	SE progressive (%)	84.2	15.8	0.000	0.88
SE unknown etiology (%)	44.4	55.6	0.002	0.97	SE unknown etiology (%)	77.8	22.2	0.006	0.85
SE duration (days)	**2.17**	**12.5**	**0.094**	**0.048**	SE duration (days)	6.91	13.3	0.093	0.47

Table 2 (continued)

Markers	**Mean values for good outcome patients**	**Mean values for poor outcome patients**	Mean R^2	p value	Markers	**Mean value for surviving patients**	**Mean value for died patients**	Mean R^2	p value
Refractory SE (%)	**29.8**	**70.2**	**0.229**	**0.007**	Refractory SE (%)	79.0	21.0	0.021	0.47
mRS baseline	1.34	0.93	0.022	0.43	mRS baseline	1.04	1.43	0.012	0.75
Super-refractory SE (%)[a]	**25.0**	**75.0**	**0.212**	**0.007**	Total cholesterol/HDL-C (TC/HDL-C) (AU)[a]	**5.47**	**11.3**	**0.150**	**0.044**
Prolonged super-refractory SE (%)[a]	**20.7**	**79.3**	**0.138**	**0.045**	Apolipoprotein A1/HDL-C (ApoA1/HDL-C) (AU)[a]	**3.07**	**4.78**	**0.171**	**0.044**
					Esterification ratio (EC/TC) (AU)[a]	**0.64**	**0.52**	**0.159**	**0.044**
					TC/Phospholipids (AU)[a]	**0.75**	**0.62**	**0.124**	**0.044**

The variables in bold represent the variables significantly associated with the risk of poor outcome or mortality at discharge

[a]Markers not considered for multivariate analyses

ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; AU = Arbitrary Unit; mRS = modified Rankin Score; NSE = Neuron Specific Enolase; SE = Status Epilepticus; TC = Total Cholesterol

potassium, chloride, platelet count, hemoglobin, white blood cell count and $mRS_{baseline}$. We defined the association of these ten variables as the "SVM-functional model". The AUC of the "SVM-functional model" was better than those obtained with STESS (cut-off at 3, AUC = 0.63) and mSTESS (cut-off at 4, AUC = 0.53) ($p < 0.001$) (Table3). The combination of these 10 markers allowed to predict the poor outcome for 74% of the cases (positive predictive value, PPV = 0.74, $p = 0.004$). Our model also accurately predicted which patients will have good outcome (i.e. a steady state) at discharge (negative predictive value, NPV = 0.73, $p = 0.001$).

Multivariate logistic regression analysis revealed that the combination of three clinico-biological variables (*"Refractory SE*", a binary variable which takes the value of 1 in case of refractory SE or 0 in case of non-refractory SE, "*FC*" the concentration of free cholesterol (g/L) and "*phospholipids*" the concentration of phospholipids (g/L)) yielded similar results to the SVM-functional model (AUC = 0.78 [0.67–0.88], PPV = 0.80, $p < 0.001$; Table3). This logistic regression model defined as "LR-functional model" resulted in a 24% improvement in AUC over the STESS and 47% over the mSTESS ($p < 0.001$).

Prediction of the degree of worsening at discharge

Forty-six of the 81 patients (57%) had poor outcome after SE. The difference between their $mRS_{baseline}$ and their $mRS_{discharge}$ scores was of 1 for 13 patients (28%), 2 for 6 patients (13%), 3 for 7 patients (15%), 4 for 7 patients (15%), 5 for 9 patients (20%) and 6 for 4 patients (9%).

Eighteen clinical and biochemical markers were significantly correlated with the difference "$mRS_{discharge} - mRS_{baseline}$" in the univariate analyses (Table4). By linear regression analysis, we identified the three most relevant variables to predict the degree of disability: the total cholesterol level (g/L), the $mRS_{baseline}$ and the creatinine value (µmol/L).

The Bland–Altman analysis reported a 95% agreement between − 2.7 and 2.73 with a bias of 0.034 between the real ($mRS_{discharge} - mRS_{baseline}$) and the predicted degree. Moreover, significant correlation coefficients between both measurements are revealed in all states (Spearman's $\rho = 0.637$, $p < 0.001$).

Prediction of mortality at discharge

Fourteen patients died at hospital discharge (mean delay after SE onset, 47 (±40) days), mostly after the withdrawal of life sustaining therapy (11 patients, 79%) (Fig. 2). Twelve of the 57 patients with RSE (21%) died at hospital discharge compared to 2 of the 24 patients (8.3%) with non-refractory SE ($p = 0.34$). Nine of the 29 patients with prolonged super-refractory SE (31%) died at hospital discharge compared to only 5 of the 52 patients with non-prolonged super-refractory SE (9.6%) ($p = 0.074$). The risk of death was not found to be significantly higher for patients with RSE or prolonged

Table 3 Predictive performance of the models obtained by SVM classifier and logistic regression

Analysis	Methods	Se	Sp	PPV	NPV	Accuracy	AUC	F1 score[a]
Poor outcome at discharge	SVM-functional model (10 variables)[b]	0.75 [0.50–0.92]	0.70 [0.45–0.91]	0.74 [0.58–0.90]	0.73 [0.55–0.91]	0.73 [0.57–0.87]	0.72 [0.54–0.88]	0.74 [0.54–0.91]
	LR-functional model	0.69 [0.52–0.86]	0.71 [0.45–0.92]	0.80 [0.50–0.95]	0.56 [0.33–0.82]	0.69 [0.55–0.79]	0.78 [0.67–0.88]	0.74 [0.51–0.90]
	STESS (cut-off 3)	0.49	0.77	0.71	0.56	0.62	0.63	0.58
	mSTESS (cut-off 4)	0.29	0.77	0.60	0.48	0.51	0.53	0.39
Death at discharge	SVM-mortality model (8 variables)[c]	0.87 [0.75–1.0]	0.78 [0.58–1.0]	0.49 [0.30–1.0]	0.97 [0.92–1.0]	0.79 [0.61–0.96]	0.83 [0.68–0.97]	0.63 [0.43–1.0]
	STESS (cut-off 3)	0.46	0.65	0.21	0.85	0.62	0.56	0.29
	mSTESS (cut-off 4)	0.46	0.78	0.30	0.88	0.72	0.62	0.36
Recovery at 6–12 months	SVM-recovery model (11 variables)[d]	0.86 [0.60–1.0]	0.90 [0.75–1.0]	0.93 [0.75–1.0]	0.85 [0.60–1.0]	0.88 [0.67–1.0]	0.89 [0.65–1.0]	0.89 [0.67–1.0]

The values are represented as mean [CI 95%]

AUC area under the receiver operating characteristic curve, *NPV* negative predictive value, *PPV* positive predictive value, *Se* sensitivity, *Sp* specificity, *SVM* support vector machine

[a]F1 score is calculated as: $2 \times Se \times PPV/(Se + PPV)$

[2]The most relevant markers are: phospholipids, NSE, gamma GT, sodium, potassium, chloride, platelet count, hemoglobin, white blood cell count, $mRS_{baseline}$

[c]The most relevant markers are: apolipoprotein B, free cholesterol, progranulin, alanine aminotransferase, sodium, creatinine, platelet count, white blood cell count

[d]The most relevant markers are: apolipoprotein B, lipoprotein(a), phospholipids, NSE serum value, sodium, chloride, urea, creatinine, white blood cell count, total SE duration and $mRS_{baseline}$

super-refractory SE due to lack of statistical power. Half of the 14 died patients presented with SE of acute etiology and five of the 14 died patients had previously been diagnosed with epilepsy (36%).

Six biochemical markers were significantly different between the 14 died patients and the 67 surviving patients in the univariate analyses (Table2): esterified cholesterol, progranulin, total cholesterol/HDL-cholesterol ratio, apolipoprotein 1/HDL-cholesterol ratio, esterification ratio, total cholesterol/phospholipids ratio. Nevertheless, none of these biomarkers had a sufficient R^2 value to be used alone to predict the risk of death after SE. Therefore, we looked for combined clinico-biological markers that optimally predicted the risk of mortality at discharge.

The SVM analysis revealed that the association of all the 26 non-binary variables retained for multivariate analyses failed in most cases (AUC = 0.44 [0.24–0.64]) to predict mortality. However, the prediction performance was improved using the following 8 most relevant markers, identified by a pruning procedure, (AUC = 0.83 [0.68–0.97], $p < 0.001$): apolipoprotein B, free cholesterol, progranulin, alanine aminotransferase, sodium, creatinine, platelet count and white blood cell count. We defined the association of these 8 markers as the "SVM-mortality model". The prediction of the "SVM-mortality model" was clearly better than those obtained with STESS (cut-off at 3, AUC = 0.56) and mSTESS (cut-off at 4, AUC = 0.62) ($p < 0.001$) (Table 3). The combination of the 8 most discriminant variables allowed to predict the death after SE in almost 50% of cases (PPV = 0.49, $p = 0.002$) and the survival in 97% of cases (NPV = 0.97, $p < 0.001$). As the number of observations was unequal in our two groups, we also computed the F1 score, which is a more appropriate metrics for imbalanced scenarios, and defined as the harmonic mean of precision (PPV) and recall (sensitivity) [42]. The F1 score of the "SVM-mortality model" was of 0.63 [0.43–0.1.0]; a higher value than those obtained by STESS (0.29) and mSTESS (0.36) scales.

Table 4 Estimation of the degree of worsening at discharge

Markers	Spearman's ρ estimate	p value
Age (years)	− 0.068	0.88
Total cholesterol (g/L)	− 0.303	0.14
Triglycerides (g/L)	**0.377**	**0.047**
HDL-cholesterol (g/L)	**− 0.482**	**0.009**
Apolipoprotein B (g/L)	0.092	0.79
Lipoprotein(a) (g/L)	− 0.162	0.58
Apolipoprotein E (mg/dL)	**0.372**	**0.047**
Free cholesterol (g/L)	0.156	0.58
Esterified cholesterol (g/L)	**− 0.474**	**0.009**
Phospholipids (g/L)	0.074	0.86
NSE (µg/L)	0.099	0.79
S100B (µg/L)	0.226	0.37
Progranulin (ng/mL)	**0.464**	**0.011**
AST (UI/L)	0.273	0.20
ALT (UI/L)	0.214	0.37
γGT (UI/L)	0.177	0.51
Sodium (mmol/L)	− 0.128	0.65
Potassium (mmol/L)	0.097	0.79
Chloride (mmol/L)	− 0.004	0.99
Urea (mmol/L)	0.007	0.99
Creatinine (µmol/L)	**− 0.377**	**0.047**
Platelet count (G/L)	0.028	0.95
Hemoglobin (g/dL)	**− 0.378**	**0.047**
White blood cell count (G/L)	0.099	0.79
Previous epilepsy (%)	**− 1.739**	**0.037**
SE acute (%)	**2.031**	**0.007**
SE remote (%)	**− 1.443**	**0.034**
SE progressive (%)	− 0.656	0.65
SE unknown etiology (%)	− 0.486	0.62
SE duration (days)	**0.491**	**0.0088**
Refractory SE (%)	1.502	0.88
mRS baseline	**− 0.415**	**0.028**
Prolonged super-refractory status epilepticus (%)	**1.977**	**0.028**
Apolipoprotein A1 (g/L)[a]	**− 0.584**	**0.0018**
TC/HDL-C (AU)[a]	**0.367**	**0.047**
Esterification ratio (EC/TC) (AU)[a]	**− 0.496**	**0.0088**
TC/Phospholipids (AU)[a]	**− 0.477**	**0.009**
GCS at enrollment[a]	**− 0.421**	**0.028**

The correlation between the markers and the difference between $mRS_{discharge}$ and $mRS_{baseline}$ was assessed with Spearman correlation analysis

The variables in bold were significantly associated with the degree of worsening at discharge

ALT alanine aminotransferase, *AST* aspartate aminotransferase, AU arbitrary unit, *GCS* Glasgow Coma Scale, *mRS* modified Rankin score, *NSE* neuron specific enolase, *SE* status epilepticus

[a]Markers not considered for multivariate analyses

Outcome prediction at long-term

Prediction of recovery at long-term

All 32 surviving patients with poor outcome after SE underwent a follow-up neurological evaluation at 6–12 months. Eighteen patients (56%) showed partial or total recovery of neurologic symptoms (Fig. 2).

Not one of the 51 evaluated biomarkers were significantly different between the 18 patients who recovered and the remaining 14 patients in the univariate analyses (Table 5). Nevertheless, we assessed their outcome predictive potential by multivariate analyses.

The SVM analysis revealed that the association of all the 26 non-binary variables retained for multivariate analyses had a moderate predictive value (AUC = 0.56 [0.20–0.95]) for the patient evolution. Nevertheless, the prediction performance was improved using the 11 most relevant markers, identified by a pruning procedure, (AUC = 0.86 [0.60–1.0], $p < 0.001$): apolipoprotein B, lipoprotein(a), phospholipids, NSE, sodium, chloride, urea, creatinine, white blood cell count, SE duration, and $mRS_{baseline}$. This "SVM-recovery model" was able to predict the recovery for 93% of the cases (PPV = 0.93, $p < 0.001$). Moreover, it was able to predict which patients will have persistent disability in 85% of the cases (negative predictive value, NPV = 0.85, $p < 0.001$).

Discussion

To better manage SE, tools that accurately predict outcome, at discharge and at long-term, are needed. Current tools cannot be used to follow all SE patients over time: STESS and mSTESS scales can be applied for all patients but these scales used only pre-hospitalized data, and cannot be repeated to follow patient evolution in ICU; EMSE algorithm covered only some SE etiologies; and END-IT scale requires MRI data [5–8]. Here, using a cohort of 81 patients and applying statistical methods to clinical and biochemical data, we found new clinico-biological markers able to accurately predict SE outcome at both short- and long-term.

Outcome prediction at discharge

We confirmed the higher risk of poor outcome for patients with RSE, higher SE duration and the lower risk for patients previously diagnosed with epilepsy [2, 3, 5, 8, 43]. We proposed two clinico-biological models able to accurately predict outcome at discharge. The SVM-functional model identified 10 variables that can be obtained quickly in all biochemistry departments and reflected non-neurologic

Table 5 Prognosis value of selected markers in predicting recovery after 6–12 months

Markers	Mean values for patients without recovery	Mean values for patients with recovery	Mean R^2	*p* value
Age (years)	54.6	48.7	0.027	0.66
Total cholesterol (g/L)	1.90	1.54	0.216	0.62
Triglycerides (g/L)	1.60	1.84	0.022	0.86
HDL-cholesterol (g/L)	0.44	0.34	0.099	0.62
Apolipoprotein B (g/L)	1.08	0.97	0.039	0.66
Lipoprotein(a) (g/L)	0.44	0.53	0.011	0.86
Apolipoprotein E (mg/dL)	5.66	5.64	0.010	0.98
Free cholesterol (g/L)	0.69	0.58	0.030	0.62
Esterified cholesterol (g/L)	1.24	1.00	0.106	0.62
Phospholipids (g/L)	2.32	2.20	0.015	0.83
NSE (µg/L)	18.24	17.01	0.008	0.86
S100B (µg/L)	0.19	0.13	0.042	0.62
Progranulin (ng/mL)	143.1	134.6	0.008	0.86
AST (UI/L)	141.3	42.8	0.034	0.62
ALT (UI/L)	150.1	51.2	0.053	0.62
γGT (UI/L)	110.8	185.5	0.031	0.62
Sodium (mmol/L)	142.1	140.2	0.046	0.62
Potassium (mmol/L)	3.64	3.87	0.067	0.62
Chlorine (mmol/L)	104.6	102.9	0.021	0.66
Urea (mmol/L)	5.40	5.70	0.005	0.86
Creatinine (µmol/L)	69.1	65.3	0.006	0.86
Platelet count (G/L)	223.1	359.1	0.130	0.62
Hemoglobin (g/dL)	11.6	10.3	0.143	0.62
White blood cell count (G/L)	10.7	10.4	0.006	0.90
Previous epilepsy (%)	40.0	60.0	0.003	0.86
SE acute (%)	40.0	60.0	0.010	0.86
SE remote (%)	37.5	62.5	0.002	0.86
SE progressive (%)	66.7	33.3	0.058	0.62
SE unknown etiology (%)	33.3	66.7	0.004	0.86
SE duration (days)	11.1	26.4	0.054	0.62
Refractory SE (%)	46.4	53.6	0.017	0.66
mRS baseline	1	0.5	0.060	0.62

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *mRS* modified Rankin score, *NSE* neuron specific enolase, *SE* status epilepticus

organ failure (hepatic [gamma GT, phospholipids] and systemic dysfunctions [sodium, potassium, chloride]) [13], SE related brain injury [NSE] [29], critical illness severity or complications of treatment [platelet count, hemoglobin, white blood cell count] [33–37], and the functional state before SE highlighted by the $mRS_{baseline}$ [43]. The LR-functional model revealed the 3 most important markers to predict poor outcome: RSE, free cholesterol (FC) and phospholipids levels. Patients with RSE were more likely to have poor outcome at discharge [13]. Similarly, patients with higher FC levels had poor outcome more frequently. Accumulation of FC in neuronal cells was found responsible to neuronal death [31]. This can lead to neurocognitive sequelae and may explain the poorer prognosis. Conversely, patients with higher phospholipids levels had better outcome. Phospholipids composed cellular membranes and are essential for the proper functioning of membrane-bound proteins [44]. Decreased levels may disturb cellular membranes properties and induce a membrane conformational change that would enhance cellular dysfunctions and subsequent sequelae [45]. Both models have similar performances to predict poor outcome but performances were lower for LR-functional model to predict good outcome (NPV = 0.56 *vs* NPV = 0.73). Conversely to STESS and mSTESS scales, our both models might be applied several times during the ICU stay of the same patient, because they were built on data that can be monitored over time (with the exception of a clinical data measured only once for both scores, respectively $mRS_{baseline}$ for the SVM model and SE refractoriness for logistic regression model). The evolution of the model

results could reflect the impact of neuroprotective or antiepileptic drugs on the outcome (i.e., if the NSE levels decreased after the introduction of a new therapeutic, the results of the SVM-functional model will change and we should except a better prognosis at discharge). Alternatively, changes of the model results in the opposite way may indicate an increased risk of poor outcome.

To our knowledge, we proposed for the first time to combine clinico-biological data to predict the degree of worsening induced by SE. Our approach is particularly relevant to better manage SE and organize the medical care when leaving the ICU by providing information to physicians and families. The linear regression analysis revealed that the $mRS_{baseline}$, the total cholesterol level and the creatinine level are the best markers to assess the degree of worsening. Patients with lower $mRS_{baseline}$ are more likely to have a higher degree of worsening at discharge. This result may be related to the frequency (22%) of New-Onset Refractory Status Epilepticus (NORSE) in our cohort. NORSE occurs in patients often young and without medical history [21]. These patients had the poorest outcome and the longest stay duration in ICU. They are often dependent in the first months after SE due to cognitive and motor sequelae. The high percentage of NORSE patients in our cohort can be explained by the enrollment of patients in an ICU unit specialized in super-refractory SE management. Patients with lower total cholesterol levels are more likely to present with a higher degree of worsening. We previously reported that SE patients had lower total cholesterol levels when compared with control or epileptic patients [19]. The decrease of total cholesterol levels in SE patients hide different trends from the two subtypes of cholesterol: an increase of the free cholesterol, which is metabolically active, and a decrease of the esterified cholesterol, an inactive form stored in the liver. The decrease of total cholesterol content could therefore reflect an increase of the free cholesterol content which could induce neuronal death and impair outcome [31, 32]. Patients with lower creatinine levels presented with a higher degree of worsening. This may reflect the muscular atrophy induced by prolonged ICU stay, with a higher risk of critical illness neuropathy making patients dependent on walking with a value of $mRS_{discharge}$ above 3.

Conversely to previous studies, we did not find a higher risk of mortality for older patients, patients with acute SE or with RSE [3, 5, 8, 43]. This can be explained by an enrollment bias: most of our patients who presented with a super-refractory SE were young and improved under immunotherapy [3, 46]. Our SVM-mortality model using the 8 most relevant markers was able to predict with a good accuracy the risk of mortality (AUC = 0.83, PPV = 0.49). The 8 variables can be obtained quickly and are either routinely available or easy to implement in all biochemistry departments, potentially allowing for easier integration in ICU. They reflected non-neurologic organ failure (hepatic [apolipoprotein B, free cholesterol, alanine aminotransferase], renal [creatinine] and systemic dysfunctions [sodium]), of which a part is known to be associated with the risk of SE and its prognosis [37, 47], illness severity and complications of treatment [platelet count, white blood cell count] [33–37], and the inflammation process related to SE [progranulin] [29]. The SVM-mortality model allowed also to predict survival.

Outcome prediction at long-term

We provided for the first-time a tool allowing the prediction of recovery at long-term without brain MRI. It is particularly relevant in SE management: a high probability of recovery may prompt clinicians to continue anesthesia for an extended period of time before deciding to discontinue life sustaining therapies. It is also relevant to provide accurate long-term prognostication to families. Our SVM-recovery model predicted accurately the recovery with 11 variables. The selected variables reflected non-neurologic organ failure (hepatic [apolipoprotein B, lipoprotein(a), phospholipids], renal [urea, creatinine] and systemic dysfunctions [sodium, chloride]) [13], brain injury induced by SE [NSE] [26], illness severity (white blood cell count), and the disease severity highlighted by the SE duration [43]. The $mRS_{baseline}$ was also retained by the algorithm: patients without previous disability may recover more easily. We may hypothesize that lower phospholipids levels may induce higher cellular dysfunctions and that disturbances may be less reversible.

There are three main findings in this study. First, we identified new clinico-biological markers that can be applied for hospitalized SE patients, to predict functional outcome and mortality at discharge. Second, we identified three variables that could estimate the degree of worsening induced by SE, which can help to adapt therapeutics. Finally, we identify a set of variables that accurately predicted recovery at long-term when including variables obtained upon admission.

In our cohort, the SVM-functional model and SVM-mortality model presented better results to assess the poor outcome and the mortality than previous scales—STESS and mSTESS. Nonetheless, these results have to be confirmed in an independent cohort and could be explained by an enrollment bias. Indeed, our study was conducted in a single cohort of patients, with various SE etiologies and duration. Seventy percent of our patients presented with a refractory SE. We specifically observed that patients with non-refractory SE and a poor outcome at discharge were most frequently misclassified. The higher percentage of refractory SE patients in our cohort could explain why previous publications using STESS and mSTESS scales reported better performances to assess poor outcome at discharge [10,

48, 49]. Therefore, the model's performance for future use might be lower for patients with non-refractory SE. We did not identify reason for the misclassification of patients who will die after SE. Misclassified patients did not shared common pre-existing morbidities. The prediction of mortality at discharge has to be interpreted with caution as almost 80% of the patients died after the withdrawal of life sustaining therapies. Therefore, selected variables and performances might have been different in centers with other protocols. In addition, we were not able to distinguish, with the modified Rankin scale, patients with poor outcome related to peripheral neurologic sequelae, with great chances of recovery, and those with central neurologic sequelae, potentially irreversible. Therefore, we believe that clinicians will not be able to rely solely on the model's result to decide to withdrawal life sustaining therapies.

This study is the first that provides an efficient framework to predict functional outcome, mortality at discharge, and recovery at long-term. The reproducibility in statistical studies using machine learning models is a concern [50], wherein performance measures observed in one cohort may not be generalizable to others, possibly due to overfitting. To minimize the model overfitting and improve generalizability, we used a 1000-fold cross validation procedure and a 1000-fold permutation test to control classifier's performance. Our scores integrate biochemical data to reflect pathophysiological mechanisms involved in SE excitotoxicity and consequences. Contrary to previous scales, these clinico-biological models can be applied for all hospitalized SE patients, as the selected biochemical data are either routinely available or easy to implement in all biochemical department. To address the issue of their clinical liability, these clinico-biological models can be highly operable in mobile devices, which would facilitate their use in routine ICU setting [51]. Moreover, the output of the SVM and LR models which is simply a probabilistic risk score between 0 and 1 is easily translatable in most settings because, unlike MRI and EEG, expertise of trained technicians and physicians is not required. Nonetheless, the association of neuroimaging (MRI) or neurophysiological (EEG) data to these clinico-biological models may also improve model's performance. It might be particularly interesting to look at EEG periodic discharges which have been demonstrated associated with poorer outcome [52]. Similarly, the consequences of status epilepticus can be visualized on MRI, which could be used to predict long-term recovery [53].

As the biochemical data can be evaluated several times during the ICU stay, it would be interesting to evaluate the capacity of these models to monitor SE patients over time and to follow the impact of a new therapeutic. In addition, as data can be obtained quickly, these models could be useful to define, upon admission, a targeted, sufficiently homogenous, population for further clinical trials to permit precise estimation of treatment effect. Further studies are needed to evaluate the models' performance in cohorts from other centers and to determine whether these models could be applied equally well whatever the SE refractoriness. In addition, further studies should evaluate the models' performance for patients developing SE in the context of an acute brain injury.

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Author contributions Conception and design of the study: AH, MC, VN. Acquisition and analysis of data: AH, SD, VL, BR, CM, MB, AD, RB, JAD, FIB, FL, BR, DBR, MC, VN. Drafting a significant portion of the manuscript or figures: AH, SD, VL, BR, CM, MB, AD, JLB, RB, JAD, FIB, FL, BR, DBR, MC, VN. Statistical analysis: AH, MC. Study supervision: SD, DBR, MC, VN.

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Availability of data and material All data are available on request upon the corresponding author.

Code availability The codes are available on request upon the corresponding author.

Declarations

Conflicts of interest AH, SD, MC and VN have a patent pending related to the current research. VN reports personal fees from UCB Pharma, EISAI, GW Pharma and LivaNova, outside the submitted work. AD reports grants, personal fees and non-financial support from Philips and Lungpacer, personal fees from Baxter, Getinge, Lowenstein and Gilead, personal fees and non-financial support from Fisher & Paykel and Respinor and grants from French Ministry of Health, outside the submitted work. SD reports individual payment from UCB Pharma, Regeneron and ARGENX. The other authors report no disclosures related to the current research.

Ethics approval The protocol was approved by our local (2012, CPP Paris-VI) and by the INSERM ethic committees (C16-16, 20152482). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate Patients or relatives were informed and give their consent.

Consent for publication Patients or relatives were informed and give their consent.

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