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ORIGINAL ARTICLE

Out-of-hospital versus in-hospital status epilepticus: The role of etiology and comorbidities

Francesco Brigo[1] | Gianni Turcato[2] | Simona Lattanzi[3] | Niccolò Orlandi[4,5] | Giulia Turchi[4] | Arian Zaboli[2] | Giada Giovannini[4,5,6] | Stefano Meletti[4,5]

[1]Department of Neurology, Hospital of Merano-Meran (SABES-ASDAA), Merano-Meran, Italy

[2]Emergency Department, Hospital of Merano (SABES-ASDAA), Merano-Meran, Italy

[3]Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy

[4]Neurology Department, Azienda Ospedaliera-Universitaria di Modena, Modena, Italy

[5]Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio-Emilia, Modena, Italy

[6]PhD Program in Clinical and Experimental Medicine, University of Modena and Reggio-Emilia, Modena, Italy

Correspondence
Stefano Meletti, Neurology Department, Azienda Ospedaliera-Universitaria di Modena, Ospedale Civile Baggiovara, Via Giardini 1355, 41126 Modena, Italy.
Email: stefano.meletti@unimore.it

Abstract

Background and purpose: Our objectives were to identify differences in clinical characteristics between patients with out-of-hospital and in-hospital status epilepticus (SE) onset, and to evaluate the influence of SE onset setting on 30-day mortality and SE cessation.

Methods: We included consecutive patients with SE admitted from 2013–2021 at Modena Academic Hospital. A propensity score was obtained with clinical variables unevenly distributed between the two groups.

Results: Seven hundred eleven patients were included; 55.8% (397/711) with out-of-hospital and 44.2% (314/711) with in-hospital onset. Patients with in-hospital SE onset were older and had a higher frequency of comorbidities, acute and/or potentially fatal etiologies, impaired consciousness before treatment, and nonconvulsive or myoclonic SE. No difference was found in SE cessation between the groups. Patients with in-hospital SE had higher 30-day mortality (127/314, 62.9% vs. 75/397, 37.1%; $p < 0.001$). In-hospital onset was an independent risk factor for 30-day mortality (adjusted odds ratio = 1.720; 95% confidence interval = 1.107–2.674; $p = 0.016$). In the propensity group ($n = 244$), no difference was found in 30-day mortality and SE cessation between out-of-hospital and in-hospital SE onset groups (36/122, 29.5% vs. 34/122, 27.9%; $p = 0.888$; and 47/122, 38.5% vs. 39/122; 32%; $p = 0.347$, respectively).

Conclusions: In-hospital SE is associated with higher 30-day mortality without difference in SE cessation. The two groups differ considerably for age, acute and possibly fatal etiologies, comorbidities, and SE semiology. The patient location at SE onset is an important prognostic predictor. However, the increased mortality is probably unrelated to the setting of SE onset and reflects intrinsic prognostic predictors.

KEYWORDS
mortality, prognosis, propensity score, status epilepticus

INTRODUCTION

Status epilepticus (SE) is "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]. Its annual incidence rates range from 1.29 to 73.7 per 100,000 adults (95% confidence interval [CI] = 76.6–80.3) [2]. SE is a potentially life-threatening condition that needs to be promptly

Francesco Brigo, Gianni Turcato, Giada Giovannini, and Stefano Meletti contributed equally.

recognized and adequately treated to minimize the risk of long-term consequences and mortality.

Several factors predicting short-term mortality have been identified, and some of them have been incorporated into outcome scoring systems like the Status Epilepticus Severity Score (STESS) [3] and the Epidemiology-Based Mortality Score in Status Epilepticus (EMSE) [4]. The main prognostic factors include age, level of consciousness impairment, SE semiology, history of previous seizures, etiology, comorbidities, and electroencephalographic (EEG) patterns. The knowledge of the factors that predict the outcome is important, because their control could guide treatment strategies and improve prognosis. For instance, identification of the underlying cause of SE through a rapid diagnostic workup is crucial for effective etiological treatment [5]. Therefore, considering the clinical context in which SE occurs may shorten diagnostic assessment and allow proper and tailored management, possibly reducing morbidity and mortality.

Studies comparing the clinical characteristics and prognosis of patients with out-of-hospital SE onset and those with SE developed during the hospital stay (de novo in-hospital onset) are scarce [6, 7]. One comparative study showed that patients with in-hospital SE had more fatal etiologies and comorbidities, refractory SE, less return to functional baseline, and increased mortality compared to patients with out-of-hospital SE [7]. The difference in prognosis could be explained by the underlying etiology and comorbid medical conditions, as patients with in-hospital SE onset are more likely to have been admitted with acute or potentially fatal brain injuries, metabolic disturbances, or comorbidities that may influence the outcome.

Although patients already admitted to the hospital have more comorbidities and acute/possibly fatal etiologies, one could argue that in-hospital SE onset is recognized and treated more promptly compared to SE occurring out-of-hospital. Similar to cardiac arrest, which has a better prognosis if occurring in the hospital compared to out of the hospital [8], a prompt diagnosis and treatment could counterbalance the intrinsically negative prognostic features associated with in-hospital SE onset.

This study aimed to identify differences in clinical characteristics between patients with out-of-hospital and de novo in-hospital SE onset and to evaluate the influence of SE onset setting on 30-day mortality and SE cessation.

METHODS

Study design, setting, and patients

We reviewed consecutive episodes of SE occurring in patients aged 14 years and older and prospectively registered at Baggiovara Civil Hospital (Modena, Italy) from September 1, 2013 to October 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 [9]. After 2015, the definition by the International League Against Epilepsy (ILAE) was systematically adopted and prospectively applied [1]. 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 (S.M. and G.G.) to ensure that all met the ILAE diagnostic criteria. The cases of nonconvulsive SE were diagnosed according to the Salzburg EEG criteria [10, 11].

A specific data set 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 [1] in which acute symptomatic causes were divided into hypoxic or nonhypoxic, impairment of consciousness before treatment, worst seizure type according to the STESS [3], EEG patterns according to the EMSE [4], scores of the EMSE and STESS [3, 4], and modified Rankin Scale (mRS) at SE onset, at discharge, and after 30 days. 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 http://salute.regione.emilia-romagna.it/percorso-epilessia/PDTASE_AOU.pdf) based on the recommendations of international guidelines [12–14].

In our hospital, every patient with a suspicion or diagnosis of SE is referred to the consultant neurologist, both for diagnostic confirmation and treatment. The consultant neurologist and an EEG recording are available 24 h a day, 7 days per week, even in the intensive care units.

Outcome

SE cessation was defined according to the Sustained Effort Network for Treatment of Status Epilepticus (SENSE) study as follows: cessation of SE within the first hour after treatment initiation for generalized convulsive SE and cessation of SE within 12 h after treatment initiation for other SE types [15].

Data on follow-up of patients, SE cessation, and their 30-day mortality were obtained from the SE data set used to collect information and confirmed through the registry office.

Statistical analysis

The categorical variables were described as percentage and number of events out of the total, and the univariate comparisons were performed with the Fischer exact test or the χ^2 test. Continuous variables were reported as median and interquartile range (IQR) or as mean and SD, depending on the underlying distribution. Comparisons were made with the Mann-Whitney or *t* tests. The possible independent association between in-hospital SE onset and

30-day mortality was studied through a multivariate model with logistic regression and adjusted stepwise method for variables that had been found significant in univariate analyses and included as possible multivariate confounders. Survival analysis between the two treatment groups (out-of-hospital and in-hospital SE onset) was conducted with the Kaplan-Meier method through the log-rank test.

Subsequently, considering the different baseline conditions that could have influenced the outcome and the fact that the study did not have preenrollment selection criteria, the baseline variables that were found to be unbalanced between the two groups were included in a propensity score matching.

After propensity score matching, the analyses were repeated to estimate the independent association between SE onset setting and 30-day mortality. All tests were two-sided, and a p value <0.050 was considered statistically significant. Statistical analyses were performed with Stata version 16.0 (StataCorp).

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.

Data availability

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

RESULTS

Seven hundred eleven patients with SE observed during the study period were included. There were 55.8% (397/711) who had an out-of-hospital SE onset, whereas 44.2% (314/711) had an in-hospital onset. Patient baseline characteristics were strongly unbalanced between the two study groups (Table 1). Patients with de novo in-hospital SE onset were older (median = 76 years, IQR = 66–82 vs. 71 years, IQR = 57–81; p <0.001) and had a higher frequency of ischemic heart disease, cerebrovascular disease, diabetes mellitus, heart failure, dementia, peripheral vascular disease, and chronic kidney disease. A previous history of epilepsy was found more frequently among patients with in-hospital onset (230, 73.2% vs. 231, 58.2%; p <0.001). Acute symptomatic causes (hypoxic and nonhypoxic) were more frequent in patients with in-hospital SE, whereas remote and progressive symptomatic causes were found more frequently among patients with out-of-hospital onset. An impaired consciousness before treatment and nonconvulsive SE occurred more frequently among in-hospital onset patients, whereas generalized convulsive SE, focal motor, focal non-motor, absence, and myoclonic SE complicating idiopathic generalized epilepsy were more frequent in the out-of-hospital group. A higher proportion of EEG patterns with after status ictal discharges, generalized sharply and/or triphasic period potentials, lateralized periodic discharges, or spontaneous burst suppression was found among patients with in-hospital SE onset.

The severity of SE, evaluated by the STESS and EMSE, was higher in those with in-hospital onset. No difference was found in mRS at baseline, whereas it was higher at discharge and at 30 days among patients with in-hospital SE onset.

Patients with in-hospital onset had higher 30-day mortality (127/314, 40.4%) than those with out-of-hospital onset (75/397, 18.9%) (p <0.001). No difference was found in SE cessation between the groups, with about 35% of SE episodes fulfilling the definition of SE cessation according to the SENSE study. The Kaplan-Meier analysis showed that out-of-hospital SE onset had a longer mean survival compared to in-hospital SE onset (27.3, SD = 0.4 vs. 23.9, SD = 0.6; log-rank test p <0.001) (Figures 1 and 2).

Characteristics associated with 30-day mortality are reported in Table 2. Of note, nonconvulsive SE occurred more frequently in nonsurvivors, whereas generalized convulsive SE, focal motor, focal nonmotor, absence, and myoclonic SE complicating idiopathic generalized epilepsy were more frequent in survivors. Comorbidities associated with increased mortality were ischemic heart disease, cerebrovascular disease, dementia, ulcer, tumor, peripheral vascular disease, chronic obstructive pulmonary disease, chronic kidney disease, and liver failure. Hypoxic acute symptomatic causes were more frequent among nonsurvivors, whereas remote and progressive symptomatic causes were more frequent in survivors.

In the multivariate analysis performed with a logistic regression using the stepwise regression method, the in-hospital onset was an independent risk factor for mortality at 30 days, with an adjusted odds ratio of 1.720 (95% confidence interval = 1.107–2.674; p = 0.016).

A propensity score was performed with the clinical variables found to be differently distributed between the two groups. A one-to-one statistical matching was carried out, obtaining a restricted data set of 244 patients equally distributed into 122 pairs (i.e., 122 out-of-hospital and 122 in-hospital SE onset). The characteristics of the patient group obtained after propensity score matching are reported in Table 3.

In the propensity group (n = 244), no difference was found in 30-day mortality between patients with out-of-hospital SE onset (34/122; 27.9%) and patients with in-hospital onset (36/122, 29.5%) (p = 0.888). Similarly, no difference was found in SE cessation between out-of-hospital (47/122, 38.5%) and in-hospital onset SE cases (39/122, 32%) (p = 0.347). Finally, no difference was found in mRS before SE onset, at discharge from the hospital, and at 30 days. The Kaplan-Meier analysis in the propensity data set did not show differences in the time to 30-day mortality between the two study groups (p = 0.857) (Supplementary Material).

TABLE 1 Baseline characteristics between the two groups

Variable	Out-of-hospital SE onset	In-hospital SE onset	*p* value
Patients, *n* (%)	397 (55.8)	314 (44.2)	
Age, years, median (IQR)	71 (57–81)	76 (66–82)	<0.001
Sex, *n* (%)			0.250
Male	169 (42.6)	120 (38.2)	
Female	228 (57.4)	194 (61.8)	
Comorbidities, *n* (%)			
Ischemic heart disease	40 (10.1)	51 (16.2)	0.017
Cerebrovascular disease	45 (11.3)	67 (21.3)	<0.001
Connective tissue disease	9 (2.3)	10 (3.2)	0.489
Diabetes mellitus	62 (15.6)	74 (23.6)	0.009
Heart failure	18 (4.5)	28 (8.9)	0.021
Dementia	77 (19.4)	40 (12.7)	0.019
Ulcer	18 (4.5)	11 (3.5)	0.569
Hemiplegia	35 (8.8)	28 (8.9)	1.000
Tumor	48 (12.1)	24 (7.6)	0.060
Peripheral vascular disease	8 (2.0)	28 (8.9)	<0.001
COPD	39 (9.8)	30 (9.6)	1.000
Liver failure	17 (4.3)	10 (3.2)	0.555
Chronic kidney disease	29 (7.3)	39 (12.4)	0.028
Prior history of epilepsy, *n* (%)	228 (57.9)	230 (73.2)	<0.001
Etiological classification, *n* (%)			
Acute symptomatic, hypoxic	20 (5.0)	58 (18.5)	<0.001
Acute symptomatic, nonhypoxic	181 (45.6)	192 (61.1)	<0.001
Remote symptomatic	87 (21.9)	30 (9.6)	<0.001
Progressive symptomatic	86 (21.7)	27 (8.6)	<0.001
Other	23 (5.8)	7 (2.2)	0.023
Impaired consciousness before treatment, *n* (%)	82 (20.7)	168 (53.5)	<0.001
Worst seizure type according to STESS, *n* (%)			
Focal without impairment of consciousness,[a] focal with impaired consciousness,[b] absence, myoclonic complicating IGE	208 (52.4)	116 (36.9)	<0.001
Generalized-convulsive	137 (34.5)	55 (17.5)	<0.001
Nonconvulsive status epilepticus in coma	52 (13.1)	143 (45.5)	<0.001
EEG, *n* (%)			<0.001
No LPDs, GPDs, or ASIDs	269 (68.3)	168 (53.5)	
ASIDs, LPDs, GPDs	113 (28.7)	138 (43.9)	
Spontaneous burst suppression	12 (3.0)	8 (2.5)	
Prognostic scores, point, mean (SD)			
STESS	2.7 (1.6)	3.9 (1.7)	<0.001
EMSE	48.7 (36.1)	66.4 (34.4)	<0.001
SE cessation, *n* (%)[c]			0.937
No	256 (64.5)	204 (65)	
Yes	141 (35.5)	110 (35)	
30-day mortality, *n* (%)			<0.001
No	322 (81.1)	187 (59.6)	
Yes	75 (18.9)	127 (40.4)	

Variable	Out-of-hospital SE onset	In-hospital SE onset	*p* value
mRS before, median (IQR)	2 (0–3)	2 (0–4)	0.093
mRS after, median (IQR)	4 (1–5)	5 (4–6)	<0.001
mRS 30 days, median (IQR)	3 (1–5)	5 (5–6)	0.037

Abbreviations: ASIDs, after status ictal discharges; COPD, chronic obstructive pulmonary disease; EEG, electroencephalogram; EMSE, Epidemiology-Based Mortality Score in Status Epilepticus; GPDs, generalized sharply and/or triphasic period potentials; IGE, idiopathic generalized epilepsy; IQR, interquartile range; LPDs, lateralized periodic discharges; mRS, modified Rankin Scale; SE, status epilepticus; STESS, Status Epilepticus Severity Score.

[a]The term corresponds to the terminology reported in the current definition of SE [1]. The original term reported in the STESS was simple-partial [3].

[b]The term corresponds to the terminology reported in the current definition of SE [1]. The original term reported in the STESS was complex-partial [3].

[c]SE cessation was defined according to the Sustained Effort Network for Treatment of Status Epilepticus study as follows: cessation of SE within the first hour after treatment initiation for generalized convulsive SE and cessation of SE within 12 h after treatment initiation for other SE types [15].

DISCUSSION

This study has identified clinical and prognostic differences between patients with out-of-hospital and de novo in-hospital SE onset.

SE cessation did not differ between groups, whereas 30-day mortality was higher among patients with in-hospital onset.

In this study, we pragmatically defined SE treatment response according to criteria proposed in the SENSE registry. We chose this definition for two reasons. The first is that the SENSE study evaluated the pharmacological treatment of SE in a real-life setting, as in our study. The second reason is that we could expect lower and later response rates in the out-of-hospital onset group compared to the in-hospital SE onset, and the definition of SE cessation provided by the SENSE registry appears particularly appropriate for the present study. With regard to this issue, in our study the percentage of patients who met the SE cessation criterion was very close to that reported in the SENSE study, and as previously commented by the authors of the SENSE study, lower than SE treatment response reported in clinical trials [16–20]. Second, unlike what could be expected, the intra- or extrahospital onset was not associated with a different response to pharmacological treatment.

The higher mortality in patients with in-hospital SE onset observed in our population (about 40%) is consistent with data available in the literature. One study found that in this patient group the mortality (60%) was higher than the overall mortality rate associated with refractory SE derived from prior studies including mixed (i.e., in-hospital and out-of-hospital SE) populations [6]. A subsequent 10-year comparative cohort study showed that in-hospital SE was associated with short-term mortality of about 30% and with more potentially fatal etiologies and comorbid conditions, longer duration and treatment refractoriness, and more infrequent return to functional baseline [7].

The poor outcome among patients with in-hospital SE onset can be explained by the fact that these patients are admitted for an intrinsically severe or critical condition, usually for acute or potentially fatal brain injuries, metabolic disturbances, or comorbidities. Each of these factors is associated with a high risk of death. The combination of structural brain abnormalities and metabolic disturbances appears to be particularly predictive of short-term mortality [21].

In our study, patients with in-hospital SE onset were older, confirming the finding that age is a nonmodifiable predictor of mortality following SE, as consistently reported in the literature [22–26]. Differences in comorbidities were found between the two groups and were more frequent among patients with in-hospital onset. Of note, no comorbidity was found more often in the out-of-hospital group. Attention should be paid to specific comorbidities associated with poor outcomes; treating comorbidities could, hence, lead to a better prognosis reducing the risk of short-term mortality.

Furthermore, patients with out-of-hospital and in-hospital SE onset differed markedly with regard to underlying etiologies. In the latter group, acute and/or potentially fatal SE causes occurred more frequently [26–29].

The higher mortality rate in patients with in-hospital SE can be explained by the older age, higher morbidity, higher prevalence of periodic EEG patterns or spontaneous burst suppression, and a higher proportion of possibly fatal etiologies, but also by SE semiology. Interestingly, generalized convulsive SE occurred more frequently in the out-of-hospital onset and survivors, whereas non-convulsive SE was more frequent in the in-hospital group and in patients who died within 30 days from SE. These findings are in line with the results of a large retrospective population-based study, which showed that prominent motor phenomena are associated with lower mortality; in this study, convulsive semiology at the end of SE, or as its only semiology had a case fatality of zero, whereas impaired awareness with somnolence, stupor, or coma was associated with higher mortality compared to awake patients [30]. The different prognosis can be explained by the fact that generalized convulsive SE with bilateral tonic–clonic activity is probably recognized much more quickly by bystanders, leading to prompter treatment than nonconvulsive SE. Furthermore, unlike the latter, SE with generalized prominent motor phenomena could reflect a still preserved cerebral ability to seize without homeostatic metabolic or electric exhaustion [31].

Compared to out-of-hospital onset, the in-hospital onset was an independent risk factor for mortality at 30 days, but also for poorer functional outcome, as shown by higher mRS at discharge and at 30 days. Although patients already admitted to the hospital

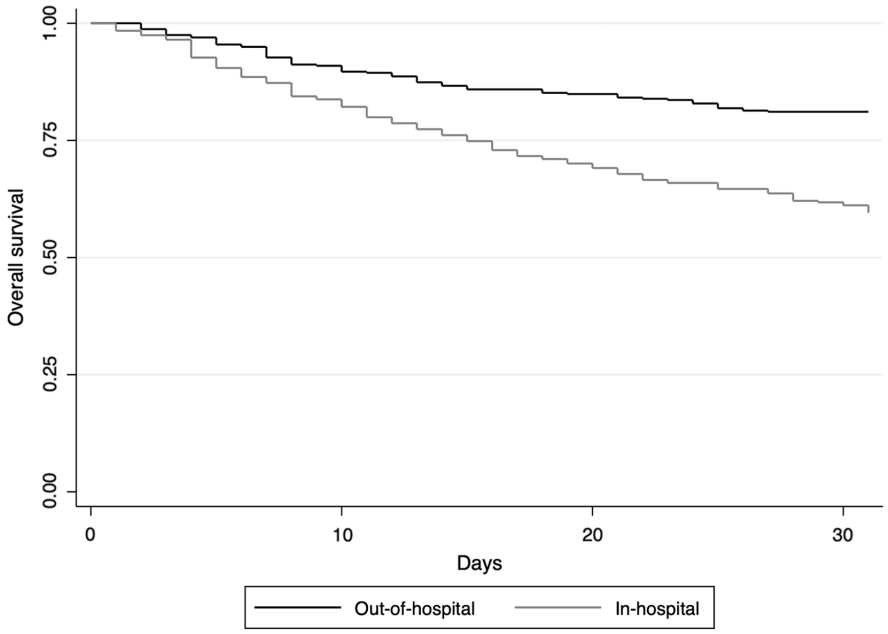

FIGURE 1 Kaplan-Meier curve showing overall survival in the out-of-hospital and in-hospital status epilepticus onset groups [Colour figure can be viewed at wileyonlinelibrary.com]

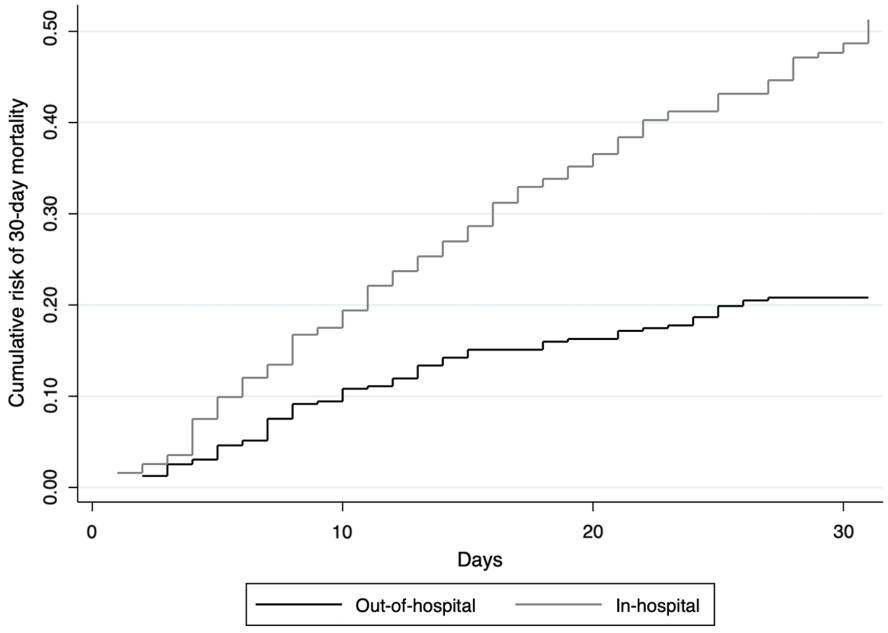

FIGURE 2 Kaplan-Meier curve showing cumulative risk of 30-day mortality in the out-of-hospital and in-hospital status epilepticus onset groups [Colour figure can be viewed at wileyonlinelibrary.com]

have more comorbidities and acute/possibly fatal etiologies, one could argue that in-hospital SE onset is recognized and treated more promptly compared to SE occurring out-of-hospital. Similar to cardiac arrest, which has a better prognosis if occurring in the hospital compared to outside the hospital [8], prompter diagnosis and treatment could counterbalance the intrinsically more negative prognostic features associated with in-hospital SE onset. After balancing the clinical variables that were differently distributed between the out-of-hospital and the in-hospital SE onset groups by the propensity score matching, no difference was found in 30-day mortality or functional outcome assessed with mRS. This further confirms that the different prognosis is likely to be unrelated to the setting of SE onset but reflects intrinsic differences in relevant prognostic factors between the groups.

This study has a few limitations. This study was conducted in one single tertiary care center, possibly limiting the generalizability of the findings. We investigated episodes of SE instead of patients with first SE, which might have biased the results. We had no data on total SE duration and on time of SE onset. This is particularly relevant for non convulsive status epilepticus (NCSE); however, in this condition it is very challenging and sometimes impossible to identify with precision the time of SE onset. In patients with out-of-hospital hypoxic SE, the diagnosis was made after the patient was admitted to the hospital; the etiological diagnosis of hypoxic SE due

TABLE 2 Characteristics associated with 30-day mortality after SE

Variable	Survivors	Nonsurvivors	*p* value
Patients, *n* (%)	509 (71.6)	202 (28.4)	
Age, years, median (IQR)	70 (57–79)	80 (73–86)	<0.001
Sex, *n* (%)			0.352
Male	201 (39.5)	88 (43.6)	
Female	308 (60.5)	114 (56.4)	
SE onset, *n* (%)			<0.001
Out of hospital	322 (63.3)	75 (37.1)	
In hospital	187 (36.7)	127 (62.9)	
Comorbidities, *n* (%)			
Ischemic heart disease	50 (9.8)	41 (20.3)	<0.001
Cerebrovascular disease	63 (12.4)	49 (24.3)	<0.001
Connective tissue disease	13 (2.6)	6 (3.0)	0.798
Diabetes mellitus	90 (17.7)	46 (22.8)	0.139
Heart failure	28 (5.5)	18 (8.9)	0.127
Dementia	73 (14.3)	44 (21.8)	0.019
Ulcer	15 (2.9)	14 (6.9)	0.020
Hemiplegia	42 (8.3)	21 (10.4)	0.381
Tumor	41 (8.1)	31 (15.3)	0.006
Peripheral vascular disease	15 (2.9)	21 (10.4)	<0.001
COPD	37 (7.3)	32 (15.8)	0.001
Liver failure	13 (2.6)	14 (6.9)	0.009
Chronic kidney disease	30 (5.9)	38 (18.8)	<0.001
Prior history of epilepsy, *n* (%)	304 (59.7)	157 (77.7)	<0.001
Etiological classification, *n* (%)			
Acute symptomatic, hypoxic	28 (5.5)	50 (24.8)	<0.001
Acute symptomatic, nonhypoxic	263 (51.7)	110 (54.5)	0.507
Remote symptomatic	101 (19.8)	16 (7.9)	<0.001
Progressive symptomatic	93 (18.3)	20 (9.9)	0.006
Other	24 (4.7)	6 (3.0)	0.408
Impaired consciousness before treatment, *n* (%)	136 (26.7)	114 (56.4)	<0.001
Worst seizure type according to STESS, *n* (%)			
Focal without impairment of consciousness,[a] focal with impaired consciousness,[b] absence, myoclonic complicating IGE	251 (49.3)	73 (36.1)	0.002
Generalized-convulsive	163 (32.0)	29 (14.4)	<0.001
Nonconvulsive SE in coma	95 (18.7)	100 (49.5)	<0.001
Prognostic scores, points, mean (SD)			
STESS	2.8 (1.6)	4.2 (1.6)	<0.001
EMSE	46.4 (31.8)	81.9 (34.8)	
SE cessation, *n* (%)[c]			0.223
No	322 (63.3)	138 (68.3)	
Yes	187 (36.7)	64 (31.7)	

Abbreviations: COPD, chronic obstructive pulmonary disease; EMSE, Epidemiology-Based Mortality Score in Status Epilepticus; IGE, idiopathic generalized epilepsy; IQR, interquartile range; SE, status epilepticus; STESS, Status Epilepticus Severity Score.

[a]The term corresponds to the terminology reported in the current definition of SE [1]. The original term reported in the STESS was simple-partial [3].

[b]The term corresponds to the terminology reported in the current definition of SE [1]. The original term reported in the STESS was complex-partial [3].

[c]SE cessation was defined according to the Sustained Effort Network for Treatment of Status Epilepticus study as follows: cessation of SE within the first hour after treatment initiation for generalized convulsive SE and cessation of SE within 12 h after treatment initiation for other SE types [15].

TABLE 3 Characteristics of the data set obtained after propensity score matching

Variable	Out-of-hospital SE onset	In-hospital SE onset	*p* value
Patients, *n* (%)	122 (50.0)	122 (50.0)	
Age, years, median (IQR)	73 (65–84)	72 (63–79)	0.210
Sex, *n* (%)			0.436
Male	54 (44.3)	47 (38.5)	
Female	68 (55.7)	75 (61.5)	
Comorbidities, *n* (%)			
Ischemic heart disease	22 (18.0)	12 (9.8)	0.095
Cerebrovascular disease	19 (15.6)	24 (19.7)	0.502
Connective tissue disease	2 (1.6)	1 (0.8)	1.000
Diabetes mellitus	27 (22.1)	24 (19.7)	0.753
Heart failure	10 (8.2)	7 (5.7)	0.616
Dementia	19 (15.6)	19 (15.6)	1.000
Ulcer	6 (4.9)	3 (2.5)	0.500
Hemiplegia	13 (10.7)	11 (9.0)	0.830
Tumor	15 (12.3)	9 (7.4)	0.282
Peripheral vascular disease	6 (4.9)	3 (2.5)	0.500
COPD	14 (11.5)	13 (10.7)	1.000
Liver failure	5 (4.1)	6 (4.9)	1.000
Chronic kidney disease	10 (8.2)	14 (11.5)	0.520
Prior history of epilepsy, *n* (%)	77 (63.1)	76 (62.3)	1.000
Etiological classification, *n* (%)			
Acute symptomatic, hypoxic	16 (13.1)	17 (13.9)	1.000
Acute symptomatic, non-hypoxic	67 (54.9)	70 (57.4)	0.796
Remote symptomatic	18 (14.8)	13 (10.7)	0.442
Progressive symptomatic	14 (11.5)	17 (13.9)	0.701
Other	7 (5.7)	5 (4.1)	0.769
Impaired consciousness before treatment, *n* (%)	44 (36.1)	43 (35.2)	1.000
Worst seizure type according to STESS, *n* (%)			
Focal without impairment of consciousness,[a] focal with impaired consciousness,[b] absence, myoclonic complicating IGE	54 (44.3)	54 (44.3)	1.000
Generalized-convulsive	33 (27.0)	31 (25.4)	0.884
Nonconvulsive status epilepticus in coma	35 (28.7)	37 (30.3)	0.888
EEG, *n* (%)			0.668
No LPDs, GPDs, or ASIDs	68 (65.4)	63 (60.6)	
ASIDs, LPDs, GPDs	34 (32.7)	40 (38.5)	
Spontaneous burst suppression	2 (1.9)	1 (1.0)	
Prognostic scores, points, mean (SD)			
STESS	3.4 (1.6)	3.3 (1.6)	0.585
EMSE	58.9 (40.5)	60.3 (34.9)	0.628
SE cessation, *n* (%)[c]			0.348
No	83 (68)	75 (61.5)	
Yes	39 (32)	47 (38.5)	
30-day mortality, *n* (%)			0.888
No	88 (72.1)	86 (70.5)	
Yes	34 (27.9)	36 (29.5)	
mRS before, median (IQR)	2 (0–4)	2 (0–4)	0.538
mRS after, median (IQR)	5 (2–6)	5 (4–6)	0.110
mRS 30 days, median (IQR)	5 (2–6)	5 (3–6)	0.553

Abbreviations: ASIDs, after status ictal discharges; COPD, chronic obstructive pulmonary disease; EEG, electroencephalogram; EMSE, Epidemiology-Based Mortality Score in Status Epilepticus; GPDs, generalized sharply and/or triphasic period potentials; IGE, idiopathic generalized epilepsy; IQR, interquartile range; LPDs, lateralized periodic discharges; mRS, modified Rankin Scale; SE, status epilepticus; STESS, Status Epilepticus Severity Score.

[a]The term corresponds to the terminology reported in the current definition of SE [1]. The original term reported in the STESS was simple-partial [3].

[b]The term corresponds to the terminology reported in the current definition of SE [1]. The original term reported in the STESS was complex-partial [3].

[c]SE cessation was defined according to the Sustained Effort Network for Treatment of Status Epilepticus study as follows: cessation of SE within the first hour after treatment initiation for generalized convulsive SE and cessation of SE within 12 h after treatment initiation for other SE types [15].

to cardiorespiratory arrest was hence made retrospectively. Finally, we did not have enough data to calculate the Charlson Comorbidity Index score [32], which is useful for assessing the burden of comorbidities, and had no information on single EEG patterns. Hence, further studies conducted in different cohorts and hospital settings are required to confirm our findings.

The major strengths of this study include the large sample size and the use of propensity score matching, a statistical sampling

technique that can limit the selection bias of two study groups. Through propensity score matching we obtained a subgroup of patients adequately matched 1 to 1 between the two study groups (out-of-hospital and in-hospital SE onset) to obtain a balance in basal characteristics.

In our hospital, patients from various departments in whom there is a suspicion of SE are referred to the consultant neurologist, available 24 h a day, 7 days per week, both for diagnostic confirmation and treatment following an internal standardized protocol; hence, there are almost no differences according to the department that initially evaluates the patients. The management of patients in the intensive care units also involves the consultant neurologist. This greatly reduces the heterogeneity in the diagnostic process and treatment of patients with in-hospital SE onset. Conversely, it is possible that the initial management of out-of-hospital SE cases is affected by higher heterogeneity in treatment.

In conclusion, our study has shown that patients with in-hospital SE are at a higher risk of 30-day mortality compared to those with out-of-hospital SE. The two groups differ considerably in terms of age, acute and possibly fatal etiologies, comorbidities, and SE semiology. The patient location at SE onset has important prognostic relevance. However, the increased mortality is probably unrelated to the setting of SE onset but reflects the presence of clinical factors with relevant impact on prognosis. Promptly identifying and addressing modifiable risk factors could positively affect SE short-term mortality.

AUTHOR CONTRIBUTIONS

Francesco Brigo: Conceptualization (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Gianni Turcato:** Conceptualization (equal); formal analysis (equal); methodology (equal); writing – original draft (equal). **Simona Lattanzi:** Conceptualization (equal); writing – review and editing (equal). **Niccol Orlandi:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Giulia Turchi:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Arian Zaboli:** Methodology (equal); visualization (equal); writing – review and editing (equal). **G Giovannini:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Stefano Meletti:** Supervision (equal); validation (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ORCID

Francesco Brigo https://orcid.org/0000-0003-0928-1577
Simona Lattanzi https://orcid.org/0000-0001-8748-0083
Stefano Meletti https://orcid.org/0000-0003-0334-539X

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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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