BRIEF COMMUNICATION

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Acute symptomatic status epilepticus: Splitting or lumping? A proposal of classification based on real-world data

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Abstract

This study aimed to group acute symptomatic etiologies of consecutive episodes of status epilepticus (SE) into different subcategories and explore their associations with clinical outcome. Etiologies were first categorized as "acute," "remote," "progressive," "SE in defined electroclinical syndromes," and "unknown." Four subcategories of acute etiologies were then defined: (1) withdrawal, low levels, or inappropriate prescription of antiseizure medications, or sleep deprivation in patients with pre-existing epilepsy; (2) acute insults to central nervous system (CNS; "acute-primary CNS"); (3) CNS pathology secondary to metabolic disturbances, systemic infection, or fever ("acute-secondary CNS"); and (4) drug/alcohol intoxication or withdrawal. Poor outcome at discharge, defined as worsening of clinical conditions (modified Rankin Scale [mRS] at discharge higher than mRS at baseline), was reported in 55.6% of cases. The etiological categories of acute-primary CNS (odds ratio [OR] = 3.61, 95% confidence interval [CI] = 2.11–6.18), acute-secondary CNS (OR = 1.80, 95% CI = 1.11–2.91), and progressive SE (OR = 2.65, 95% CI = 1.57–4.47), age (OR = 1.05, 95% CI = 1.04–1.06), nonconvulsive semiology with coma (OR = 3.06, 95% CI = 1.52–6.17), and refractoriness (OR = 4.31, 95% CI = 2.39–7.77) and superrefractoriness to treatment (OR = 8.24,

95% CI = 3.51–19.36) increased the odds of poor outcome. Heterogeneity exists within the spectrum of acute symptomatic causes of SE, and distinct etiological subcategories may inform about the clinical outcome.

KEYWORDS
acute symptomatic, antiseizure medications, etiology, status epilepticus

1 | INTRODUCTION

Status epilepticus (SE) is a neurologic emergency caused by disorders and diseases that affect the central nervous system (CNS), and etiology represents axis II of the diagnostic classification system proposed by the International League Against Epilepsy (ILAE).[1] The etiology is divided into subcategories of known (i.e., symptomatic) and unknown (i.e., cryptogenic) causes, and the former are further distinguished into acute, remote, progressive, and defined electroclinical syndromes.[1]

Etiology represents one of the main prognostic factors, and acute symptomatic etiology has been associated with poor outcome.[2–4] The definition of acute symptomatic etiology, however, can be misleading, as this is a heterogeneous group that encompasses a variety of causes.

In this study, we proposed different subcategories of acute symptomatic etiologies and explored their associations with clinical outcome in patients with non-hypoxic SE.

2 | MATERIALS AND METHODS

2.1 | Participants

At Baggiovara Civil Hospital (Modena, Italy), a prospective SE registry (Modena Status Epilepticus Registry) has existed since 2013. Consecutive episodes of SE occurring in patients ≥14 years old without hypoxic–anoxic brain injury from September 1, 2013 to August 1, 2019 were reviewed and included in this study. Details about treatment management and collected data can be found in the online Appendix S1 and previous reports.[5–8] Patients with SE following hypoxic–anoxic encephalopathy were excluded, as this etiology is mostly associated with a distinct course compared to other acute causes of SE and is characterized by a high risk of poor outcome.[9]

Etiologies of SE were first categorized as "acute," "remote," "progressive," "SE in defined electroclinical syndromes," and "unknown" (i.e., cryptogenic).[1] Four subcategories of acute etiologies were then defined (and labeled): (1) withdrawal, low levels, or inappropriate prescription of antiseizure medications (ASMs), febrile illnesses, or sleep deprivation in patients with pre-existing epilepsy ("acute-triggering factors in epilepsy [TFE]"); (2) acute primary CNS pathology, including cerebrovascular diseases, active CNS infections, or head trauma ("acute-primary CNS"); (3) secondary CNS pathology, including metabolic disturbances (e.g., electrolyte imbalances, glucose imbalance, organ failure, acidosis, renal failure, hepatic encephalopathy), systemic infection, or fever ("acute-secondary CNS"); and (4) drug or alcohol intoxication and withdrawal ("acute-toxic"; Figure S1).

The primary study outcome was poor outcome at discharge, defined as worsening of clinical conditions (modified Rankin Scale [mRS] at discharge higher than mRS at baseline). The secondary outcome was in-hospital mortality.

2.2 | Statistical analysis

Values are presented as median (interquartile range [IQR]) for continuous variables and as the number (percent) of patients for categorical variables. Comparisons were made through Mann–Whitney test or chi-squared test; Bonferroni method was used to correct for multiple comparisons. Logistic regression model was fitted using a backward stepwise selection with variable entry set at $p = .05$ and removal at $p = .10$ to explore the relationship between the etiology of SE and study outcomes. The etiologies of SE were categorized as: acute-TFE, acute-primary CNS, acute-secondary CNS, acute-toxic, remote, progressive, SE in defined electroclinical syndromes, and unknown. Age, SE semiology (convulsive, focal motor, myoclonic, nonconvulsive without coma, and nonconvulsive with coma), consciousness before treatment initiation (alert/somnolent and stuporous/comatose), and treatment responsiveness (responsive, refractory, and superrefractory SE) were selected as independent variables for their known association with functional outcome.[10] Model 1 was adjusted for age, SE semiology, and consciousness before treatment initiation; model 2 was adjusted for the same variables as model 1 plus treatment responsiveness. Results were reported as odds ratio with associated 95% confidence interval. Data analysis was performed using Stata/IC 13.1 (StataCorp).

2.3 | Standard protocol approvals, registrations, and patient consents

The local ethics committee approved the study (556/2018/ OSS/AOUMO–RF-2016-02361365). All participants or their legal representatives gave informed written consent according to the Declaration of Helsinki.

3 | RESULTS

A total of 633 episodes of nonhypoxic SE were identified, which occurred in 564 subjects. The median age at SE onset was 74 (IQR = 61–82) years, and 245 (38.7%) episodes occurred in males. The most common etiology of SE episodes was acute symptomatic (58.8%), followed by remote (18.5%) and progressive (18.0%). Within SE episodes with acute symptomatic etiology, the most common causes were primary and secondary CNS insults. Demographic and clinical characteristics of SE episodes are summarized in Table 1.

Poor outcome at discharge was reported in 352 (55.6%) cases. Episodes of SE associated with poor outcome occurred in older subjects, more commonly had a nonconvulsive semiology with coma, and were more commonly refractory and superrefractory to treatment compared to episodes not associated with a worsening of clinical conditions. Demographic and clinical characteristics of SE episodes according to the clinical outcome are summarized in Table 1. The clinical outcome according to the different etiological groups is shown in Figure 1A. Statistically significant comparisons after Bonferroni correction included acute-TFE versus acute-primary CNS (21.4% vs. 76.9%, $p < .001$), acute-TFE versus acute-secondary CNS (21.4% vs. 59.2%, $p < .001$), acute-TFE versus progressive (21.4% vs. 58.8%, $p < .001$), acute-primary CNS versus acute-secondary CNS (76.9% vs. 59.2%, $p = .001$), acute-primary CNS versus remote (76.9% vs. 39.3%, $p < .001$), acute-primary CNS versus progressive (76.9% vs. 58.8%, $p = .002$), acute-secondary CNS versus remote (59.2% vs. 39.3%, $p = .001$), acute-primary CNS versus defined electroclinical syndromes (76.9% vs. 9.1%, $p < .001$), acute-secondary CNS versus defined electroclinical syndromes (59.2% vs. 9.1%, $p = .001$), and progressive versus defined electroclinical syndromes (58.8% vs. 9.1%, $p = .001$).

Multivariable analyses showed that groups of acute-primary CNS, acute-secondary CNS, and progressive SE etiology, as well as age, nonconvulsive semiology with coma, and refractoriness and superrefractoriness to treatment were significantly associated with increased odds of poor outcome at discharge (Table S1).

The overall rate of in-hospital mortality was 23.2% (147/633), and the rates by etiological groups were 7.1% in acute-TFE, 30.6% in acute-primary CNS, 32.0% in acute-secondary CNS, 7.1% in acute-toxic, 13.7% in remote, 19.3% in progressive, and 31.6% in unknown causes of SE. There were no deaths among cases of SE in defined electroclinical syndromes (Figure 1B). Statistically significant comparisons after Bonferroni correction included acute-TFE versus acute-secondary CNS ($p = .001$), acute-primary CNS versus remote ($p = .001$), and acute-secondary CNS versus remote ($p < .001$). The logistic regression model adjusted for age, SE semiology, and consciousness before treatment initiation showed that the etiological groups of acute-primary CNS, acute-secondary CNS, progressive SE, and SE of unknown cause, age, and impaired consciousness were significantly associated with increased odds of in-hospital mortality (Table S2). In the fully adjusted model, remote etiology was significantly associated with decreased odds of in-hospital mortality, and age, stuporous/comatose level of consciousness, and refractoriness and superrefractoriness to treatment increased the risk of in-hospital death (Table S2).

4 | DISCUSSION

The current study highlights how patients with SE due to acute symptomatic etiology carry a different risk of poor outcome at discharge according to the underlying cause of SE. Patients with SE due to acute primary CNS pathology presented the highest risk of clinical worsening, which was significantly higher than the risk of patients with SE due to secondary CNS insults. Conversely, patients with acute symptomatic SE due to withdrawal of or low levels of ASMs or other triggering factors in epilepsy presented the most favorable prognosis.

These findings point out the vast heterogeneity within the spectrum of acute symptomatic causes of SE and suggest the opportunity to consider different etiological subcategories that may inform about the clinical outcome of this group of patients.

The underlying etiology of SE is a well-known important determinant of outcome, and SE should be considered a symptom of the causative condition rather than a disease on its own. A distinction between SE in subjects with known epilepsy and SE in subjects without history of epilepsy has been proposed.[4] In subjects with a prior diagnosis of epilepsy, SE can be related to triggering factors, such as withdrawal of ASMs, reduced ASM plasmatic levels due to concurrent situations as vomiting, diarrhea, and drug–drug interactions, and poor adherence to therapy.[4] SE in the context of a previously diagnosed epilepsy has been associated with a relatively good outcome compared to SE associated with other causes like stroke, meningoencephalitis, and cerebral anoxia.[4,11] Etiology not

**TABLE 1** Characteristics of status epilepticus episodes and their comparison according to clinical outcome.

Characteristic	Status epilepticus episodes, $n = 633$	Poor outcome at discharge		p
		No, $n = 281$	Yes, $n = 352$	
Sex, n (%)				.408
Male	245 (38.7)	113 (40.2)	132 (37.5)	
Female	388 (61.3)	168 (59.8)	220 (62.5)	
Age, years [IQR]	74 [61–82]	66 [51–78]	78 [68–84]	<.001
Semiology, n (%)				<.001
Convulsive	114 (18.0)	71 (25.3)	43 (12.2)	
Focal motor	186 (29.4)	82 (29.2)	104 (29.6)	
Myoclonic	9 (1.4)	5 (1.8)	4 (1.1)	
Nonconvulsive without coma	237 (37.4)	110 (39.1)	127 (36.1)	
Nonconvulsive with coma	87 (13.7)	13 (4.6)	74 (21.0)	
Consciousness, n (%)				<.001
Alert/somnolent	459 (72.5)	235 (83.6)	224 (63.6)	
Stuporous/comatose	174 (27.5)	46 (16.4)	128 (36.4)	
STESS score [IQR]	3 [2–4]	2 [1–3]	3 [3–5]	<.001
Etiology, n (%)				<.001
Acute				
Acute-TFE	42 (6.6)	33 (11.8)	9 (2.6)	
Acute-primary CNS	147 (23.2)	34 (12.1)	113 (32.1)	
Acute-secondary CNS	169 (26.7)	69 (24.6)	100 (28.4)	
Acute-toxic	14 (2.2)	8 (2.8)	6 (1.7)	
Remote	117 (18.5)	71 (25.3)	46 (13.1)	
Progressive	114 (18.0)	47 (16.7)	67 (19.0)	
Unknown	19 (3.0)	9 (3.2)	10 (2.8)	
Status epilepticus in defined electroclinical syndromes	11 (1.8)	10 (3.5)	1 (.3)	
mRS before status epilepticus [IQR]	2 [0–4]	2 [0–4]	2 [0–4]	.878
Response to treatment, n (%)				<.001
Responsive	464 (74.0)	246 (88.8)	218 (62.3)	
Refractory	105 (16.8)	21 (7.6)	84 (24.0)	
Superrefractory	58 (9.3)	10 (3.6)	48 (13.7)	

Abbreviations: CNS, central nervous system; IQR, interquartile range; mRS, modified Rankin Scale; STESS, Status Epilepticus Severity Score; TFE, triggering factors in epilepsy.

being available at presentation in most cases, history of previous seizures has been considered as a surrogate and included in the Status Epilepticus Severity Score as a favorable prognostic factor associated with decreased risk of mortality.[12] In the Epidemiology-Based Mortality Score in Status Epilepticus, drug reduction/withdrawal and poor compliance are the etiological categories linked with the fewest points and, hence, the lowest risk of mortality.[13] In a cohort of 81 adult patients with SE admitted and prospectively followed at the Pitié-Salpêtrière Hospital, 57% of the whole study population had an mRS score at discharge higher than the score at baseline; the rate of poor

FIGURE 1 Clinical outcome at discharge and in-hospital mortality according to the etiology of status epilepticus. (A) Clinical outcome at discharge. (B) In-hospital mortality. Proportion of episodes of status epilepticus associated with poor outcome at discharge (A) and in-hospital mortality (B) are shown by etiological group. Poor outcome was defined as a worsening of clinical conditions at discharge (mRS at discharge higher than mRS at baseline). Acute symptomatic etiologies are grouped within the red rectangle. See text for details. CNS, central nervous system; mRS, modified Rankin Scale; TFE, triggering factors in epilepsy.
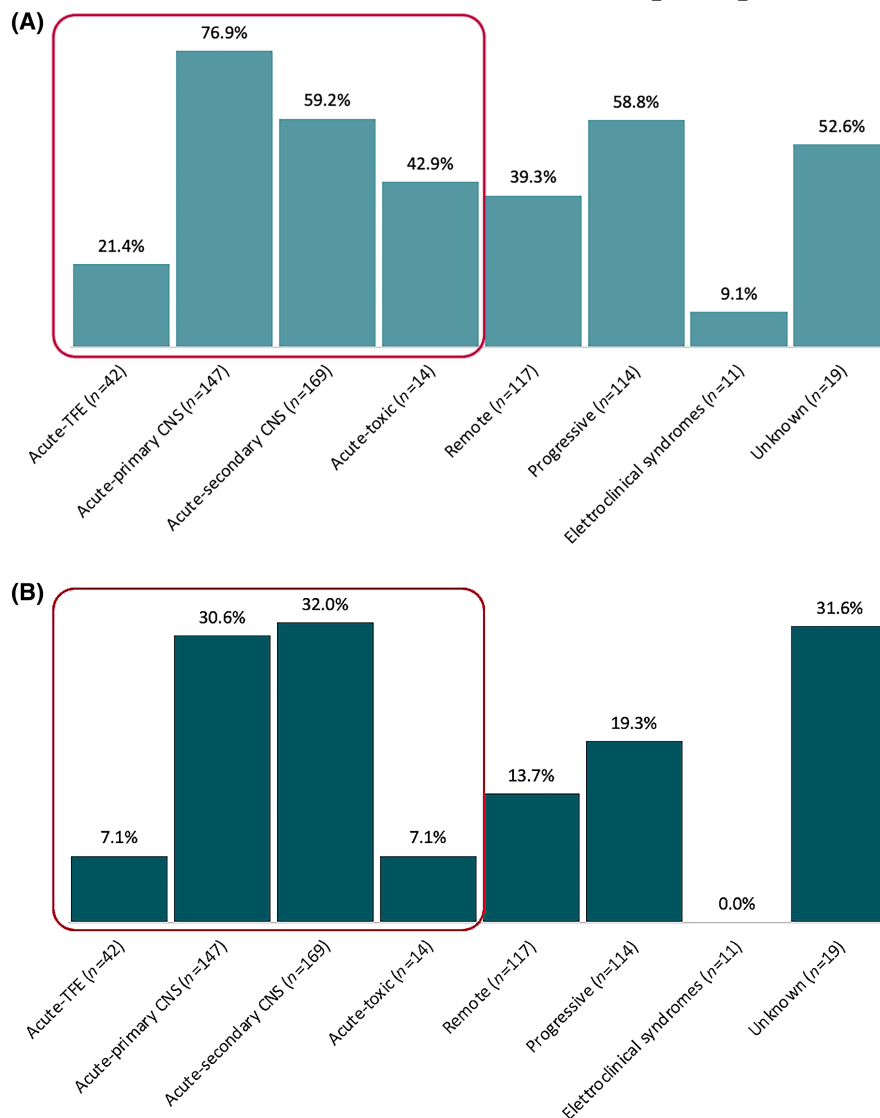
outcome in patients who had previously been diagnosed with epilepsy was 39% and was significantly lower compared with the rate of 72% found in the other patients.[14]

Acute symptomatic causes of SE other than withdrawal of or low levels of ASMs or other triggering factors in people with epilepsy, however, still represent a basket of etiologies with different prognostic profiles. A modified etiology categorization that included "potentially fatal etiology" has been proposed and appeared better suited to predict bad outcome as compared to the traditional acute symptomatic classification.[15] Potentially fatal etiologies were defined as potentially leading to death independently of SE and included acute large vessel ischemic stroke, acute cerebral hemorrhage, acute CNS infection, severe systemic infection, malignant brain tumor, acquired immunodeficiency syndrome with CNS complications, chronic renal insufficiency requiring dialysis, systemic vasculitis, metabolic disturbance, and acute intoxication sufficient to cause coma in the absence of SE,

eclampsia, and intracranial tumor surgery.[15] Conversely, ASM withdrawal, and remote or progressive symptomatic conditions such as previous trauma, stroke, CNS infection, and dementia were considered not potentially fatal. Among 96 patients with incident SE episodes, potentially fatal etiology showed the highest association with poor outcome; it was recorded in 34.3% of patients who returned to baseline clinical conditions at hospital discharge compared to 72.1% of those who did not, with the difference reaching statistical significance.[15] Of note, this dichotomous classification still put together conditions that are likely to have different prognosis, such as ASM withdrawal and progressive symptomatic etiologies, and pooled some acute, remote, and progressive etiologies irrespective of the distinction indicated by the ILAE framework for SE classification.

Although the study design did not allow inferring causation but only associations, the higher risk of worsening of clinical conditions for patients with SE due to

acute primary than secondary CNS pathology may be interpreted within the frame of the "burden model" for SE.[16] In this regard, it can be hypothesized that primary CNS insults are accompanied by higher structural damage of the brain, a lower functional brain reserve, or a combination of both, which ultimately increases the extent of decompensation and negatively affects the clinical outcome.

This study built upon current classification systems of SE etiology and, focusing on acute symptomatic causes, proposed a more granular perspective, including different subcategories anchored to evidence-based differences in clinical outcome. Of note, results were obtained from a large, hospital-based cohort of patients and remained statistically significant after adjustment for a variety of clinical variables, including the responsiveness to treatment. Some shortcomings need, however, to be acknowledged. The low number of alcohol-related SE episodes and SE due to intoxication did not allow drawing definitive conclusions about their association with outcome and prognostic differences compared to other acute causes of SE; similarly, SE in defined electroclinical syndromes and SE due to unknown causes were poorly represented categories, limiting the power to identify statistically significant results. Although patients with SE following hypoxic–anoxic encephalopathy generally have a distinct course compared to other acute causes of SE and a high risk of poor outcome irrespective of treatment,[9] this etiological category could be further considered in future comparisons. An intrinsic heterogeneity necessarily exists within each category, and additional tools should be implemented to further stratify the degree of severity of any individual causes of SE. The data collection performed in a real-world setting may have introduced potential sources of bias, and the recruitment at a single center may hamper the representativeness of the results; in this regard, however, all information was collected prospectively through a consistent form over years[7,8]; further, the center is the main referral point for a wide, both urban and rural, geographical area covering almost 1 million inhabitants, and this feature can also justify the high rate of SE cases admitted over time. Deterioration of clinical conditions is a relevant and informative measure of outcome from the clinical perspective, but the functional status at discharge may depend on the time of discharge, and further analyses adjusted for the length of hospital stay may provide more accurate estimates. Although different rates of in-hospital mortality were found across the acute etiologies, the inclusion of strong predictors like responsiveness to treatment and the overall low number of observed events may have masked significant associations in the fully adjusted model; multivariable analyses in larger populations could allow exploring the actual contribution of the etiological subgroups to in-hospital death. Future, ideally prospective, studies including more variables and data are warranted to validate the findings in independent cohorts.

The heterogeneity of SE makes the prognostication of outcome challenging. Although etiology is one of the main prognostic predictors, the current frameworks do not fully consider the relationship between the cause and clinical outcome of SE, and novel classification systems may prove useful in both clinical research and practice.

AUTHOR CONTRIBUTIONS

Simona Lattanzi planned and designed the study, performed the statistical analyses, interpreted the data, and drafted and revised the manuscript. Giada Giovannini and Niccolò Orlandi acquired and interpreted the data, and revised the manuscript. Francesco Brigo and Eugen Trinka revised the manuscript. Stefano Meletti planned and designed the study, interpreted the data, contributed to the inaugural draft, and revised the manuscript. All authors approved the final submitted version.

CONFLICT OF INTEREST STATEMENT

S.L. has received speaker or consultancy fees from Angelini Pharma, Eisai, GW Pharmaceuticals, and UCB Pharma and has served on advisory boards for Angelini Pharma, Arvelle Therapeutics, Bial, Eisai, GW Pharmaceuticals, and Rapport Therapeutics outside the submitted work. E.T. has received consultancy fees from Arvelle Therapeutics, Argenx, Clexio, Celegene, UCB Pharma, Eisai, Epilog, Bial, Medtronic, Everpharma, Biogen, Takeda, LivaNova, Newbridge, Sunovion, GW Pharmaceuticals, and Marinus; speaker fees from Arvelle Therapeutics, Bial, Biogen, Böhringer Ingelheim, Eisai, Everpharma, GSK, GW Pharmaceuticals, Hikma, LivaNova, Newbridge, Novartis, Sanofi, Sandoz, and UCB Pharma; and research funding (directly or to his institution) from GSK, Biogen, Eisai, Novartis, Red Bull, Bayer, and UCB Pharma outside the submitted work. E.T. receives Grants from the Austrian Science Fund, Österreichische Nationalbank, and the European Union. E.T. is the CEO of Neuroconsult. S.M. received research grant support from the Ministry of Health and the nonprofit organization Fondazione Cassa di Risparmio di Modena; and has received personal compensation as a scientific advisory board member for UCB,

Jazz Pharmaceuticals, and Eisai outside the submitted work. The remaining authors have no conflicts of interest.

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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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