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RESEARCH ARTICLE

Prognostic factors and impact of management strategies for status epilepticus: The STEPPER study in the Emilia-Romagna region, Italy

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Abstract

Objective: The STEPPER (Status Epilepticus in Emilia-Romagna) study aimed to investigate the clinical characteristics, prognostic factors, and treatment approaches of status epilepticus (SE) in adults of the Emilia-Romagna region (ERR), Northern Italy.

Methods: STEPPER, an observational, prospective, multicentric cohort study, was conducted across neurology units, emergency departments, and intensive care units of the ERR over 24 months (October 2019–October 2021), encompassing incident cases of SE. Patients were followed up for 30 days.

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Results: A total of 578 cases were recruited (56% female, mean age = 70 years, 32% with previous diagnosis of epilepsy, 43% with in-hospital onset, 35% stuporous/comatose, 46% with nonconvulsive SE). Etiology was known in 87% (acute 43%, remote 24%, progressive 17%, definite epileptic syndrome 3%). The mean pre-SE Rankin Scale score was 2, the Status Epilepticus Severity Score was ≥4 in 33%, the Epidemiology-Based Mortality Score in Status Epilepticus score was ≥64 in 61%, and 34% were refractory. The sequence of treatments followed current clinical practice guidelines in 63%. Benzodiazepines (BDZs) were underused as first-line therapy (71%), especially in in-hospital onset cases; 15% were treated with continuous intravenous anesthetic drugs. Mortality was 24%; 63% of survivors had functional worsening. At the two-step multivariable analysis, incorrect versus correct treatment sequence with correct BDZ dose was the strongest predictor of failure to resolve SE in the in-hospital group (odds ratio [OR] = 4.42, 95% confidence interval [CI] = 1.86–10.5), with a similar trend in the out-of-hospital group (OR = 2.22, 95% CI = .98–5.02). In turn, failure to resolve was the strongest predictor of 30-day mortality (OR = 11.3, 95% CI = 4.16–30.9, out-of-hospital SE; OR = 6.42, 95% CI = 2.79–14.8, in-hospital SE) and functional worsening (OR = 5.83, 95% CI = 2.05–16.6, out-of-hospital SE; OR = 9.30, 95% CI 2.22–32.3, in-hospital SE).

Significance: The STEPPER study offers insights into real-world SE management, highlighting its significant morbidity and functional decline implications. Although nonmodifiable clinical factors contribute to SE severity, modifiable factors such as optimized first-line therapies and adherence to guidelines can potentially influence prognosis.

KEYWORDS

antiseizure medications, cohort studies, EEG, natural history studies, status epilepticus

1 | INTRODUCTION

Status epilepticus (SE) is a neurological emergency characterized by prolonged seizure activity, with a significant risk of morbidity and mortality, that has not significantly decreased in the past decades.[1] Although the urgency of prompt recognition and treatment is well established, SE is a complex condition with various clinical presentations and underlying causes. Of these, convulsive SE (CSE) represents the most severe presentation and demands immediate intervention to reduce adverse outcomes. Nevertheless, the diverse etiologies, symptomatology, duration, and context of SE contribute to a wide range of prognoses, making tailored and swift management essential for positive patient outcomes.[2–8]

Historically, the definition of SE has evolved, with progressive shortening of timelines to emphasize the importance of early intervention. Although evidence supports the efficacy of treatments during the earlier stages,[9] refractory SE (RSE) and superrefractory SE remain areas with limited available evidence, presenting challenges for clinicians seeking to optimize patient care.

Key points

- SE is confirmed as a condition with high mortality and morbidity, with a 30-day mortality rate of 24% in our study population.
- The in-hospital SE onset subgroup showed a poorer prognosis in terms of mortality compared to the out-of-hospital population.
- In our population, incorrect treatment sequence is the major prognostic factor for failure to resolve SE, which in turn has the greatest impact on mortality.
- Modifiable factors such as optimized first-line treatments and adherence to guidelines can potentially impact the prognosis of SE.

Current treatment algorithms propose a three-stage approach, with benzodiazepines (BDZs) as first-line agents, intravenous antiseizure medications (ASMs) as a second line, and continuous intravenous anesthetic drugs (CIVADs) as a third line. However, approximately 30% of cases progress to RSE,[10] requiring the infusion of anesthetic agents in an intensive care setting to terminate seizures.

Despite guidelines in place, there is evidence of underdosing of BDZs and lack of adherence to treatment escalation protocols, highlighting the importance of further research and improvement in clinical practice.[11,12] Moreover, most current guidelines focus on CSE treatment, whereas indications on other forms of SE constitute a "gray area" where the risk–benefit ratio of each action is challenging to assess.

Over the past two decades, epidemiological and prognostic investigations focused on SE have been conducted in the northern Italian region of Emilia-Romagna.[13–20] Throughout this timeframe, the 30-day case fatality rates largely varied between a minimum of 5% and a maximum of 50%.[13–15,17,20] Such differences may be, at least in part, related to different treatment approaches as suggested by a study conducted in this region.[8]

Furthermore, evidence suggests that the patient location at SE onset is a significant prognostic predictor,[6–8] with higher mortality in in-hospital (IH) de novo SE, presumably due to a different selection of other prognostic factors,[7] but possibly also to different treatment approaches.

The STEPPER (Status Epilepticus in Emilia-Romagna) study was conducted in the Emilia-Romagna region (ERR) over 2 years to shed light on this critical medical condition. The study aimed to comprehensively investigate the clinical characteristics and management strategies of SE, with a specific focus on administered therapies, adherence to guidelines, and prognostic factors, according to patient's location at SE onset (out-of-hospital [OH] and IH).

2 | MATERIALS AND METHODS

The STEPPER study is an observational, prospective, and multicentric cohort study. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed.[21]

2.1 | Standard protocol approvals, registrations, and patient consent

The study was approved by the ethics committee of the Area Vasta Emilia Centro of the ERR (CE-AVEC: 18036). Written informed consent was obtained from all the patients/guardians of participants in the study. In the absence of a legally authorized representative, the ethics committee granted a waiver for consent if the patient's clinical condition did not allow him/her to provide it.

2.2 | Setting and study population

The study was conducted in all neurology units, emergency departments, and intensive care units (ICUs) serving the adult population of the ERR (3 741 002 residents). The study included incident cases of SE in adult patients over 24 months (October 2019–October 2021). The study adopted the definitions and classification provided by the International League Against Epilepsy.[9]

2.3 | Procedures

A designated neurologist acted as the reference neurologist for each neurology unit, responsible for proactive surveillance of the eligible patients in neurological wards, neurological consultations, electroencephalographic (EEG) recording, and interaction with the related emergency departments and ICUs. Data collection was facilitated through a dedicated website and a centralized electronic database (electronic clinical record form [eCRF]) accessed with personal usernames and passwords. Each eCRF was identified with a unique number corresponding to an individual patient, allowing for anonymous data treatment.

The enrolled patients underwent a follow-up assessment 30 days after SE onset.

2.4 | Variables

The collected clinical data included demographic characteristics (age, gender, residence, ethnicity, weight, height); date of admission to the observation unit; SE onset date and time; history of seizures, other SE episodes, or epilepsy prior to SE; where applicable, ongoing ASM therapy, its dosage (pre-SE), and withdrawal date and time; OH/IH onset; ongoing neuroprotection pre-SE; modified Rankin Scale (mRS) score pre-SE; SE etiology and classification; prognostic scores (Epidemiology-Based Mortality Score in Status Epilepticus [EMSE], Status Epilepticus Severity Score [STESS]); diagnostic procedures at onset (date and time of the first neurological consultation and the first EEG; time of any lumbar puncture, acute brain computed tomography [CT] scan, perfusion CT scan, brain

magnetic resonance imaging, or other neuroimaging; body temperature; blood tests); pharmacological treatment of SE (type of medication; loading dose; date, time, and route of administration); IH complications; and date and destination of discharge.

Among all the pharmacological treatments administered to the patients, only the BDZs and ASMs administered with a loading dose and the anesthetics that after the loading dose were subsequently provided in continuous infusion were considered as the acute drug treatment of SE.

We assessed the appropriateness of drug treatment and its adherence to clinical practice guidelines (CPG)[22] by focusing on three aspects:

1. Order of administration. We considered as according to CPG only the administration of BDZs as the first line, ASMs as the second line, and CIVADs as the third line. Oral administration was considered appropriate only for drugs that cannot be administered intravenously (for example, perampanel). A maximum of two doses of the same or two different BDZs was considered appropriate. For CSE, we considered correct a maximum of two attempts with intravenous ASMs. For the other types of SE, more than two attempts with ASMs were considered appropriate if the proper sequence of administration was respected; escalation to CIVADs was not considered mandatory for the appropriateness of the treatment.
2. Dosing. This analysis was limited to BDZs, because the patient's weight was often missing; therefore, we were not able to determine whether ASM and CIVAD doses were appropriate in most patients. Because only adult patients were included, we considered that most of them weighed >32 kg; therefore, doses of at least 10 mg of midazolam and diazepam and 4 mg of lorazepam were considered correct.[12,23–25]
3. Route of administration. We considered appropriate the intravenous administration of BDZs, ASMs, and anesthetics and the intramuscular or buccal administration of midazolam when used as first-line treatment as well as rectal administration of diazepam.

Based on these assumptions, we classified the possible therapeutic combinations administered to patients into six patterns: correct sequence with correct BDZs dose; correct sequence with underdosed BDZs; correct sequence without CIVADs; incorrect sequence without CIVADs; correct sequence with CIVADs; and incorrect sequence with CIVADs.

The following outcomes were evaluated during the follow-up period: SE resolution at discharge; "functional worsening," defined as an increase of at least 1 point on the mRS scale at the last follow-up compared with the pre-SE mRS score; and 30-day mortality.[26]

2.5 | Statistical plan and analysis

In the descriptive analysis, the cohort's characteristics were presented as mean and SD or median and interquartile range (IQR) for continuous variables and as absolute (n) and relative (%) frequency for categorical variables.

All the subsequent analyses were stratified for IH and OH SE onset. We decided to consider IH and OH onset SE separately because previous studies have shown that the prognosis of IH onset SE is worse, as it is associated with nonmodifiable variables such as age and comorbidities.[6–8] Moreover, the care pathways and professionals the patients encounter could be different between the two settings.

Then, we conceptualized prognostic factors according to the following categories (Figure 1): pre-onset factors (sex, age, mRS score pre-SE, comorbidities assessed by the comorbidity subsection of the EMSE, ASMs), onset factors (SE etiology and classification, state of consciousness, EEG), and first-level (general management, appropriateness of pharmacological treatment) and second-level (failure to resolve) dynamic factors.

The chi-squared and Kruskal–Wallis tests were used to evaluate the univariable association between outcomes (SE resolution, functional worsening, and 30-day mortality) and categorical or continuous variables, respectively. Three different multilevel mixed-effect logistic regression models were implemented to describe the prognosis after SE corresponding to the three outcomes. The center of recruitment was considered a cluster variable in all multivariable regressions. In the first stratified model, we evaluated the association between SE failure to resolve (dependent variable) and the baseline factors (sex, EMSE comorbidity), the SE factors (SE etiology and classification, state of consciousness), and the first-level dynamic factor (appropriateness of drug treatment). In the second and third stratified models, we evaluated the association between 30-day mortality and functional worsening (dependent variables) and the baseline factors (age, mRS pre-SE, EMSE comorbidity), the SE factors (SE etiology and classification, state of consciousness), and the second-level dynamic factor (SE failure to resolve). The results are presented as odds ratio (OR) and the relative 95% confidence interval (CI).

Statistical analysis was conducted using Stata 14.2.

3 | RESULTS

We recruited 610 patients, of whom 32 postanoxic SE cases were excluded from the analysis because of the well-known poor prognosis of this condition; therefore, the whole cohort

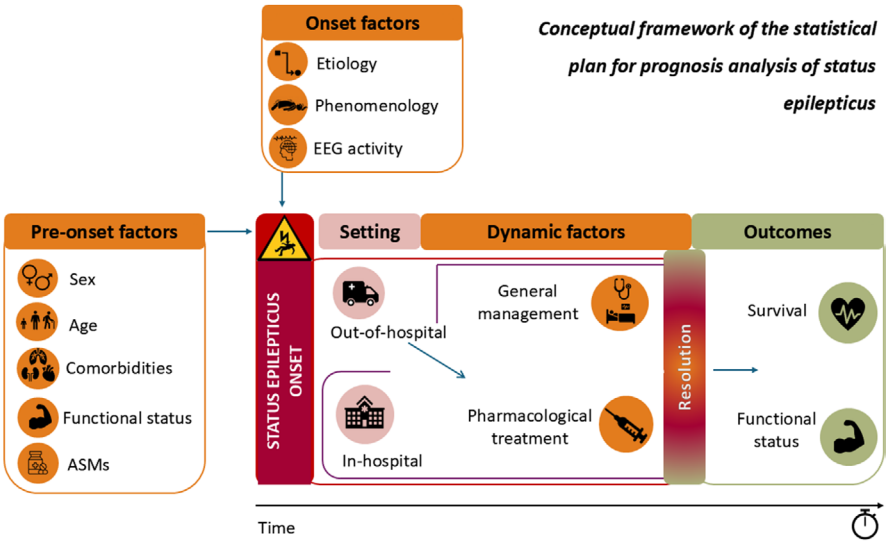

FIGURE 1 Conceptual framework of the statistical plan for prognosis analysis of status epilepticus (SE). Prognostic factors are categorized as pre-onset factors (sex, age, comorbidities assessed by the comorbidity subsection of the Epidemiology-Based Mortality Score in Status Epilepticus scale, modified Rankin Scale score pre-SE [functional status], antiseizure medications [ASMs]), onset factors (SE etiology, SE classification [phenomenology], electroencephalographic [EEG] activity), first-level dynamic factors (general management, pharmacological treatment), and second-level dynamic factors (resolution). Prognostic outcomes are failure to resolve (intermediate outcome), functional worsening (according to modified Rankin Scale score), and survival at 30 days.

includes 578 patients. Table 1 summarizes the demographic and clinical characteristics of the entire cohort and the two main subpopulations, the IH and the OH onset subgroups.

3.1 | Demographic data

Of the 578 patients, 322 (56%) were females, the mean age was 70 years, the median pre-SE mRS was 2 (IQR = 0–4), and 32.4% had a previous diagnosis of epilepsy.

3.2 | Phenomenology, etiology, STESS, and EMSE

Approximately one third (35%) of the patients had a level of consciousness that qualified as stuporous or comatose. SE with prominent motor symptoms accounted for 54% of cases (15% CSE). Nonconvulsive SE (NCSE) cases comprised 46%: 14% with coma and 32% without coma. Forty-three percent of the patients had IH onset.

Among the 501 patients with a known etiology, this was acute in 43%, progressive in 17%, and remote in 24%; only 3% of patients presented with SE in a definite epilepsy syndrome. Among the acute causes, cerebrovascular (38%) was the most frequent one, followed by sepsis/fever (23%), metabolic (10%), and central nervous system infection (encephalitis/meningitis, 10%). In 6% of the patients, the supposed etiology was the discontinuation of ASMs/BDZs, and in 2.5% it was toxic substances intake. An autoimmune etiology was present in 2.5% of the cases. Within the progressive etiologies, brain tumors accounted for 79% of the cases and dementia for 14%. Prior stroke accounted for 61% of the remote etiologies, followed by post-traumatic (12%).

STESS score was 4–6 in 33% of patients, whereas 61% had an EMSE score > 64.

The IH and OH subgroups significantly differed in the following variables: age, mRS pre-SE, STESS, consciousness EMSE, SE semiology, SE etiology, and previous diagnosis of epilepsy (see Table 1).

3.3 | Diagnostic procedures

EEG, brain CT scan and blood tests at onset were performed in most patients (93%, 89%, and 84%, respectively). A perfusion CT scan was performed in 9% of the population (52/578) and 13% of the NCSE cases, after a median of 3 h (range = .58–6.8) from onset.

For the 147 patients for whom the timing (time to SE onset) could be calculated, the first EEG was obtained after a median of 6 h after onset (3.25 h in NCSE).

3.4 | Therapy

The patients received a median of three treatments (range = 1–13); 20% received one treatment, 35% two treatments, and 43% three or more.

TABLE 1 Baseline characteristics between the two groups: in-hospital and out-of-hospital onset.

Characteristic	Total cohort, *N* = 578	Out-of-hospital onset, *n* = 329	In-hospital onset, *n* = 249	*p*
Sex—female, *n* (%)	322 (55.7)	172 (52.3)	150 (60.2)	.056
Age, years, mean (SD)	70.4 (16.6)	68.8 (17.4)	72.6 (15.2)	.019
Center, *n* (%)				.016
Bologna	148 (25.6)	73 (22.2)	75 (30.1)	
Modena	170 (29.4)	102 (31.0)	68 (27.3)	
Reggio Emilia	17 (2.9)	13 (4.0)	4 (1.6)	
Parma	67 (11.6)	39 (11.9)	28 (11.2)	
Ferrara	54 (9.3)	23 (7.0)	31 (12.5)	
Piacenza	27 (4.7)	15 (4.6)	12 (4.8)	
Romagna	95 (16.4)	64 (19.5)	31 (12.5)	
mRS pre-SE, median (IQR)	2 (0–4)	2 (0–3)	3 (1–4)	.012
mRS post-SE, median (IQR)	3 (1–5)	3 (1–4)	4 (3–5)	<.001
STESS score ≥4, *n* (%)	187 (33.3)	79 (24.9)	108 (44.3)	<.001
	17 missing	12 missing	5 missing	
Consciousness, *n* (%)				<.001
Alert/somnolent	360 (65.0)	231 (73.6)	129 (53.8)	
Stuporous/comatose	194 (35.0)	83 (26.4)	111 (46.2)	
	24 missing	15 missing	9 missing	
EMSE total score ≥64, *n* (%)	332 (61.1)	161 (53.0)	171 (71.6)	<.001
	35 missing	25 missing	10 missing	
EMSE comorbidity score ≥60, *n* (%)	50 (8.7)	29 (8.8)	21 (8.4)	.872
SE classification, *n* (%)				<.001
Prominent motor symptoms—other	225 (38.9)	114 (34.7)	111 (44.6)	
Prominent motor symptoms—convulsive	86 (14.9)	58 (17.6)	28 (11.2)	
Nonconvulsive with coma	79 (13.7)	26 (7.9)	53 (21.3)	
Nonconvulsive without coma	188 (32.5)	131 (39.8)	57 (22.9)	
Etiology, *n* (%)				<.001
Acute	248 (42.9)	90 (27.4)	158 (63.5)	
Progressive	100 (17.3)	74 (22.5)	26 (10.4)	
Remote	136 (23.5)	97 (29.5)	39 (15.7)	
SE in defined epileptic syndrome	17 (3.0)	14 (4.2)	3 (1.2)	
Unknown	77 (13.3)	54 (16.4)	23 (9.2)	
Intensive care unit admission—yes, *n* (%)	114 (22.3)	48 (17.3)	66 (28.2)	.003
	66 missing	51 missing	15 missing	
Refractoriness—yes, *n* (%)	201 (34.8)	90 (27.4)	111 (44.6)	<.001
Use of third-line treatment [denominator is refractoriness—yes], *n* (%)	91 (46.4)	34 (39.1)	57 (52.3)	.065
Reason for not using third-line treatment, *n* (%)				.020
"Benign" SE	28 (27.5)	20 (38.5)	8 (16.0)	
Severe clinical conditions	66 (64.7)	27 (51.9)	39 (78.0)	
Other	8 (7.8)	5 (9.6)	3 (6.0)	
Epilepsy—yes, *n* (%)	187 (32.4)	131 (39.8)	56 (22.6)	<.001

TABLE 1 (Continued)

Characteristic	Total cohort, $N = 578$	Out-of-hospital onset, $n = 329$	In-hospital onset, $n = 249$	p
Failure to resolve SE, *n* (%)	95 (16.4)	44 (13.4)	51 (20.5)	.022
Mortality 30 days after SE, *n* (%)	140 (24.4)	51 (15.6)	89 (35.9)	<.001
	3 missing	2 missing	1 missing	
Functional worsening [1-point worsening on mRS], *n* (%)	355 (63.4)	166 (52.5)	189 (77.5)	<.001
	18 missing	13 missing	5 missing	

Abbreviations: EMSE, Epidemiology-Based Mortality Score in Status Epilepticus; IQR, interquartile range; mRS, modified Rankin Scale; SE, status epilepticus; STESS, Status Epilepticus Severity Score.

Only 27% of cases (156 patients) reported the exact time of SE onset and of the first treatment administration; among these patients, the median interval between onset and first treatment was 1.05 h (IQR = .25–2.8).

Table 2 summarizes the characteristics of SE treatments in terms of frequency and combinations.

Considering all the medications that were administered to the patients, the class of medications most often used were ASMs (54%), followed by BDZs (37%) and CIVADs (9%; Table 2).

The most frequently administered BDZ was diazepam (51%). Levetiracetam was the most used ASM (35%), followed by lacosamide (28%) and valproate (19%). Among CIVADs, propofol was used in 57%, midazolam in 25%, ketamine in 14%, and thiopentone in 4% of the patients who received a third-line therapy.

3.5 | First-line treatment

The first drug administered to treat SE was a BDZ in 71% of cases, of which 74% were at the correct dose (Table 2). The propensity to employ BDZs as the first treatment and use them at the correct dosage varied according to the prescriber and the assistance setting. When emergency medical services (EMS) administered the first treatment, it consisted of a BDZ in 95% of cases, but in only 51% of cases the dose was correct. Neurologists prescribed BDZs first in 64% of cases, of which 79% were correctly dosed. The emergency doctors used BDZs first in 98% of cases, and in 81% of them, they were at a correct dose. Moreover, IH onset cases were treated first with a BDZ less often than patients with OH onset (60% vs. 80%, respectively).

ASMs are the most common second pharmacological attempt (70%), but almost one quarter of patients received a BDZ (22%) and a minority a CIVAD (7.4%). At each further attempt until the sixth, the use of ASMs, BDZs, and anesthetics varied between 71%–60%, 18%–7%, and 9.5%–30% of cases, respectively. We subsequently divided the study population into four subgroups according to semiology: CSE, SE with prominent motor symptoms non-CSE, NCSE in coma, and NCSE without coma. The four groups did not differ substantially regarding drug class used at each pharmacological attempt (see Figure 2).

3.6 | Combinations of treatments

The correct sequence of treatments was administered in 63% of cases, of which 74% received the correct dose of BDZ (Table 2). Patients treated with CIVADs comprised 15.5% (88 patients); in 65% of these cases (57 patients), an incorrect treatment sequence was used. SE was considered RSE in 34% of cases, of which only 45% received CIVADs. The reason anesthetics were not used was explicitly asked; considering the benefits and risks associated with the use of CIVADs and orotracheal intubation, the referring physician chose a less aggressive strategy in most cases (60%) because the SE was considered a "benign condition," but in 30% of cases because the patient's condition was considered "too severe".

3.7 | Outcomes at follow-up

SE eventually resolved in 84% of cases after a median interval from onset of 2.8 h (the onset and resolution times were specifically reported in only 22% of cases).

Mortality at 30-day follow-up was 24% in the whole population, 37% in the subgroup of NCSE with coma, and 38% in RSE. Among the survivors, 63% had a functional worsening at follow-up, with a median post-SE mRS of 3.

Figure 3 and Table 1 show the proportion of patients for each outcome in each of the two subpopulations. IH onset patients had a worse prognosis, as 30-day mortality, failure to resolve, and functional deterioration were significantly higher compared to the OH group. However,

TABLE 2 Status epilepticus drug treatment in the STEPPER cohort with details according to type of drugs, benzodiazepine use, and correct or incorrect sequence.

Type of drug	Specific treatment/all treatments, *n* (%)
Benzodiazepine	643/1728 (37)
Diazepam	328/643 (51)
Lorazepam	206/643 (32)
Midazolam	109/643 (17)
Antiseizure medication	931/1728 (54)
Levetiracetam	324/931 (35)
Lacosamide	258/931 (28)
Valproate	173/931 (19)
Phenytoin	119/931 (13)
Perampanel	26/931 (3)
Anesthetics	154/1728 (9)
Propofol	88/154 (57)
Midazolam	38/154 (25)
Ketamine	22/154 (14)
Thiopental	6/154 (4)

Benzodiazepine use	Patients treated with BDZ/patients treated, *n* (%)[a]	Patients correctly treated with BDZ/patients treated with BDZ, *n* (%)
All cohort	404/567 (71)	298/404 (74)
By administrator		
Emergency medical services (ambulance)	69/73 (95)	35/69 (51)
Neurologist	257/401 (64)	204/257 (79)
Emergency department doctor	43/44 (98)	35/43 (81)
Anesthesiologist	2/12 (17)	2/2 (100)
Other	35/37 (95)	11/35 (31)
By setting		
In-hospital onset	148/247 (60)	111/148 (75)
Out-of-hospital onset	256/320 (80)	187/286 (73)

Drug treatment sequence	Patients with correct sequence/patients treated, *n* (%)[a]	Patients with incorrect sequence/patients treated, *n* (%)[a]
All cohort	356/567 (63)	211/567 (37)
Correct BDZ dose	264/567 (46)	
Underdosed BDZ	92/567 (16)	
With CIVADs	31/567 (6)	57/567 (10)
Without CIVADs	325/567 (57)	155/567 (27)

Abbreviations: BDZ, benzodiazepine; CIVAD, continuous intravenous anesthetic drug; STEPPER, Status Epilepticus in Emilia-Romagna.

[a]Eleven patients not treated or data missing.

30-day mortality was higher in those SE cases that failed to resolve (48.8% in the OH group and 70.8% in the IH group).

Table S1 in supplementary material shows the associations between the possible prognostic variables and each of the three outcomes according to the univariable analysis in the two subpopulations.

According to the multivariable analysis (Table 3), in the OH group, the failure to resolve was associated with stupor/coma (OR = 2.75, 95% CI = 1.08–6.98) and, as a trend, with the use of an incorrect sequence of treatment (OR = 2.22, 95% CI = .98–5.03), female sex, and EMSE comorbidity score ≥ 60. In the IH group, the failure to resolve was associated with an incorrect sequence of treatment

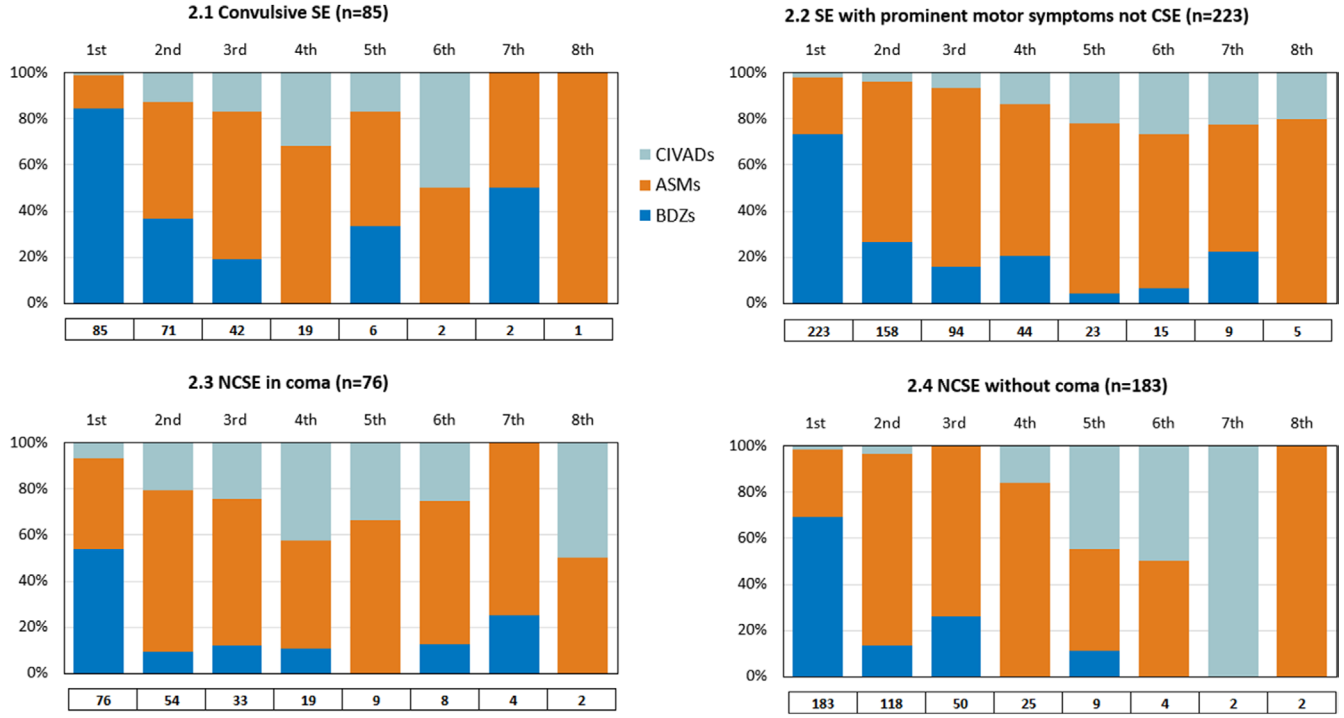

FIGURE 2 Pharmacological treatment of status epilepticus (SE) in the four groups: convulsive SE (CSE), SE with prominent motor symptoms not CSE, nonconvulsive SE (NCSE) in coma, NCSE without coma. Each bar represents the percentage of patients receiving each drug class (antiseizure medications [ASMs]/benzodiazepines [BDZs]/continuous intravenous anesthetic drugs [CIVADs]) at each therapeutic attempt, from the first to the last in temporal order. The total number of patients treated at each therapeutic attempt is indicated below the bars.

(OR = 4.42, 95% CI = 1.86–10.5) and inversely associated with NCSE without coma.

The following variables were associated with 30-day functional worsening (Table 3) in the multivariable analysis: age and failure to resolve (OR = 5.83, 95% CI = 2.05–16.6, OH group; OR = 9.30, 95% CI = 2.34–36.9, IH group), in both the subgroups; mRS pre-SE and stupor/coma, only in the IH group; and CSE and acute and progressive etiologies, only in the OH subgroup.

Finally, age, progressive etiology and failure to resolve (OR = 11.3, 95% CI = 4.16–30.9, OH group; OR = 6.42, 95% CI = 2.79–14.8, IH group) were independently associated with 30-day mortality (Table 3) in both the IH and OH subgroups, whereas a comorbidity score ≥60 and stupor/coma significantly impacted on mortality only in the IH subgroup.

4 | DISCUSSION

This is a real-life observational study conducted on a large cohort of adult patients prospectively enrolled at 17 centers in the ERR. We found that incorrect treatment sequence is the major prognostic factor of failure to resolve SE in patients with IH onset and shows a similar trend in patients with OH onset. Failure to resolve is, in turn, the major prognostic factor of 30-day mortality and 30-day poor functional status (according to mRS) in both subgroups.

Regarding treatment choices, we compared our results with the studies conducted in the ERR in the early 2000s.[13–20] The predilection for diazepam among BDZs has remained unchanged, even though studies have decreed that nonintravenous midazolam should be the drug of choice in the prehospital phase[27,28] and that intravenous lorazepam might be better than intravenous diazepam.[29] Conversely, the use of levetiracetam (35%) has increased, becoming the most prescribed ASM, displacing phenytoin (13%), which was the most widely used in the previous studies.[13–15] The common use of levetiracetam and lacosamide (28%) is presumably the result of choices based on safety profiles, real or perceived, and of the characteristics of our study population (advanced age, various comorbidities), in which drugs with few interactions are preferred. The preferential use of levetiracetam could also be explained by the predominant cerebrovascular etiology in our cohort (38%) and is in line with the same trend of use in poststroke epilepsy in Italy.[30]

Regarding CIVADs, our data align with the "European" trend highlighted in the 2019 international audit to prefer propofol to midazolam.[31] Despite the growing evidence of its potential in treating SE, we have observed limited use of ketamine.[32–35]

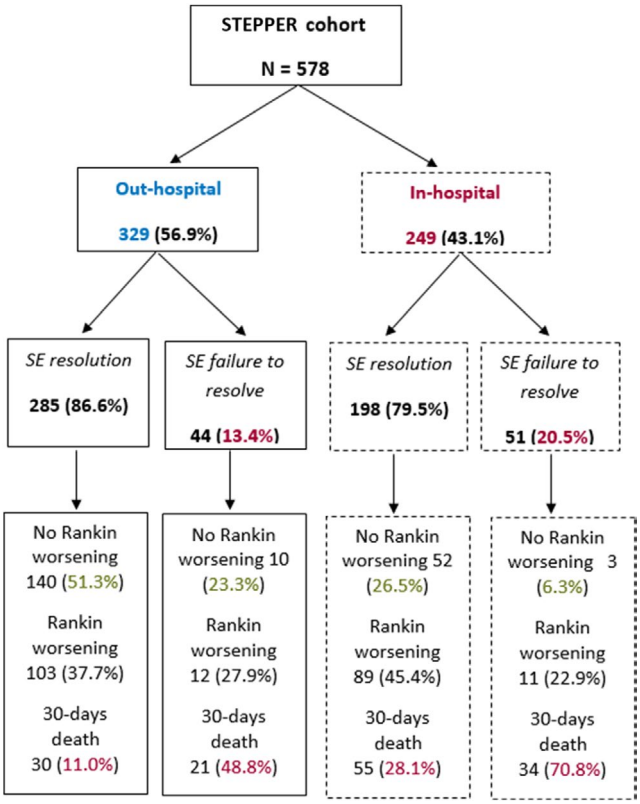

FIGURE 3 Status epilepticus (SE) outcome is shown in the two groups: in-hospital and out-of-hospital onset.

We confirm a high 30-day mortality rate of 24% in our study population, which aligns with previous studies conducted in our geographic area but surpasses rates reported in more recent research. Several characteristics of our population, including advanced age, high prevalence of comorbidities, unfavorable etiologies, and elevated EMSE score, may partially account for the relatively poor prognosis observed, given that they are known unmodifiable risk factors for mortality. Consistently, we found higher mortality in the IH subgroup, which showed statistically significant differences from the OH population precisely in those unmodifiable characteristics: age, mRS pre-SE, STESS, EMSE, SE semeiology, and SE etiology. This finding echoes a recent study by Brigo et al.[7] that observed a poorer prognosis in terms of mortality and functional outcome in the IH population, which was attributed to the presence of unfavorable clinical factors.

It is important to acknowledge that deviations from treatment CPG may also have contributed to the negative prognosis observed in our patients. Our study provides evidence that certain treatment approaches, such as incorrect treatment sequencing and underdosing of BDZs, may play an independent role in increasing the risk of SE persistence, at least in the IH subgroup. Persistence of SE, in turn, emerged as an independent risk factor for mortality and functional worsening at follow-up in both subgroups.

Concerning the misuse of BDZs, Kellinghaus et al. found likewise that the initial administration of a BDZ versus a non-BDZ ASM predicts earlier SE cessation.[36] Our study reveals a notable trend: the probability of BDZ use as the first line of treatment is higher when administered outside the hospital by EMS personnel. However, they are less likely to use BDZs at the correct dosage. Conversely, IH onset cases are less frequently treated with BDZs, especially when managed by neurologists, who typically adhere to proper dosage guidelines. The underdosing of BDZs, a phenomenon observed in prior studies[12,37–41] and known to increase the risk of RSE,[40] may be in part explained by the higher perceived risk of drug-induced respiratory failure using "high" doses of BDZs, especially in patients with comorbidities or severe general conditions.[41] This concern might have also applied to the IH cases in our cohort.

Although there is evidence of suboptimal utilization of BDZs as a first-line therapy, there is a counterintuitive trend toward their repeated use in subsequent lines of treatment, extending well beyond the second therapeutic attempt, irrespective of whether SE presents with prominent motor symptoms. Such misuse of BDZs has previously been linked to poorer outcomes, including a higher risk of intubation, ICU admission, and respiratory depression/insufficiency.[11]

Regarding deviations from guidelines in general, we initially expected that they would have been less frequent in cases of CSE than in NCSE. This assumption was based on the guidelines allowing more discretion to clinicians, especially concerning the use of CIVADs, in cases of RSE. Surprisingly, our study found similar clinician behavior across different subtypes of SE, with inadequate utilization of CIVADs even in cases of CSE. Previous studies have highlighted the importance of correct medication management, emphasizing that deviations from treatment guidelines can significantly impact clinical outcomes. For instance, De Stefano et al. observed a decrease in the likelihood of returning to premorbid function with each additional nonanesthetic antiseizure drug administered before anesthesia.[42] A prospective comparison of 57 adults with SE in the ERR disclosed that correct medical management (i.e., correct type, dosage, and sequence of the drugs administered) versus incorrect treatment was strongly and independently related to clinical outcome (OR = 21.09).[8] However, the effect of adherence to treatment guidelines on mortality and functional prognosis remains debated. Whereas some studies suggest a significant impact, others find it to be less influential. For instance, a prospective study conducted on 225 incident cases of SE observed at a single center by Rossetti et al. found that better application of SE treatment guidelines has an insignificant prognostic effect on mortality and functional prognosis of

TABLE 3 Variables associated with the three different outcomes at multivariable analysis: failure to resolve, mRS worsening, and 30-day mortality.

Independent variable	OR (95% CI)	*p*	OR (95% CI)	*p*
Outcome: failure to resolve	**Out-of-hospital onset, *n* = 329**		**In-hospital onset, *n* = 249**	
Sex				
Female vs. male	2.16 (.99–4.73)	.054	.64 (.30–1.37)	.251
EMSE comorbidity score				
≥60 vs. <60	2.61 (.87–7.86)	.088	2.40 (.73–7.91)	.149
Consciousness				
Stuporous/comatose vs. alert/somnolent	2.75 (1.08–6.98)	.033	1.07 (.48–2.41)	.862
SE classification [vs. prominent motor symptoms—other]				
Prominent motor symptoms—convulsive	1.72 (.56–5.26)	.339	.96 (.31–3.01)	.948
Nonconvulsive with coma	.57 (.13–2.63)	.474	.90 (.31–2.59)	.842
Nonconvulsive without coma	1.32 (.51–3.38)	.564	.31 (.10–.94)	.039
Etiology				
Acute vs. other	.95 (.37–2.42)	.907	.78 (.33–1.87)	.579
Progressive vs. other	1.71 (.71–4.13)	.233	1.21 (.32–4.57)	.780
SE treatment sequence				
Incorrect vs. correct with correct BDZ dose	2.22 (.98–5.02)	.057	4.42 (1.86–10.5)	.001
Correct with underdosed BDZ vs. correct with correct BDZ dose	.90 (.32–2.53)	.847	2.17 (.66–7.13)	.202
Outcome: mRS worsening	**Out-of-hospital onset, *n* = 316**		**In-hospital onset, *n* = 244**	
Age				
Years	1.05 (1.03–1.07)	<.001	1.04 (1.01–1.06)	.002
mRS pre-SE				
3 vs. 0–2	1.33 (.59–2.98)	.490	.30 (.11–.83)	.020
4–5 vs. 0–2	.61 (.29–1.29)	.197	.12 (.05–.29)	<.001
EMSE comorbidity score				
≥60 vs. <60	1.35 (.45–4.01)	.589	6.01 (.70–51.3)	.101
Consciousness				
Stuporous/comatose vs. alert/somnolent	1.56 (.67–3.61)	.300	3.00 (1.22–7.40)	.017
SE classification [vs. prominent motor symptoms—other]				
Prominent motor symptoms—convulsive	.31 (.11–.85)	.023	3.06 (.70–13.3)	.137
Nonconvulsive with coma	1.39 (.30–6.47)	.672	1.17 (.39–3.54)	.779
Nonconvulsive without coma	1.12 (.57–2.21)	.742	1.44 (.56–3.70)	.445
Etiology				
Acute vs. other	2.27 (1.15–4.48)	.010	1.51 (.68–3.37)	.308
Progressive vs. other	6.79 (3.02–15.3)	<.001	1.02 (.24–4.32)	.981
Failure to resolve vs. resolution of SE	5.83 (2.05–16.6)	.001	9.30 (2.34–36.9)	.002
Outcome: 30-day mortality	**Out-of-hospital onset, *n* = 327**		**In-hospital onset, *n* = 248**	
Age				
Years	1.06 (1.03–1.10)	.001	1.05 (1.03–1.08)	<.001

(Continues)

TABLE 3 (Continued)

Outcome: 30-day mortality	Out-of-hospital onset, $n = 327$		In-hospital onset, $n = 248$	
EMSE comorbidity score				
≥60 vs. <60	1.34 (.39–4.60)	.637	6.03 (1.76–20.7)	.004
Consciousness				
Stuporous/comatose vs. alert/somnolent	1.89 (1.28–6.47)	.204	2.29 (1.09–4.83)	.029
SE classification [vs. prominent motor symptoms—other]				
Prominent motor symptoms—convulsive	1.38 (.42–4.57)	.600	1.43 (.49–4.12)	.511
Nonconvulsive with coma	2.23 (.60–8.36)	.233	1.22 (.47–3.14)	.686
Nonconvulsive without coma	.70 (.26–1.89)	.485	1.66 (.70–3.90)	.248
Etiology				
Acute vs. other	1.12 (.42–4.57)	.600	1.12 (.53–2.37)	.763
Progressive vs. other	3.46 (1.35–8.87)	.010	.22 (.05–.99)	.048
Failure to resolve vs. resolution of SE	11.3 (4.16–30.9)	<.001	6.42 (2.79–14.8)	<.001

Abbreviations: BDZ, benzodiazepine; CI, confidence interval; EMSE, Epidemiology-Based Mortality Score in Status Epilepticus; mRS, modified Rankin Scale; OR, odds ratio; SE, status epilepticus.

SE. Yet, the authors suggest that further research is necessary to understand the implications of incorrect medication sequencing on SE prognosis.[43] Finally, a recent systematic review on outcomes of deviation from treatment guidelines in SE, including 22 studies published between 1970 and 2018, revealed that nonadherence to SE management guidelines was associated with an increased chance of worse outcomes, including ICU admission and mortality.[11]

One limitation of our study is that, despite being a prospective study, data related to the onset of SE, the timing of treatment administration, and the correct dosage were frequently missing or not detectable, given the intrinsic difficulty of identifying this condition, particularly in cases of NCSE. Consequently, our analysis focused solely on the correctness of drug sequencing and route of administration, without considering dosage and timing in relation to SE onset. On the other hand, this may suggest that applying the correct treatment sequence impacts prognosis even when the exact duration of SE is unknown, as frequently happens in clinical practice, where NCSE onset is often not definable. Another limitation, theoretically intrinsic in this kind of prognostic study and probable in a complex condition such as SE, is the presence of unmeasured confounding factors associated with outcomes (e.g., genetic factors, health organization influences).

In conclusion, our study shows that improved use of first-line therapies and greater adherence to treatment guidelines are associated with a higher likelihood of resolution of SE and, consequently, lower mortality. SE remains a condition burdened by high morbidity and functional worsening in survivors. Although undoubtedly nonmodifiable factors such as etiology, comorbidities, and age, to name a few, certainly play a role in determining the severity of this situation, our case analysis reveals that there are potentially modifiable factors that can influence its course. Further studies are needed to confirm the impact of treatment strategies on SE prognosis.

Enhancing SE management by emphasizing both organizational and educational aspects for health care personnel involved in its treatment may foster adherence to treatment guidelines, ensuring timely and proper interventions. This, in turn, has the potential to ameliorate the prognosis associated with this condition, which remains one of the main emergencies in the neurological field. Further studies are needed to refine our understanding of modifiable factors in SE management.

AUTHOR CONTRIBUTIONS

Drafting/revision of the manuscript for content, including medical writing for content: Lidia Di Vito, Eleonora Matteo, Stefano Meletti, Corrado Zenesini, Luca Vignatelli, Paolo Tinuper, and Francesca Bisulli. *Major role in the acquisition of data:* Lidia Di Vito, Eleonora Matteo, Stefano Meletti, Giorgia Bernabè, Chiara Bomprezzi, Maria Chiara Casadio, Carlo Alberto Castioni, Edward Cesnik, Carlo Coniglio, Marco Currò-Dossi, Patrizia De Massis, Elisa Fallica, Irene Florindo, Giada Giovannini, Maria Guarino, Elena Marchesi, Andrea Marudi, Elena Merli, Giulia Monti, Niccolò Orlandi, Elena Pasini, Daniela Passarelli, Rita Rinaldi, Romana Rizzi, Michele Romoli, Mario Santangelo, Valentina Tontini, Giulia Turchi, Mirco Volpini, Andrea Zini, Lucia Zinno, Roberto Michelucci, Paolo Tinuper, and Francesca Bisulli. *Study concept or design:* Stefano Meletti, Roberto Michelucci, Luca Vignatelli, Paolo Tinuper, and Francesca Bisulli. *Analysis or interpretation of data:* Lidia Di Vito, Eleonora Matteo, Corrado Zenesini, and Luca Vignatelli.

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CONFLICT OF INTEREST STATEMENT

F.B. has received grants or contracts from the Italian Ministry of Health; has received consulting fees from Eisai, Angelini, UCB, and Takeda; has received support for attending meetings and/or travel from LivaNova; and has been a member of the Lafora advocacy group executive board. E.C. has received support for attending meetings and/or travel from Eisai and Angelini Pharma. L.D.V. has received grants or contracts from the Italian Ministry of Health and has received support for attending meetings and/or travel from Angelini. I.F. has received payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Angelini; and has received support for attending meetings and/or travel from Angelini. S.M. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from UCB Pharma, Eisai, Jazz Pharmaceuticals, and Angelini; and has received support for attending meetings and/or travel from UCB Pharma, Eisai, Angelini, and Jazz Pharmaceuticals. R.M. has received support for attending meetings and/or travel from Angelini and Eisai. N.O. has received payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Eisai. M.R. has participated on the steering committee of the FibER trial. A.Z. has received consulting fees from Boehringer-Ingelheim, CSL Behring, and Angels Initiative; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events AstraZeneca, Daiichi Sankyo, and Angels Initiative; has received payment for expert testimony (Alexion–AstraZeneca); and has participated on a data safety monitoring or advisory board for Bayer and AstraZeneca. L.V. has received grants or contracts from the Italian Ministry of Health. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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