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Perspective

Progression to refractory status epilepticus: A machine learning analysis by means of classification and regression tree analysis

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ABSTRACT

Background and Objectives: to identify predictors of progression to refractory status epilepticus (RSE) using a machine learning technique.
Methods: Consecutive patients aged ≥ 14 years with SE registered in a 9-years period at Modena Academic Hospital were included in the analysis. We evaluated the risk of progression to RSE using logistic regression and a machine learning analysis by means of classification and regression tree analysis (CART) to develop a predictive model of progression to RSE.
Results: 705 patients with SE were included in the study; of those, 33 % (233/705) evolved to RSE. The progression to RSE was an independent risk factor for 30-day mortality, with an OR adjusted for previously identified possible univariate confounders of 4.086 (CI 95 % 2.390–6.985; $p < 0.001$). According to CART the most important variable predicting evolution to RSE was the impaired consciousness before treatment, followed by acute symptomatic hypoxic etiology and periodic EEG patterns. The decision tree identified 14 nodes with a risk of evolution to RSE ranging from 1.5 % to 90.8 %. The overall percentage of success in classifying patients of the decision tree was 79.4 %; the percentage of accurate prediction was high, 94.1 %, for those patients not progressing to RSE and moderate, 49.8 %, for patients evolving to RSE.
Conclusions: Decision-tree analysis provided a meaningful risk stratification based on few variables that are easily obtained at SE first evaluation: consciousness before treatment, etiology, and severe EEG patterns. CART models must be viewed as potential new method for the stratification RSE at single subject level deserving further exploration and validation.

1. Introduction

Status epilepticus (SE) is a medical and neurological emergency that is currently defined by the International League Against Epilepsy (ILAE) as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures" [1]. According to this definition, its age- and sex-adjusted incidence of a first SE episode is 36.1 (95 % confidence interval [CIs] 26.2–48.5) per 100 000 adults per year [2].

A prompt diagnosis and rapid and accurate treatment are mandatory to reduce the risk of negative long-term consequences, including high morbidity and mortality [3–5]. Usually, the pharmacological management of SE follows as stepwise approach, with benzodiazepines representing the first-line option, followed by intravenous antiseizure medications (ASMs) as second-line treatment [4–8]. If SE persists, the condition is termed refractory SE (RSE).

Refractoriness to treatment is likely multifactorial and it is difficult to identify reliable predictors [9,10]. Across studies, demographic, clinical, EEG, and biochemical variables have been associated with

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refractoriness. Validated scoring systems for the prediction of refractoriness do not exist, however, and this still represents an unmet need in clinical practice. A prediction model of responsiveness may also guide studies comparing the efficacy of different therapeutic strategies. Therefore, identifying predictors of evolution to RSE and their related risk of short-term mortality could prove useful for risk stratification and could affect individualized therapeutic decisions within an integrated framework of personalized medicine.

The aim of this study was to identify predictors of progression to RSE using a data-driven machine learning technique by means of a classification and regression tree analysis (CART) to develop a predictive model that can be used in clinical practice for patients' stratification.

2. Methods

2.1. Study design, setting, and patients

We reviewed consecutive episodes of SE occurring in patients aged ≥ 14 years and prospectively collected in our SE registry (Modena Status Epilepticus Registry – MoSER –) at Baggiovara Civil Hospital (Modena, Italy) from September 1, 2013 to December 31, 2021. Before 2015, SE was considered to be a continuous seizure that lasts 5 min or longer or two or more discrete seizures without complete recovery of consciousness between them [11]. After 2015, the definition by the International League Against Epilepsy (ILAE) was systematically adopted and prospectively applied. Accordingly, the operational time indicating when a seizure is likely to be prolonged leading to continuous seizure activity (i.e., SE), was set at 5 min for tonic-clonic SE, 10 min for focal SE with impaired consciousness, and 10–15 min for absence SE. All cases of SE that occurred before 2015 were reviewed by two of the authors (SM and GG) to ensure that all met the ILAE diagnostic criteria. The cases of nonconvulsive SE (NCSE) were diagnosed according to the Salzburg electroencephalographic (EEG) criteria [12,13].

A specific dataset was used to collect demographic and clinical information, including age, gender, setting of SE onset (out-of-hospital or in-hospital), medical history and comorbid medical conditions, prior history of epilepsy, etiological ILAE classification in which acute symptomatic causes were divided into hypoxic or non-hypoxic, impairment of consciousness before treatment (stupor/coma), and SE semiology according to ILAE classification [1]. We considered as 'severe EEG patterns' the following EEG patterns, when present in the first EEG recording that qualified the episode as SE, according to the American Clinical Neurophysiology Society (ACNS) terminology [14,15]: lateralized periodic discharges; generalized periodic discharges, and spontaneous burst suppression. The form was filled in by the first physician (neurologist or neurointensivist) taking care of the patient.

Treatment followed an internal protocol (publicly available at https://salute.regione.emilia-romagna.it/percorso-epilessia/PDTASE_AOU.pdf) based on the recommendations of international guidelines [6–8].

2.2. Outcome

Data on the evolution of SE over time and 30-day mortality were obtained from the SE dataset used to collect information and confirmed through the registry office.

2.3. Statistical analysis

We described categorical variables as percentage and proportions, and continuous variables as mean and standard deviation (SD) or as median and interquartile range (IQR), depending on the underlying distribution. Univariate comparisons were performed with the Fisher's Exact test, chi-square test, Mann–Whitney test, and the Kruskal–Wallis test, as appropriate.

The statistical analysis was conducted to evaluate the risk of progression to RSE using logistic regression and a data-driven machine learning analysis; subsequently, in patients with RSE, the risk of death was evaluated using logistic regression analysis.

Initially, we performed a multivariate analysis to identify the possible predictors of evolution to RSE. The multivariate analysis was performed with a binary logistic regression using stepwise method. The odds ratio (ORs) and their 95 % CIs were reported for the variables that were found to be independent risk factors for evolution to RSE. Then, we performed a classification and regression tree analysis (CART) to develop a predictive model of progression to RSE in SE patients using IBM SPSS Statistics version 25 software (IBM Corp, Armonk, USA).

CART analysis is a powerful machine-learning statistical data mining technique [16,17]. Through recursive partitioning, the data set is successfully divided into increasingly homogeneous subgroups by hierarchically selecting the explanatory variables that most influence the object variable. At each level (node), the CART algorithm selects the explanatory variable and its division value that provides the best discrimination between two classes of results. The result is a hierarchical level flow-chart that identifies groups of patients with identical characteristics and homogeneous risk. At the first level of subdivision, the node at the top of the hierarchy that is identified represents the "root" node. Subsequent levels are identified by parent nodes, which are followed by further nodes at lower levels. The terminal nodes that are not further subdivided into other nodes are called "leaf" nodes; they identify subgroups of patients who share the same risk. The resulting decision-tree not only provides an overall picture of the most significant variables for the risk of RSE, but also shows the relationship between the explanatory variables themselves and between the explanatory variables and the risk of RSE. The general principle of pruning is that the best-sized tree would have the lowest misclassification rate for an individual not in the original data. The clinical variables found to be significantly associated with the presence of RSE in the previous univariate analysis were added to the CART model as possible explanatory variables. In the model, the minimum number of parents, child node, and maximum depth were set at 50, 25, and 5, respectively.

A tenfold cross-validation procedure was conducted to avoid data overfitting problems and improve the performance of the CART model. In this procedure, all data was randomly divided into 10 subsets. Nine of these subsets were used to evaluate the accuracy of the model using data from another subset. This was repeated for other subsets so that all subsets were used as a test sample.

Finally, in the cohort of patient with RSE, a multivariate analysis was conducted to identify the predictors of mortality at 30 days. The multivariate analysis was performed with a binary logistic regression using stepwise method. The odds ratio (ORs) with their own CIs were reported for the variables that were found to be independent risk factors for death.

We calculated the overall prediction accuracy of the CART model (i.e., the percentage of success in classifying patients) as the degree of correlation between the prediction resulting from the decision tree analysis and the actual risk of progression to RSE. A correlation of 100 % indicates a perfect prediction accuracy.

All tests were two-sided and a p-value < 0.050 was considered statistically significant. Statistical analyses were performed using STATA 16.1 (StataCorp, College Station, TX, USA) and SPSS (IBM Corp. Armonk, NY, USA).

2.4. Standard protocol Approvals, Registrations, and patient consents

The study was approved by the local ethical committee (Ethics Committee approval number 556/2018/OSS/AOUMO–RF-2016-02361365) and was conducted according to the ethical principles for medical research involving human subjects in the Declaration of Helsinki.

2.5. Data availability

Upon request from qualified investigators, we will share anonymized data.

3. Results

705 patients with SE were included in the study; of those, 33 % (233/705) evolved to RSE. Baseline patient characteristics are reported in Table 1.

3.1. Progression to refractory status epilepticus

According to univariate logistic regression, in-hospital SE onset, ischemic heart disease as comorbid condition, acute symptomatic hypoxic etiology, impaired consciousness before treatment, and myoclonic SE were associated with increased risk of progression to RSE. Conversely, out-of-hospital SE onset, previous history of seizure/epilepsy, dementia as comorbid condition, remote symptomatic etiology, and retained consciousness before treatment were associated with lack of progression to RSE. According to multivariate logistic regression analysis performed with the stepwise method (Table 2), in-hospital SE onset, severe EEG patterns, acute symptomatic hypoxic and impaired consciousness before treatment were independent risk factor for the progression to RSE. Conversely, a remote symptomatic etiology was a protective variable for the progression to RSE.

Table 1
Characteristics of patients with or without progression to RSE.

Variable	Responsive SE	Progression to RSE	p-value
Patients, n (%)	472 (67.0)	233 (33.0)	
Age, years, median (IQR)	74 (61–82)	73 (63–81)	0.361
Gender, n (%)			0.122
Male	183 (38.8)	105 (45.1)	
Female	289 (61.2)	128 (54.9)	
SE onset, n (%)			**<0.001**
Out-of-hospital	309 (65.5)	86 (36.9)	
In-hospital	163 (34.5)	147 (63.1)	
Comorbidities, n (%)			
Ischemic heart disease	47 (10.0)	44 (18.9)	**0.001**
Cerebrovascular disease	69 (14.6)	41 (17.8)	0.322
Connective tissue disease	12 (2.5)	7 (3.0)	0.805
Diabetes mellitus	95 (20.1)	41 (17.6)	0.478
Heart Failure	32 (6.8)	14 (6.0)	0.748
Dementia	88 (18.6)	26 (11.2)	0.012
Ulcer	16 (3.4)	11 (4.7)	0.407
Hemiplegia	44 (9.3)	17 (7.3)	0.397
Tumour	46 (9.7)	25 (10.7)	0.691
Peripheral vascular disease	20 (4.2)	16 (6.9)	0.147
COPD	46 (9.7)	23 (9.9)	1.000
Liver failure	19 (4.0)	7 (3.0)	0.671
Chronic kidney disease	42 (8.9)	26 (11.2)	0.345
No prior history of epilepsy, n (%)	279 (59.1)	178 (76.4)	**<0.002**
Etiological classification, n (%)			
Acute symptomatic, hypoxic	8 (1.7)	70 (30.0)	**<0.001**
Acute symptomatic, non-hypoxic	261 (55.3)	108 (46.4)	**0.030**
Remote symptomatic	98 (20.8)	18 (7.7)	**<0.001**
Progressive symptomatic	83 (17.6)	29 (12.4)	0.081
Other	22 (4.7)	8 (3.4)	0.554
Impaired consciousness before treatment, n (%)	82 (17.4)	166 (71.2)	**<0.001**
SE semiology, n (%)			
Generalized convulsive	79 (16.7)	40 (17.2)	0.915
Focal motor	131 (27.8)	53 (22.7)	0.172
Non convulsive	255 (54.0)	117 (50.2)	0.378
Myoclonic	7 (1.5)	23 (9.9)	**<0.001**
Severe EEG pattern,[1] n (%)	151 (30.0)	117 (57.9)	**<0.001**

Legend:
COPD: Chronic Obstructive Pulmonary Disease; IQR: interquartile range; RSE: refractory status epilepticus; SE: status epilepticus.

[1] Defined as lateralized periodic discharges; generalized periodic discharges, and spontaneous burst suppression: when present in the first EEG recording that qualified the episode as SE, according to the ACNS terminology.

Table 2
Variables independently associated with risk of progression to RSE.

Variable	OR	95 % CI	p-value
Increased risk			
Impaired consciousness before treatment	7.054	4.628–10.752	<0.0001
Acute symptomatic, hypoxic etiology	4.645	2.060–10.474	<0.0001
Severe EEG pattern[1]	2.407	1.611–3.595	<0.0001
In-hospital SE onset	1.496	0.998–2.242	0.051
Reduced risk			
Remote symptomatic etiology	0.482	0.262–0.886	0.019

[1] Defined as lateralized periodic discharges; generalized periodic discharges, and spontaneous burst suppression: when present in the first EEG recording that qualified the episode as SE, according to the ACNS terminology.

Through the decision-tree analysis (CART method), a graph was obtained to evaluate the risk of evolution to RSE based on the basal characteristics of the patients (Fig. 1). The following variables segmented the data according to the risk of progression to RSE: impaired consciousness before treatment, acute symptomatic hypoxic etiology, severe EEG patterns, non-convulsive SE, in-hospital SE onset, and remote symptomatic etiology. The most important predictive variable (root node) was impaired consciousness before treatment, followed by acute symptomatic hypoxic etiology and a severe EEG pattern. The decision tree identified 14 nodes with a risk of evolution to RSE ranging from 1.5 % (node 14) to 90.8 % (node 4)(see Fig. 1). The following node identified patients with the highest risk of evolution to RSE (90.8 %): impaired consciousness before treatment and acute symptomatic hypoxic etiology. Conversely, the following group of characteristics identified patients with the lowest risk of evolution to RSE (1.5 %): retained consciousness before treatment and lack of a severe EEG pattern and out-of-hospital SE onset and remote symptomatic etiology.

The overall predictive accuracy (or percentage of success in classifying patients) of the decision tree was 79.4 %; the percentage of accurate prediction was high, 94.1 %, for those patients not progressing to RSE and moderate, 49.8 %, for patients evolving to RSE.

3.2. Short-term mortality

Globally, 28.7 % (202/705) of all patients died within one month of onset of SE status. The characteristics of the survivors and non-survivors are reported in **Supplementary Table 1**.

Compared to survivors, patients who died were older, had more frequent in-hospital SE onset and specific comorbidity (ischemic heart disease, cerebrovascular disease, dementia, ulcer, tumor, peripheral vascular disease, chronic obstructive pulmonary disease [COPD], liver failure, and chronic kidney disease), acute symptomatic hypoxic etiology, impaired consciousness before treatment, non-convulsive or myoclonic SE, and severe EEG patterns. Conversely, survivors had more frequently remote symptomatic or progressive symptomatic etiology, and generalized convulsive SE.

The progression to RSE was an independent risk factor for 30-day mortality, with an OR adjusted for previously identified possible univariate confounders of 4.086 (CI 95 % 2.390–6.985; $p < 0.001$). Survival analysis according to the Kaplan-Meier method also demonstrated that patients who evolved to RSE have a higher risk of death at 30 days and a lower survival (Log Rank Test $p < 0.001$ (Fig. 2). Among patients with a progression to RSE ($n = 233$), those who died at 30 days were 51.1 % (119/233). The characteristics of patients with progression to RSE who died or survived at 30 days after SE onset are reported in Table 3.

Compared to survivors, patients with progression to RSE who died at 30 days were older, had more frequently specific comorbidity (ischemic heart disease, dementia, ulcer, peripheral vascular disease, COPD, liver failure, and chronic kidney disease), had a higher prevalence of acute symptomatic hypoxic etiology, and severe EEG patterns. According to

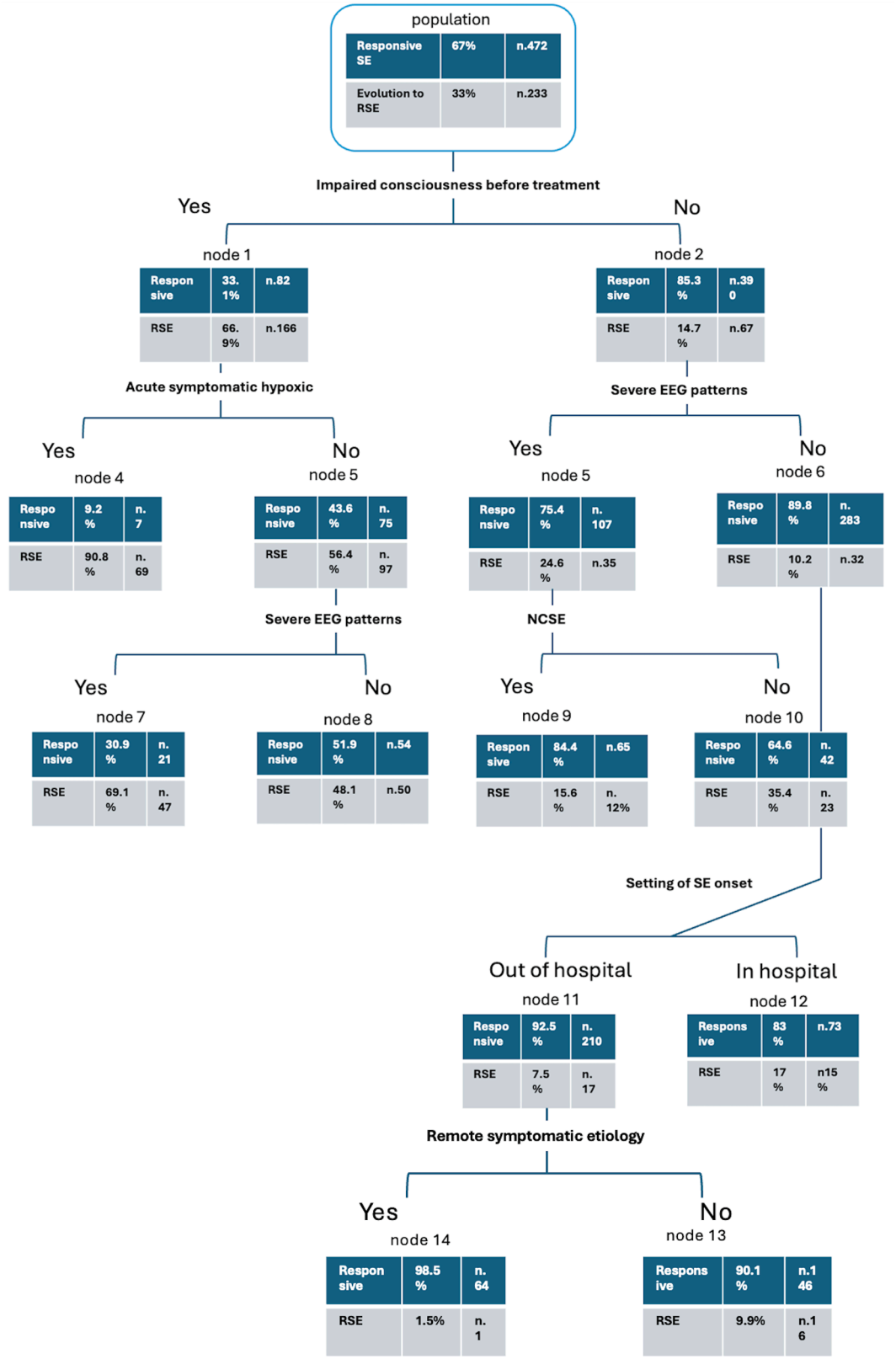

Fig. 1. Decision-tree analysis showing the risk of evolution to RSE based on the basal characteristics of the patients.

multivariate logistic regression analysis, age, COPD or chronic kidney disease as comorbidities, acute symptomatic hypoxic etiology and severe EEG patterns were independent risk factor for 30-day mortality among patients with progression to RSE (Table 4).

4. Discussion

Our study identified predictors of evolution to RSE, and their related risk of 30-day mortality.

We found that impaired consciousness before treatment was the most

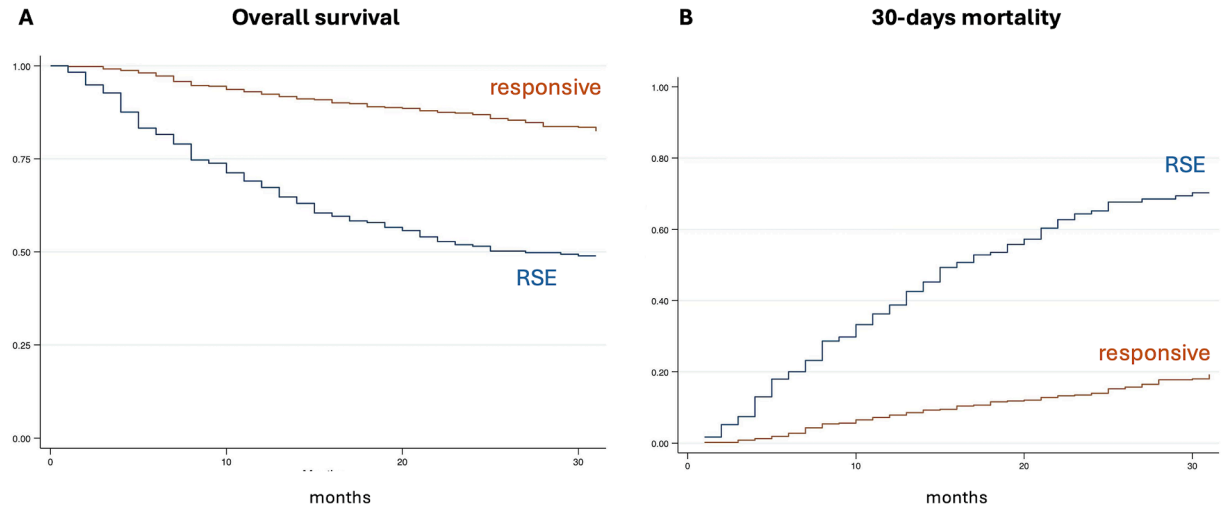

Fig. 2. A. Kaplan-Meier analysis on survival; **B.** Kaplan-Meier analysis on risk of 30-day mortality. blue: patients with Refractory SE. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Characteristics of patients with progression to RSE who survived or died at 30 days after SE onset.

Variable	Survivors	Non-survivors	p-value
Patients, n (%)	114 (48.9)	119 (51.1)	
Age, years, median (IQR)	66 (54–75)	78 (69–86)	**<0.001**
Gender, n (%)			0.694
Male	53 (46.5)	52 (43.7)	
Female	61 (53.5)	67 (56.3)	
SE onset, n (%)			0.684
Out-of-hospital	44 (38.6)	42 (35.3)	
In-hospital	70 (61.4)	77 (64.7)	
Comorbidities, n (%)			
Ischemic heart disease	14 (12.3)	30 (25.2)	**0.012**
Cerebrovascular disease	16 (14)	25 (21)	0.173
Connective tissue disease	2 (1.8)	5 (4.2)	0.447
Diabetes mellitus	19 (16.7)	22 (18.5)	0.734
Heart Failure	5 (4.4)	9 (7.6)	0.411
Dementia	7 (6.1)	19 (16)	**0.021**
Ulcer	1 (0.9)	10 (8.4)	**0.010**
Hemiplegia	7 (7.9)	10 (8.4)	0.617
Tumour	9 (8.0)	16 (13.4)	0.206
Peripheral vascular disease	3 (2.6)	13 (10.9)	**<0.001**
COPD	6 (5.3)	17 (14.3)	**0.027**
Liver failure	0 (0.0)	7 (5.9)	0.060
Chronic kidney disease	6 (5.3)	20 (16.8)	**0.006**
No prior history of epilepsy, n (%)	85 (74.6)	93 (78.2)	0.540
Etiological classification, n (%)			
Acute symptomatic, hypoxic	25 (21.9)	45 (37.8)	**0.010**
Acute symptomatic, non-hypoxic	52 (45.6)	56 (47.1)	0.869
Remote symptomatic	12 (10.5)	6 (5)	0.144
Progressive symptomatic	18 (15.8)	11 (9.2)	0.165
Other	7 (6.1)	1 (0.8)	0.033
Impaired consciousness before treatment, n (%)	80 (70.2)	86 (72.3)	0.773
SE semiology, n (%)			
Generalized convulsive	25 (21.9)	15 (12.6)	0.081
Focal motor	30 (26.3)	23 (19.3)	0.215
Non convulsive	51 (44.7)	66 (55.5)	0.116
Myoclonic	8 (7)	15 (12.6)	0.189
Severe EEG pattern, [1]n (%)	54 (47.4)	81 (68.1)	**0.002**

Legend:
COPD: Chronic Obstructive Pulmonary Disease; IQR: interquartile range; RSE: refractory status epilepticus; SE: status epilepticus.

[1] Defined as lateralized periodic discharges; generalized periodic discharges, and spontaneous burst suppression: when present in the first EEG recording that qualified the episode as SE, according to the ACNS terminology.

Table 4
Variables independently associated with 30-day mortality among patients with progression to RSE.

Variable	OR	95 % CI	p-value
Age	1.088	1.057–1.120	<0.0001
COPD	3.350	1.043–10.764	0.042
Chronic kidney disease	3.074	1.001–9.440	0.05
Acute symptomatic hypoxic etiology	2.228	1.098–4.521	0.026
Severe EEG pattern[1]	1.960	1.020–3.765	0.043

[1] Defined as lateralized periodic discharges; generalized periodic discharges, and spontaneous burst suppression: when present in the first EEG recording that qualified the episode as SE, according to the ACNS terminology.

important predictor of progression to RSE. This could reflect a higher intrinsic severity of SE at baseline, also due to its association with acute symptomatic hypoxic etiology [18–20]. Actually, these two variables alone were associated with the highest risk of progression to RSE (90.8 %). Furthermore, impaired consciousness at baseline could already indicate an evolution from a prior convulsive SE, evolved over time to non-convulsive SE with electro-mechanical dissociation due to metabolic or electric exhaustion [21], a condition associated with high case fatality [2]. The presence of some EEG patterns (i.e. LPD; GPD) was also associated with evolution to RSE, indicating that EEG can provide useful information to further modulate the individualized risk of progression to RSE.

Our findings underscore that refractoriness to treatment is multifactorial and confirms previous studies. Across the studies, demographic, clinical, EEG, and biochemical variables have been associated with refractoriness or super-refractoriness of SE. They include, but are not limited to age, acute aetiology, altered level of consciousness at SE onset, non-convulsive SE, higher modified Ranking Scale score at baseline, periodic lateralized epileptiform discharges, low levels of serum albumin at SE onset [22–29].

Here, we developed a data driven classification and regression tree analysis to develop a predictive model that can be used in clinical practice for stratification of RSE at bedside in a single patient. Decision-tree analysis provided a meaningful risk stratification based on few variables that are easily obtained at SE first evaluation. To note, all the identified predictors of SE progression and its related mortality were non-modifiable or only partly modifiable (comorbidities). So far, although comorbid conditions were shown to be associated with increased risk of mortality, it is unclear whether their aggressive management could positively affect the outcome, as well as the risk of SE

progression over time. Furthermore, it is still debated whether a strict adherence to treatment guidelines could really counteract the negative prognostic role played by the individual biological background [30], and particularly by specific etiologies associated with high mortality and risk of SE progression [18–20].

As expected, the evolution to RSE was an independent risk factor for 30-day mortality. This could reflect the longer duration of SE but also the higher intrinsic severity of SE, associated with and influenced by an older age, specific comorbidities (COPD or chronic kidney disease), higher prevalence of acute symptomatic etiologies, and severe EEG patterns. Among etiologies, acute symptomatic hypoxic-SE was particularly associated with short-term mortality. However, the risk of poor outcome was deeply influenced by age. Older age was associated with increased 30-day mortality among RSE patients. The association between older age and increased mortality has been widely reported [31–34], and was incorporated in clinical scores to predict in-hospital mortality [15,35]; in itself it could reflect more severe comorbid conditions or etiologies.

4.1. Study limitations

This study has several limitations. It was conducted in only one tertiary care center, and this could limit the generalizability of the findings. Our model needs to be replicated in independent cohorts. Although we followed a protocol relying on the current guidelines to reduce the methodological heterogeneity, we did not assess the role of treatments (and their dosage) in the selected outcomes. Furthermore, we did not have details on specific EEG patterns to evaluate their prognostic role in SE progression or mortality. Finally, especially for older cases (before 2015) included in the study, it is possible that some etiologies of RSE (particularly inflammatory autoimmune causes) went unrecognized, leading to an overrepresentation of unknown causes of SE. Giving these limitations our CART model must be viewed as an exploratory potential new method for the stratification RSE at single subject level.

5. Conclusion

Decision-tree analysis provided a meaningful risk stratification based on few variables that are easily obtained at SE first evaluation. Further studies are required to evaluate the role of specific EEG patterns, specific SE etiologies, or semeiology, and of different pharmacological treatments on risk of progression to RSE in order to obtain a more granular stratification of patients [36–39].

Disclosures.

Stefano Meletti received research grant support from the Ministry of Health (MOH); has received personal compensation as scientific advisory board member for UCB pharma, Jazz pharmaceuticals, and Eisai. Has received speaker's or consultancy fees from Eisai, GW Pharmaceuticals, and UCB Pharma.

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Simona Lattanzi has received speaker's or consultancy fees from Eisai, GW Pharmaceuticals, and UCB Pharma and has served on advisory boards for Angelini Pharma, Arvelle Therapeutics, BIAL, and GW Pharmaceuticals.

Arian Zaboli reports no disclosures.

Niccolò Orlandi reports no disclosures.

Francesco Brigo reports no disclosures.

CRediT authorship contribution statement

Stefano Meletti: Conceptualization, Investigation, Supervision, Validation, Writing – review & editing. **Giada Giovannini:** Data curation, Investigation, Resources, Writing – review & editing. **Simona Lattanzi:** Supervision, Visualization, Writing – review & editing. **Arian Zaboli:** Conceptualization, Formal analysis, Methodology, Software, Writing – review & editing. **Niccolò Orlandi:** Data curation, Investigation, Writing – review & editing. **Gianni Turcato:** Conceptualization, Formal analysis, Methodology, Writing – original draft. **Francesco Brigo:** Conceptualization, Formal analysis, Methodology, Writing – original draft.

Declaration of competing interest

The authors 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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.110005.

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