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# A one-year prospective study of refractory status epilepticus in Modena, Italy

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ABSTRACT

Refractory status epilepticus (RSE) is a particular critical condition characterized by seizures that continue despite the use of first- and second-line therapies and by high mortality. To date, only one prospective study investigated clinical features and prognostic factors in RSE. In this study, we performed a one-year prospective survey to identify clinical features, outcomes, and variables associated with the development of RSE in the adolescent and adult population of Modena, northern Italy. We observed 83 episodes of SE in 83 patients. In 31% of the cases, third-line therapy (anesthetic drug) was needed. Among this group, 14% resolved and were classified as RSE, while, in 17%, seizures recurred at withdrawal of anesthetics and were classified as super-RSE. The development of RSE/super-RSE was associated with a stuporous/comatose state at presentation and with the absence of a previous history of epilepsy. Refractory status epilepticus/super-refractory status epilepticus showed a worse outcome compared with responsive SE: 54% versus 21% for 30-day mortality; 19% versus 56% for a return to baseline condition.

This prospective study confirms stupor/coma at onset as a relevant clinical factor associated with SE refractoriness. We observed a rate of RSE comparable with previous reports, with high mortality and morbidity. Mortality in the observed RSE was higher than in previous studies; this result is probably related to the low rate of a previous epilepsy history in our population that reflects a high incidence of acute symptomatic etiologies, especially the inclusion of patients with postanoxic SE who have a bad prognosis per se.

**This article is part of a Special Issue entitled "Status Epilepticus".**



## 1. Introduction

Status epilepticus (SE) is a severe medical condition defined as an epileptic seizure that shows no clinical signs of arresting after a duration encompassing the great majority of seizures (generally 5 min) or recurrent seizures without interictal resumption of baseline central nervous system function [1].

Its incidence varies across studies from 9.9 to 41 per 100,000/year, and it has been found higher in the United States and lower in central Europe [2–8]. It is characterized by high mortality and morbidity [2–10].

Refractory status epilepticus (RSE) is a particular critical condition characterized by seizures that continue despite the use of first- and second-line therapies. Different definitions of this entity have been proposed — some take into account the time elapsed since the beginning of the SE, while some others are based on the numbers of failed trials with antiepileptic drugs (generally two or three drugs) and on the need of an anesthetic treatment [11–19]. Refractory SE develops in 24% to 43% of patients with SE, with a mortality rate ranging from 15% to 65% [12,15,18–26]. Only one study has addressed, with a prospective design, the frequency of RSE and evaluated the clinical features at onset as predictors of responsiveness/refractoriness [16]. Moreover, the majority of retrospective studies that evaluated prognostic factors in RSE were performed in tertiary academic hospitals. We performed a prospective one-year study to identify clinical features, outcomes, and variables associated with the development of RSE in the adolescent and adult population of Modena, northern Italy.

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## 2. Methods

### 2.1. Definitions adopted

We adopted an operational definition of SE that allows clinicians to rapidly treat the identified cases. Status epilepticus was defined as a continuous seizure that lasts ≥5 min or two or more discrete seizures between which there is not a complete recovery of consciousness [27].

Refractory status epilepticus was defined as SE that persists, regardless of the delay since the onset of the seizure, after failure of a trial of at least one AED and after i.v. benzodiazepine administration, appropriately chosen and at adequate dosage; thus, it needs the use of anesthetic drugs.

Super-RSE (super-refractory status epilepticus) is defined as SE that continues or recurs 24 h or more after the onset of anesthetic therapy or recurs on the reduction or withdrawal of anesthesia [28].

According to the definition given in the Guidelines for Epidemiologic Studies on Epilepsy [29] and also previously used in other epidemiologic studies [5], SE was defined as acute symptomatic, remote symptomatic, and progressive symptomatic. Status epilepticus without a clear etiology was defined as cryptogenic SE, while idiopathic SE was reserved for certain partial or generalized epileptic syndromes with particular clinical and EEG characteristics. Status epilepticus was defined as multifactorial when there were more than one of the above categories simultaneously present. Status epilepticus in patients with postanoxic SE was not excluded.

### 2.2. Inclusion criteria

We included all consecutive SE episodes observed at the hub hospitals (NOCSAE and AO Policlinico) of the Modena district in northern Italy occurring in adolescents and adults (≥14 years old) and observed from September 1st 2013 to August 31st 2014. These two hospitals are the only ones in the Modena district with a neurology service and with an intensive care unit (ICU), and they care for any potential neurological emergency.

We included all the episodes in which there was clinical evidence of continuous or repetitive seizures or, in cases of nonconvulsive status epilepticus (NCSE), those in which an electroencephalogram (EEG) classified the event as SE. Electroencephalography was defined as diagnostic if showing an ictal or periodic pattern or, if performed postictally, showing focal slowing (with or without interictal discharges) unexplained by other causes or generalized slowing with interictal epileptiform activity [30].

### 2.3. Procedures

We created a specific "Status Epilepticus Form" to collect, for each case, the information needed. The form was first filled in by the first doctor who took care of the patient (in the majority of cases, a neurologist or a neurointensivist or a physician of the emergency room) or by the staff of the neurophysiology unit who performed the first EEG examination of a suspected SE case (<24 h in every case). It is worth noting that a neurology ward serves the two hospitals 24 h/day for seven days/week, and the same neurophysiology staff records all the EEGs. A neurologist, trained in epilepsy, then revised all the forms and the EEG interpretation and completed any missing information consulting the hospital Informatics Database. As an additional quality control of the study protocol, at the end of the study, we also checked all the patients discharged from the hospital in the analyzed year with an "epilepsy" or "seizure" ICD-9 discharge code.

All subjects underwent complete electrolytic, metabolic, and hematologic workup. Brain imaging (CT scan or MRI) and lumbar puncture were performed as needed.

The information collected for each patient was as follows: age; sex; place of residence; site and date of SE observation and date of SE onset; history of epilepsy prior to SE; comorbidities; level of disability before SE (using the modified Rankin scale, mRS); level of consciousness at first medical evaluation (using the Glasgow Coma Scale, GCS); etiology; type and duration of SE before treatment; type and result of neuroradiologic studies; type, duration, and dosage of AED; anesthetic drugs; and other therapies used.

The primary study outcomes were the mortality and the level of disability measured at 30-day follow-up. We also evaluated the STESS (Status Epilepticus Severity Score), a clinical score that has been proved to be useful as a prognostic instrument for SE [20,31].

Our institutional review board approved the study.

### 2.4. Statistical analysis

The statistical analysis was performed using SPSS software. Continuous values were compared using the Mann–Whitney test for nonnormally distributed data. Categorical variables were compared using the Pearson $\chi^2$ test or the Fisher exact test where required. The statistical significance cutoff was set at 0.05.

## 3. Results

Table 1 reports an overview of the analyzed demographic and clinical variables.

**Table 1**
Demographics, clinical aspects, and etiologies of status epilepticus.

| | All (83) | | Refractory group[a] (26) | | Responsive group (48) | | p | Test |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | – | – |
| Female gender | 51 | 61% | **12** | **46%** | **34** | **71%** | **0.03** | $\chi^2$ |
| Mean age, years | 72 | | 67 | | 72 | | 0.29 | U |
| Previous history of epilepsy | 23 | 28% | **4** | **15%** | **19** | **40%** | **0.03** | Fisher |
| STESS[b] ≥ 3 | 69 | 83% | 23 | 88% | 38 | 79% | 0.52 | Fisher |
| GCS ≤ 7 | 17 | 20% | **11** | **42%** | **5** | **10%** | **0.002** | Fisher |
| Electroclinical classification | | | | | | | | Fisher |
| NCSE | 52 | 63% | 17 | 65% | 31 | 65% | 1 | |
| GCSE | 9 | 11% | 3 | 12% | 4 | 8% | 0.69 | |
| MSE | 1 | 1% | 1 | 4% | 0 | 0% | 0.35 | |
| PCSE | 21 | 25% | 5 | 19% | 13 | 27% | 0.57 | |
| Etiology classification | | | | | | | | |
| Acute symptomatic | 53 | 64% | **20** | **77%** | **27** | **56%** | **0.04** | Fisher |
| Progressive symptomatic | 13 | 16% | 3 | 12% | 9 | 19% | 0.52 | |
| Remote symptomatic | 10 | 12% | 1 | 4% | 7 | 15% | 0.24 | |
| Multifactorial | 5 | 6% | 2 | 8% | 3 | 6% | 1 | |
| Cryptogenic | 2 | 2% | 0 | 0% | 2 | 4% | 0.53 | |
| Causes | | | | | | | | |
| Postanoxic | 15 | 18% | **13** | **50%** | **1** | **2%** | **<0.001** | Fisher |
| Cerebrovascular | 15 | 18% | 3 | 12% | 10 | 21% | 0.52 | |
| Meningoencephalitis | 3 | 4% | 0 | 0% | 3 | 6% | 0.54 | |
| Cerebral tumor | 11 | 13% | 2 | 8% | 8 | 17% | 0.47 | |
| Sepsis | 11 | 13% | 3 | 12% | 6 | 13% | 1 | |
| Metabolic dysregulation | 10 | 12% | 2 | 8% | 6 | 13% | 0.70 | |
| AED discontinuation | 1 | 1% | 0 | 0% | 1 | 2% | 1 | |
| Epileptic encephalopathy | 1 | 1% | 0 | 0% | 1 | 2% | 1 | |
| Toxic | 2 | 2% | 0 | 0% | 2 | 4% | 0.53 | |
| Unknown | 2 | 2% | 0 | 0% | 2 | 4% | 0.53 | |
| Others | 2 | 2% | 1 | 4% | 1 | 2% | 1 | |
| Miscellaneous | 10 | 12% | 2 | 8% | 7 | 15% | 0.47 | |
| Complications | | | | | | | | |
| Respiratory complications | 26 | 31% | 8 | 31% | 15 | 31% | 1 | Fisher |
| Cardiac complications | 8 | 10% | 2 | 8% | 2 | 4% | 0.60 | Fisher |
| Resolution | 56 | 67% | **8** | **31%** | **48** | **100%** | **<0.001** | Fisher |
| Return to baseline conditions | 33 | 40% | **5** | **19%** | **27** | **56%** | **0.003** | Fisher |
| 30-day mRS ≥ 3 | 61 | 73% | **23** | **88%** | **31** | **65%** | **0.03** | Fisher |
| 30-day mortality | 31 | 37% | **14** | **54%** | **10** | **21%** | **0.003** | $\chi^2$ |

[a] Includes refractory and super-refractory cases.
[b] STESS is calculated by adding age (0 or 2 points, cutoff at 65), history of seizures (1 point if present), seizure type (0, 1, or 2 points), and consciousness impairment (1 point if stuporous or comatose); cutoff is 0–2 (good prognosis) versus 3–6 (bad prognosis).