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Not all patients with convulsive status epilepticus intubated in pre-hospital settings meet the criteria for refractory status epilepticus

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ABSTRACT

Introduction: Mechanically ventilated patients admitted to the intensive care unit (ICU) for generalized convulsive status epilepticus (GCSE) are a heterogeneous population. Our objective was to evaluate the number of patients who fulfilled the diagnostic criteria for refractory GCSE and describe their initial management and prognosis.

Methods: This multicenter retrospective study was conducted in four French ICUs in Pitié-Salpêtrière University Hospital in Paris and in the Hospital of Jossigny. Mechanically ventilated patients admitted to the ICU for GCSE between, January 1, 2014, and, December 31, 2016, were included. Patients with anoxia and traumatic brain injury were excluded. Their pre-hospital and ICU medical records were reviewed. The collected data included pre-hospital clinical status, pre-hospital antiepileptic treatment, reason for mechanical ventilation, duration of general anesthesia, and prognosis in the ICU. A retrospective initial diagnosis based on the findings of the analysis of the clinical records was attributed to each patient.

Results: Among the 98 patients included, 88.8% (n = 87/98) fulfilled the diagnostic criteria for GCSE; of these cases, 16.1% (n = 14/87) were refractory. Eleven percent of the patients did not fulfill the criteria for GCSE at the time of initial management (retrospective diagnosis of single convulsive seizure, repetitive convulsive seizures, or psychogenic non-epileptic seizures). Most patients were intubated for coma (58.9%, n = 56/95, missing data: n = 3). In the ICU, the median [Q1–Q3] duration of general anesthesia before weaning was 12.3 h (5.0–18.0 h); 7% of the patients had a relapse of status epilepticus, and 2% died in the ICU.

Conclusion: Among the cases of confirmed GCSE in the mechanically ventilated patients admitted to the ICU, 16.1% were refractory, with an overall good prognosis. A significant proportion of patients did not fulfill the diagnostic criteria for refractory GCSE.

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INTRODUCTION

Status epilepticus (SE) is a frequent neurological emergency [1–5] that can lead to death [4,6] or long-term functional deficits [7,8]. Generalized convulsive status epilepticus (GCSE) is a common and severe form of SE. Its drug management relies on a three-step strategy [9,10], and benzodiazepines are the first-line treatment option, followed by a long-lasting antiepileptic drug if convulsive seizures persist. Failure of the first two lines of treatment indicates the presence of refractory GCSE [5], which requires a third-line treatment with anesthetic drugs. Prospective data regarding the treatment of refractory GCSE are lacking; however, according to expert opinion, general anesthesia for 24–48 h is warranted, followed by progressive weaning for 6–12 h [9–11]. This level of treatment encompasses life-threatening risks, either related to general anesthesia itself [12] or because it implies invasive mechanical ventilation and a longer stay in the intensive care unit (ICU) [13]. Therefore, it is of utmost importance to appropriately diagnose refractory GCSE to induce therapeutic coma in the right indication. In France, the Emergency Medical Service system includes mobile ICUs with a senior physician and a nurse, enabling the start of advanced life support in the field [14]. In the case of GCSE, the three lines of treatment and mechanical ventilation can be provided at an early stage in the pre-hospital setting. Two main clinical presentations require emergency mechanical ventilation in GCSE: induction of general anesthesia for the treatment of refractory GCSE, and airway protection in case of a prolonged coma after cessation of convulsions (regardless of the etiology of coma: the absence of EEG makes the positive diagnosis of non-convulsive SE impossible in the pre-hospital setting). Hence, mechanically ventilated patients admitted to the ICU for GCSE are a heterogeneous population in terms of pre-hospital management and prognosis. The proportion of refractoriness in this setting is of prime importance when considering a clinical trial including patients with GCSE admitted to the ICU [15].

We hypothesized that the majority of cases of GCSE among patients intubated in the pre-

hospital setting would not be refractory. In this multicenter retrospective study, we systematically reviewed the records of mechanically ventilated patients admitted to the ICU with an initial diagnosis of GCSE. Our primary aim was to describe their clinical presentation and pre-hospital management to evaluate how many patients fulfilled the diagnostic criteria for overt refractory GCSE. Our secondary aim was to describe their management and evolution in the ICU. Cases of acute traumatic brain injury and cardiac arrest, in which general anesthesia is required (treatment of intracranial hypertension and induction of therapeutic hypothermia), were excluded.

METHODS

This multicenter retrospective study was conducted in four French ICUs: three from Pitié-Salpêtrière Hospital, Sorbonne University (one neurological and two general ICUs) and a general ICU in the Hospital of Jossigny (Hôpital Grand Est Francilien, Marne-la-Vallée). Consecutive patients admitted between, January 1, 2014, and, December 31, 2016, with an admission diagnosis of GCSE and who received mechanical ventilation on arrival to the ICU were included. Patients aged < 18 years; those with anoxia or acute traumatic brain injury; those transferred from another ICU; and those included in a therapeutic trial on SE (the only ongoing therapeutic trial on SE during this period was the VALSE Study, ClinicalTrials.gov NCT01791868) were excluded. The study was approved by our local ethics committee (CE SRLF Number 19-14). The requirement for informed consent was waived in owing to the retrospective nature of this study.

DEFINITIONS

GCSE was defined as an overt generalized convulsive seizure lasting for > 5 min or recurring seizures without return to normal consciousness (i.e., response to simple orders) between the seizures [16]. A single convulsive seizure was defined as a convulsive seizure lasting for < 5 min; repetitive convulsive seizures were defined as serial overt convulsive seizures with return to normal consciousness between each seizure; psychogenic non-epileptic seizures (PNESs) were

defined as paroxysmal pseudo-convulsive symptoms not caused by epileptic activity; and coma was defined by the absence of an appropriate response to painful stimuli (absence of a localizing response or defensive movements) or a Glasgow Coma Scale score of ≤ 7 . Refractory GCSE was defined as overt GCSE persisting after first- and second-line antiepileptic treatments (i.e., persistent convulsions lasting for 30 min after initiation of the drip of the second-line antiepileptic drug). Importantly, the following patients were not classified as having refractory GCSE: patients who were treated with general anesthesia for persistent convulsive seizures without prior first- and second-line antiepileptic treatments and comatose patients whose convulsions had stopped (spontaneously or after a first/second-line treatment) and who were intubated for airway protection. Non-convulsive status epilepticus (NCSE) could not be assessed in the absence of electroencephalogram (EEG) in the pre-hospital setting.

DATA COLLECTION

Electronic and handwritten medical records (including pre-hospital reports) were reviewed. The general characteristics evaluated included age, sex, weight, history of epilepsy, chronic alcoholism, and the simplified acute physiological score (SAPS II) [17]. A retrospective diagnosis was adjudicated by two neurologists (S.D. and S.Z.) for each patient based on the findings of the analysis of the medical records. The diagnosis categories were non-refractory GCSE, refractory GCSE, single or repetitive convulsive seizures, and PNES. The status epilepticus severity score (STESS, range: 0–6 [18]) and the etiology of SE (classified as acute, progressive, remote, SE in defined electroclinical syndromes, or unknown [16]) were also evaluated. Regarding pre-hospital management of SE, data on the delay of the first-line antiepileptic treatment, drugs and their doses, order of administration of the antiepileptic treatment lines, efficiency of the treatments in stopping convulsive seizures, and reason for intubation were collected. Regarding ICU stay, the data recorded included the time of admission to the ICU, anesthetic drugs used during the first 24 h in the ICU, duration of general anesthesia before initiation of weaning, and

duration of weaning until complete withdrawal of general anesthesia or the need to increase general anesthesia, and EEG data (continuous EEG or first spot EEG). The prognostic parameters studied included the relapse of SE in the ICU (defined as clinical or electrical SE diagnosed during ICU stay), length of stay in the ICU, duration of mechanical ventilation, complications during ICU stay, functional state on discharge from the ICU (based on the clinical description at the time of discharge from the ICU), and ICU death.

STATISTICS

Statistical analyses were conducted using the R software version 3.5.1, with R studio version 1.1.463. Qualitative variables were described as counts and percentages and quantitative variables as medians and first-, third-quartile values (non-normal distribution) or means and standard deviations (normal distribution). The non-parametric Wilcoxon–Mann–Whitney test was used to compare the non-normally distributed quantitative variables between the two groups of patients. For the SAPS II, which had a normal distribution, Student’s t-test was used. Associations between the qualitative variables were assessed using Fisher’s exact test or the Fisher–Freeman–Halton test in case of variables with more than two modalities. The significance threshold was set at p-values of < 0.05 . An available case analysis was performed to address the missing data.

RESULTS

CLINICAL CHARACTERISTICS AND RATE OF REFRACTORY GCSE

Among the 154 patients initially evaluated, 98 were included (Figure 1). Their median age was 55.5 years; 70.4% of them were men, and 54.1% had a known history of epilepsy. The median [Q1–Q3] STESS score was 3 [2–4], and the mean (\pm standard deviation) SAPS II was 51.4 ± 14.8 (Table 1).

	All samples (n = 98)
Age (years)	55.5 [40.0, 65.0]
Sex (male)	69 (70.4%)
Chronic alcoholic intoxication	23 (23.5%)
STESS^a	
Consciousness	
-Alert or somnolent/confused	4 (4.1%)
-Stuporous or comatose	94 (95.9%)
Worst seizure type	
-simple focal, complex focal, absence, myoclonic	0 (0.0%)
-generalized convulsive	98 (100.0%)
-non-convulsive SE in coma	0 (0.0%)
Age	
-< 65 years	70 (71.4%)
-≥ 65 years	28 (28.6%)
History of seizures	
-Yes	53 (54.1%)
-No or unknown	45 (45.9%)
TOTAL STESS	3.0 [2.0–4.0]
SAPS II	51.4 (± 14.8)

Table 1: Clinical characteristics of the patients at the time of initial management

^aranging from 0 (best) to 6 (worst)

Notes: Data are expressed as medians [first quartile to third quartile] for the continuous variables, except for the SAPS II, which is expressed as means (± standard deviations), and as numbers (percentages) for the categorical variables.

Abbreviations: SAPS, simplified acute physiological

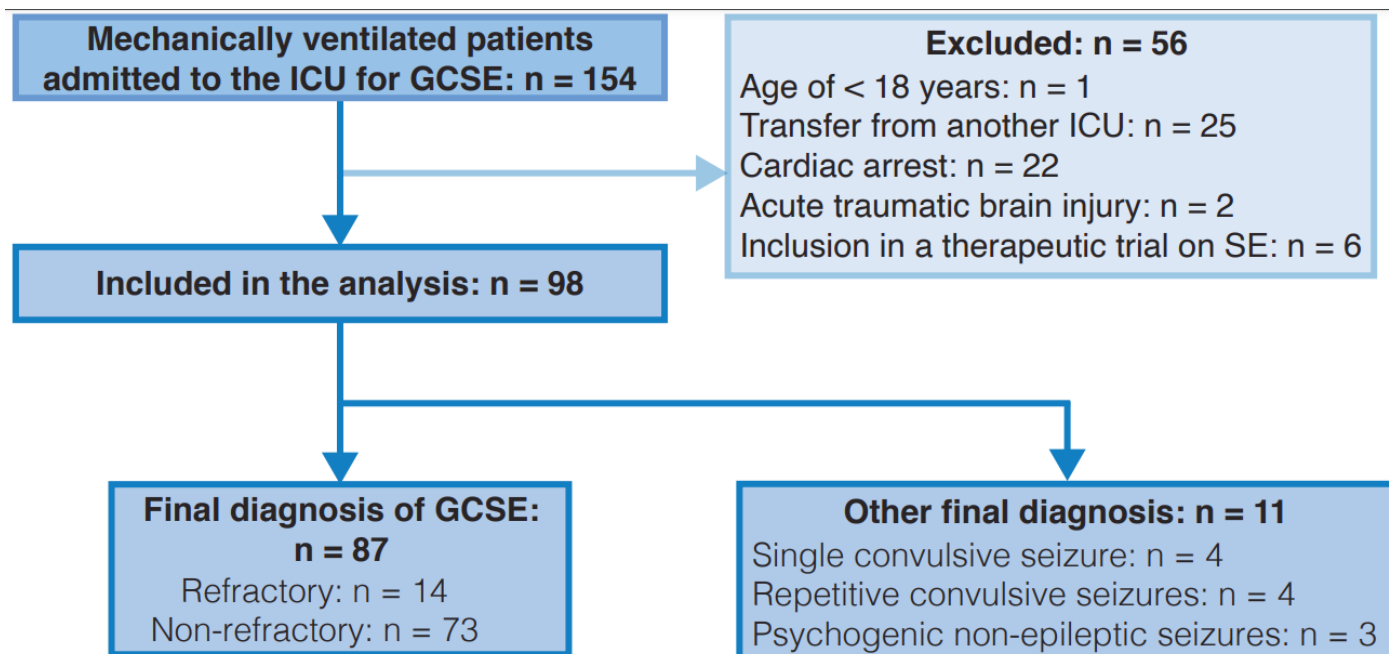


Figure 1: Flowchart of the study

Abbreviations: GCSE, generalized convulsive status epilepticus; ICU, intensive care unit; SE, status epilepticus.

	History of epilepsy (n = 48)	No history of epilepsy (n = 39)
Type of etiology (ILAE)		
Acute	32/47 (68.1%)	19/33 (57.6%)
Remote	25/47 (53.2%)	10/33 (30.3%)
Progressive	4/47 (8.5%)	9/33 (27.3%)
SE in electroclinical syndromes	0/47 (0.0%)	0/33 (0.0%)
Unknown	1/47 (2.1%)	0/33 (0.0%)
Etiology		
Acute vascular lesion	2/47 (4.3%)	7/38 (18.4%)
Chronic vascular lesion	10/47 (21.3%)	7/38 (18.4%)
Tumor	5/47 (10.6%)	6/38 (15.8%)
Other lesions	0/47 (0.0%)	2/38 (5.3%)
Trauma sequela	5/47 (10.6%)	1/38 (2.6%)
Other sequelae	7/47 (14.9%)	0/38 (0.0%)
Cerebral infection	0/47 (0.0%)	2/38 (5.3%)
Extracerebral infection	1/47 (2.1%)	0/38 (0.0%)
Inflammation	0/47 (0.0%)	1/38 (2.6%)
Metabolic	1/47 (2.1%)	4/38 (10.5%)
AED withdrawal	23/47 (48.9%)	0/38 (0.0%)
Pro-epileptogenic drug	1/47 (2.1%)	0/38 (0.0%)
Alcohol misuse or withdrawal	8/47 (17.0%)	6/38 (15.8%)
Other toxic	1/47 (2.1%)	4/38 (10.5%)
Sleep deprivation	4/47 (8.5%)	0/38 (0.0%)
None	1/47 (2.1%)	5/38 (13.2%)

Table 2: Etiologies of generalized convulsive SE

Notes: SE could be related to more than one etiology; the difference in the denominator between each category from the number of the total population is attributed to the missing data.

Abbreviations: ILAE, International League Against Epilepsy; SE, status epilepticus.

Eighty-nine percent (n = 87/98) of the patients had a retrospective diagnosis of GCSE. Of these cases, 16.1% were refractory (n = 14/87), i.e. underwent general anesthesia owing to persistent convulsions after the first- and second-line treatments. Eleven percent of the patients did not meet the criteria for refractory GCSE: 36.4% (n = 4/11) had a single convulsive seizure; 36.4% (n = 4/11) had repetitive convulsive seizures; and 27.3% (n = 3/11) had PNES (new diagnosis on video EEG [n = 2] or recurrence of known PNES [n = 1]). The etiology of GCSE was acute symptomatic in 63.8% (n = 51/80), remote in 43.8% (n = 35/80), and progressive in 16.3% (n = 13/80, missing data: n = 7). Among the patients with GCSE who had a history of epilepsy, the main etiology was withdrawal of the usual antiepileptic treatment in 48.9% (n = 23/47); 4.3% (n = 2/47) had an acute

vascular lesion (spontaneous intracerebral hemorrhage: n = 1, acute ischemic stroke: n = 1) (Table 2).

PRE-HOSPITAL MANAGEMENT

The median [Q1–Q3] first-line treatment delay duration was 45 min (17.3–65.0 min), and the majority of the patients were still convulsing upon arrival of medical assistance (79.8%, n = 75/94, missing data: n = 4). They all received an initial treatment with benzodiazepines, which stopped the convulsions in 45.3% (n = 34/75). Twenty-nine percent (n = 12/41) of the patients who had benzodiazepine-refractory convulsions received a third-line treatment immediately, which yielded complete resolution of convulsions. Seventy percent (n = 29/41) received a second-line treatment, which failed in 55.2% (n = 16/29, Figure 2); thus, a third-line treatment (general anesthesia)

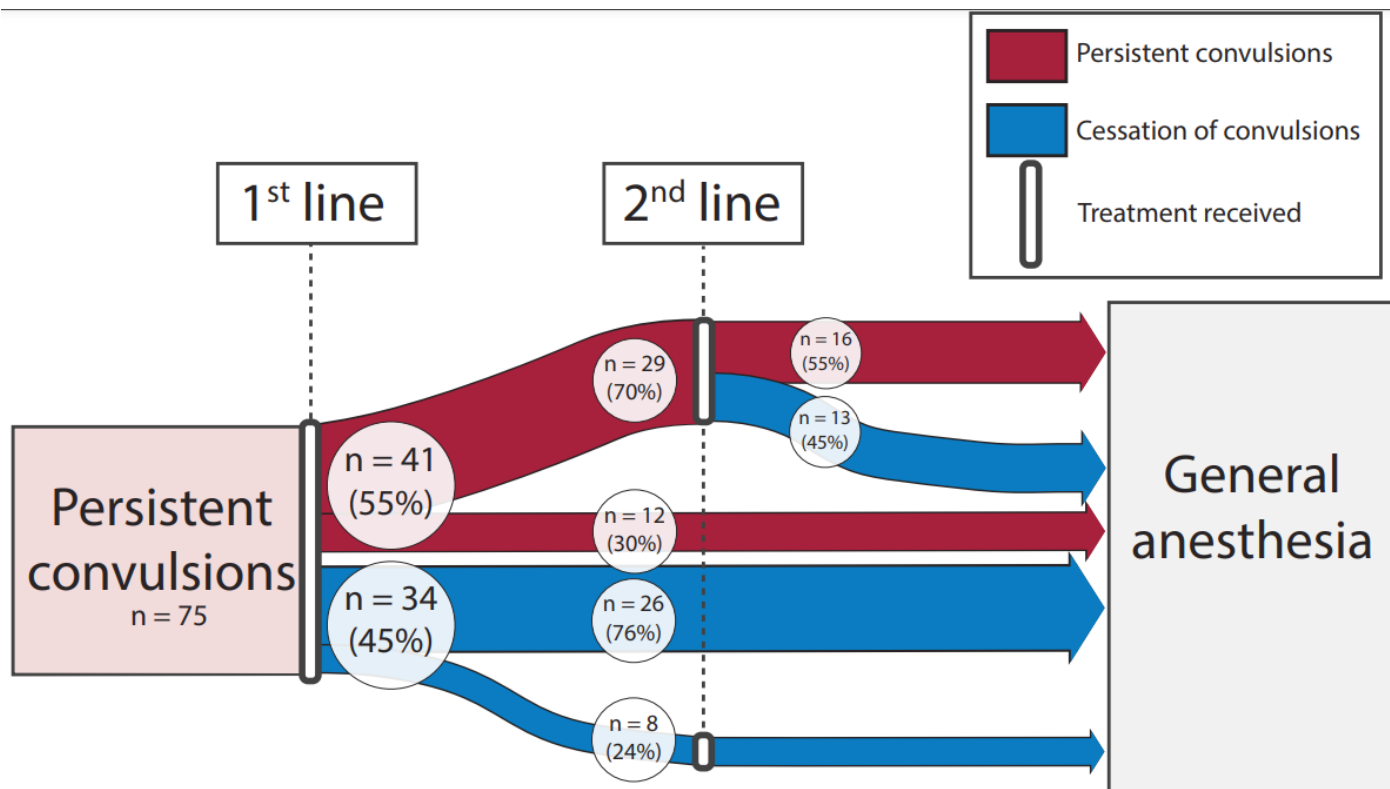


Figure 2: Pre-hospital management in the patients with persistent convulsions (n = 75)

was initiated, which yielded complete resolution of convulsions: Fourteen patients had refractory GCSE, and two were eventually diagnosed with PNES in the ICU. Finally, among the patients with confirmed GCSE who had persistent convulsions upon arrival of medical assistance (n = 67/83, missing data: n = 4), 46.3% (n = 31/67) were treated in accordance with the guidelines (first- and second-line antiepileptic treatments before the third- line treatment); 45.2% (n = 14/31) fulfilled the diagnostic criteria for refractory GCSE.

Nineteen patients stopped convulsing before arrival of the mobile ICU; 15.8% (n = 3/19) underwent intubation and general anesthesia immediately for coma. Seventy-nine percent (n = 15/19) received a benzodiazepine, followed by a second-line antiepileptic drug in 60.0% (n = 9/15), and were finally intubated for coma (93.3%, n = 14/15) or hypoxia (6.7%, n = 1/15) (Figure A.1).

Data were missing in five patients, either regarding the persistence of convulsions on arrival of medical assistance (n = 4) or regarding initial antiepileptic treatment before general anesthesia (n = 1, Figure A.1). For these five patients, GCSE was

indicated in the medical records before the arrival of medical assistance, and none of them had persistent convulsions at the time of initiation of general anesthesia. Therefore, these five patients were classified as having non-refractory GCSE.

The doses of the second-line antiepileptic drugs were not significantly different between the patients with refractory and non-refractory GCSE (Table 3); they were inferior to the recommended doses in 86.0% of the treated patients (n = 49/57, missing data: n = 7) and in 75.0% of the patients with refractory GCSE (n = 9/12, missing data: n = 2). The first-line treatment delay duration was shorter in the patients with refractory GCSE than in those with non-refractory GCSE, not significantly (30.0 [12.5–55.0] and 47.5 [30.0–65.0] min, p = 0.314).

General anesthesia was initiated mostly for mechanical ventilation for airway protection in cases of coma (58.9%, n = 56/95) and less frequently for persistent convulsions (29.5%, n = 28/95), followed by aspiration or hypoxia (5.3%, n = 5/95) or safety of brain imaging (1.1%, n = 1/95). Data were missing for three patients. The drugs

used for anesthesia were mostly midazolam (71.1%, n = 64/90), followed by propofol (18.9%, n = 17/90) and thiopental (10.0%, n = 9/90, missing data: n = 8) (Table 3).

MANAGEMENT IN THE ICU

The patients were mostly admitted to the ICU during nights or weekends (59.2%, n = 58/98). General anesthesia was withdrawn on arrival to the intensive care unit in 10.2% (n = 10/98). For the other patients, the anesthetic used during the first 24 h hours in the ICU was mostly propofol (76.1%, n = 67/88), followed by midazolam (38.6%, n = 34/88) and thiopental (2.3%, n = 2/88). Fifteen patients were treated with two different anesthetic drugs during their first 24 h hours in the ICU. The median [Q1–Q3] duration of general anesthesia before initiation of weaning was 12.3 h (5.0–18.0 h). The withdrawal of general anesthesia was abrupt in 60.2% of the patients (n = 59/98); otherwise, the median [Q1–Q3] duration of weaning was 10.0 h (5.0–20.5 h). Only 7.1% of the patients underwent continuous EEG monitoring (n = 7/98, all from the neurological ICU of Pitié-Salpêtrière Hospital, which was the only center with access to this equipment). The median [Q1–Q3] delay duration between admission to the ICU and the first EEG was 17.0 h (9.5–24.0 h), with a minimal delay of 1 h and a maximal delay of 96 h after admission. Fifteen patients had no EEG data in the ICU (11 had a known history of epilepsy).

EVOLUTION

There were no cases of super-refractory convulsive SE (i.e., persistent convulsions after at least 24 h of general anesthesia) in our cohort. Seven patients had a relapse of SE in the ICU (Table 4): four of them had focal SE or GCSE, and three had non-convulsive SE diagnosed on EEG only. All of these cases of relapse of SE occurred after complete withdrawal of general anesthesia, which was abrupt in six patients and gradual over 7.5 h for the other patient. None of the patients with SE relapse had a known history of epilepsy (vs. 58.2% [n = 53/91] of the relapse-free patients, p = 0.003). The patients with relapse had a significantly higher STESS (5 [3.5, 5.0] vs. 3 [2.0, 3.0], p = 0.003) that persisted without the item “history of

epilepsy” (p=0.017) and a higher SAPS II (65.7 (± 14.7) vs. 50.3 (± 14.3), p = 0.032) than those without. The median [Q1–Q3] duration of general anesthesia before weaning was not different between the patients with and without relapse (13.0 h [6.8–13.5 h] vs. 12.0 h [5.0–19.5 h], p = 0.362). Complications occurred in the ICU in 63.3% of the patients (n = 62/98), which mostly included aspiration pneumonia (46.8%, n = 29/62), followed by severe hypotension requiring vasopressors (27.4%, n = 17/62), ventilation-associated pneumonia (9.7%, n = 6/62), and acute respiratory distress syndrome (4.8%, n = 3/62). Two patients died in the ICU: one after withdrawal of care (owing to the underlying neurological disease) and one from septic shock (underlying severe immunodepression). Most of the patients recovered to their previous functional state upon discharge from the ICU (67.7%, n = 65/96, Table 4). The patients with a functional deficit on discharge from the ICU tended to be older and have higher STESS and SAPS II scores than did the patients who recovered to their baseline functional state. The etiologies were different between these two groups, with a more frequent progressive etiology in the group with functional deficit and a more frequent remote etiology in the group that recovered to their baseline functional state (Table A.1).

DISCUSSION

In this study, we focused on mechanically ventilated patients admitted to the ICU for an initial diagnosis of GCSE, a common situation that is not specifically addressed in the literature, and found that 16% of the cases of confirmed GCSE were refractory, while 11.2% of the whole cohort did not fulfill the definition of GCSE.

This 16% rate of refractory GCSE is important to consider when designing prospective trials in the ICU, as it might account for negative results of an intervention [15] and for difficulty in recruiting patients with refractory SE [19]. However, this rate may have been misestimated: 42.9% (n = 12/28) of the patients who underwent general anesthesia for persistent convulsions had only received a first-line treatment; therefore, it is impossible to know

	Total population (n = 98)	NRGCSE (n = 73)	RGCSE (n = 14)	p
First-line	94/98 (95.9%)	71/73 (97.3%)	14 /14 (100.0%)	
Clonazepam	82/94 (87.2%)	62/71 (87.3%)	11/14 (78.6%)	0.408
Dose (mg/kg)	0.014 [0.012–0.017]	0.015 [0.012–0.017]	0.013 [0.012–0.016]	0.382
Diazepam	12/94 (12.8%)	9/71 (12.7%)	3/14 (21.4%)	0.408
Dose (mg/kg)	0.14 [0.12–0.16]	0.13 [0.11–0.14]	0.15 [0.14–0.16]	0.373
Second-line	64/98 (65.0%)	43/73 (58.9%)	14/14 (100.0%)	
Fosphenytoin	48/64 (75.0%)	32/43 (74.4%)	10/14 (71.4%)	1.000
Dose (mg/kg)	15.7 [14.2–17.3]	15.2 [14.2–17.0]	17.1 [14.6–20.1]	0.341
Dose ≥ 20 mg/kg	8/41 (19.5%)	4/28 (14.3%)	3/8 (30.0%)	0.168
Phenytoin	7/64 (10.9%)	6/43 (14.0%)	1/14 (7.1%)	0.669
Dose (mg/kg)	17.9 [13.3–18.2]	16.6 [12.4–18.3]	17.9	1.000
Dose ≥ 20 mg/kg	0/7 (0.0%)	0/6 (0.0%)	0/1 (0.0%)	NA
Phenobarbital	6/64 (9.4%)	2/43 (4.7%)	3/14 (21.4%)	0.089
Dose (mg/kg)	10.5 [9.8–11.7]	10.0 [9.7–10.3]	12.1 [9.4–12.7]	0.800
Dose ≥ 15 mg/kg ^c	0/7 (0.0%)	0/2 (0.0%)	0/3 (0.0%)	NA
Levetiracetam ^c	3/64 (4.7%)	3/43 (7.0%)	0/14 (0.0%)	0.568
Dose (mg/kg)	15.2 [14.0–16.4]	15.2 [14.0–16.4]	NA	NA
Dose ≥ 30 mg/kg	0/2 (0.0%)	0/2 (0.0%)	NA	NA
Third-line (c-IV)	98/98 (100.0%)	73/73 (100.0%)	14/14 (100.0%)	
Midazolam	64/90 (71.1%)	51/66 (77.3%)	5/13 (38.5%)	0.030
Maximum infusion rate (mg/kg/h)	0.22 [0.06–0.31]	0.23 [0.07–0.33]	0.11 [0.02–0.26]	0.381
Propofol	17/90 (18.9%)	11/66 (16.7%)	4/13 (30.8%)	0.251
Maximum infusion rate (mg/kg/h)	0.21 [0.13–0.28]	0.24 [0.13–0.28]	0.23 [0.14–0.34]	0.661
Thiopental	9/90 (10.0%)	4/66 (6.1%)	4/13 (30.8%)	0.021
Maximum infusion rate (mg/kg/h)	0.17 [0.09–0.22]	0.15 [0.12–0.18]	0.12 [0.04–0.21]	0.886

Table 3: Pre-hospital treatment strategy

Notes: Data are expressed as medians [first quartile to third quartile] for the continuous variables and as numbers (percentages) for the categorical variables. The difference in the denominator between each category from the total population is attributed to the missing data. Abbreviations: c-IV, continuous intravenous; NA, not applicable; NRGCSE, non-refractory generalized convulsive status epilepticus; RGCSE, refractory generalized convulsive status epilepticus.

	Total cohort (n = 98)
Relapse of SE	7/98 (7.1%)
Complications during ICU stay	62/98 (63.3%)
Type of complication	
ARDS	3/62 (4.8%)
Aspiration pneumonia	29/62 (46.8%)
Central line-related bloodstream infection	1/62 (1.6%)
Severe hypotension	17/62 (27.4%)
VAP	6/62 (9.7%)
Others	6/62 (9.7%)
Mortality in the ICU	2/98 (2.0%)
Length of stay in the ICU (days)	4.0 [2.0–6.0]
Duration of mechanical ventilation (days)	2.0 [1.0–3.0]
Functional prognosis	
Return to previous functional state	65/96 (67.7%)
Cognitive disorder	14/96 (14.6%)
New neurological deficiency	11/96 (11.5%)
Worsening of pre-existing neurological deficiency	4/96 (4.2%)
Death	2/96 (2.1%)

Table 4: Evolution in the ICU

Notes: Data are expressed as medians [first quartile to third quartile] for the continuous variables and as numbers (percentages) for the categorical variables. The difference in the denominator between each category from the total population is attributed to the missing data. Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; SE, status epilepticus; VAP, ventilator-associated pneumonia.

whether they would have been refractory to a second-line treatment. Moreover, we only considered cases of refractory *convulsive* SE, and we cannot exclude the possibility that some comatose patients had *non-convulsive* SE, which is impossible to diagnose in the absence of EEG in the pre-hospital setting. In the study by DeLorenzo et al. [20], 14% of patients whose convulsive SE had been controlled had persistent NCSE diagnosed on EEG monitoring. The persistence of coma could also be related to the sedative effects of antiepileptic treatments or to a prolonged post-ictal phase. The favorable outcome, after a general anesthesia duration mostly inferior to 24 h, does not argue for a significant rate of non-convulsive refractory SE in our cohort. Among the 31 patients with confirmed and persistent GCSE who underwent the recommended protocol, 45.2% had refractory GCSE, which is comparable to that reported in the literature [21–25].

Interestingly, 75% of the patients with refractory GCSE patients received an underdosed second-line treatment, probably because in the pre-hospital setting, the weight of patients can only be estimated. In the cohort study by Rossetti et al. [26], a 37% rate of inadequation with guidelines was not associated with a worse prognosis. Data from the SENSE prospective observational registry showed that the cumulative dose of all agents applied within the first 30–60 min of treatment had a significant influence on SE cessation [27]. We could not evaluate the effect of adherence to the guidelines because patients successfully treated with first- and second-line treatments (avoiding intubation and general anesthesia) were not included; however, we cannot exclude the fact that appropriate use of a second-line treatment could have prevented some cases of refractory GCSE.

Convulsions stopped spontaneously in 19.4% of the patients, which is consistent with other study findings [28]. Many of these patients received benzodiazepines, sometimes with a second-line treatment, and were eventually intubated for prolonged coma. This practice may be motivated by the fear of seizure recurrence or persistent non-convulsive SE. In cases of spontaneous cessation of convulsions after GCSE, two risks must be evaluated: undertreat non-convulsive SE or

intubate and expose a patient to the complications of general anesthesia [29] in the post-ictal phase. The French expert guidelines advocate for abstention from immediate antiepileptic treatment in patients whose convulsions stop spontaneously and recommend urgent EEG in case of suspicion of non-convulsive SE before escalating antiepileptic treatment [11]. The development of out-of-hospital EEG caps to rule out non-convulsive SE [30] may facilitate therapeutic decision-making.

The majority (58.9%) of the patients were intubated for airway protection in cases of coma setting. In addition to specific etiologies of GCSE requiring sedation (such as severe acute traumatic brain injury or cardiac arrest), the French expert guidelines emphasize the necessity to restrict general anesthesia and mechanical ventilation to persistent convulsions after the first- and second-line treatments and to respiratory distress [11]. The generalization of simplified therapeutic algorithms, such as those from the French expert guidelines [11], may promote this approach.

Interestingly, 11.2% of the patients did not present GCSE and had either a single or repetitive convulsive seizure or PNES. This is consistent with data from the ESETT trial, which reported a 10% rate of PNES [31] and shows how difficult case ascertainment can be in the pre-hospital emergency setting.

The duration of general anesthesia in ICU was mostly inferior to 24h, even in patients with refractory GCSE. Propofol was preferred to midazolam and barbiturates in the ICU, probably because of its shorter half-life [12]. Only 7.1% of the patients had continuous EEG monitoring, with a center effect: they were all from the specialized neurological ICU in Pitié-Salpêtrière Hospital. This shows the gap between guidelines, which recommend continuous EEG monitoring to manage general anesthesia, and the poor access to this equipment. This problem is not limited to our country, as shown in an English study reporting continuous EEG monitoring in 33% of 55 ICUs [32].

Most of the patients had a favorable outcome, and only 7.1% had a relapse of SE in the ICU. They did not have a shorter duration of sedation than the relapse-free patients, and none of

them had a known epilepsy, which outlines the higher severity of *de novo* SE [21]. The low mortality rate in the ICU (2.0%) is probably linked to the exclusion of post-anoxic SE and acute traumatic brain injury and to the young age of our patients (median: 55.5 years). The causes of death in our cohort were not SE but the underlying etiology.

This study had several limitations. Owing to its retrospective nature, especially for the assessment of clinical SE, some patients could have been misclassified. It is also important to be cautious in extrapolating our results, as the presence of an emergency physician in the French Emergency Medical Service system, which is not applied in other countries, can increase the use of anesthetic drugs in the early steps of management of GCSE. However, recent data suggest a change in Europe towards the growing involvement of physicians in the pre-hospital setting [33]. We cannot exclude that the use of lorazepam (which is not commercialized in France) instead of clonazepam could have modified the results; nevertheless, the efficacy of clonazepam in GCSE has been proven in a French prospective study [34], and it is the recommended and commonly used molecule for the first-line treatment of GCSE in France. Moreover, the limited number of patients with refractory GCSE (n = 14) in our study implies caution regarding the interpretation and generalization of our results in this subgroup.

CONCLUSION

This retrospective study showed that among the patients admitted to the ICU under mechanical ventilation for confirmed GCSE, 16% had refractory convulsive SE, and most patients had been intubated for coma. A significant proportion of patients did not receive appropriate first- and second-line treatment prior to general anesthesia. These results are important to consider, as better adherence to treatment guidelines could reduce the proportion of patients needing management in the ICU and its associated complications through mechanical ventilation and general anesthesia. Further clinical trials on patients with SE admitted to the ICU should also consider this heterogeneity.

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Ethical approval: We have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The study was approved by our local ethics committee (CE SRLF Number 19-14). The requirement for informed consent was waived in owing to the retrospective nature of this study.

REFERENCES

- [1] Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive status epilepticus in California. *Neurology* 2002;58:1070–6.
- [2] DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 1996;46:1029–35.
- [3] Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus. *Ann Neurol* 1998;44:908–12. <https://doi.org/10.1002/ana.410440609>.
- [4] Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. *Neurocrit Care* 2014;20:476–83. <https://doi.org/10.1007/s12028-013-9935-x>.
- [5] Pichler M, Hocker S. Management of Status Epilepticus. *Handbook of Clinical Neurology*, vol. 140, E.F.M. Widjicks and A.H. Kramer; 2017.
- [6] Logroscino G, Hesdorffer DC, Cascino G, Hauser WA, Coeytaux A, Galobardes B, et al. Mortality after a first episode of status epilepticus in the United States and Europe. *Epilepsia* 2005;46 Suppl 11:46–8. <https://doi.org/10.1111/j.1528-1167.2005.00409.x>.
- [7] Lai A, Outin HD, Jabot J, Mégarbane B, Gaudry S, Coudroy R, et al. Functional outcome

- of prolonged refractory status epilepticus. *Crit Care* 2015;19:199.
<https://doi.org/10.1186/s13054-015-0914-9>.
- [8] Kantanen A-M, Reinikainen M, Parviainen I, Kälviäinen R. Long-term outcome of refractory status epilepticus in adults: A retrospective population-based study. *Epilepsy Res* 2017;133:13–21.
<https://doi.org/10.1016/j.eplepsyres.2017.03.009>.
- [9] Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr* 2016;16:48–61.
<https://doi.org/10.5698/1535-7597-16.1.48>.
- [10] Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012;17:3–23.
<https://doi.org/10.1007/s12028-012-9695-z>.
- [11] Outin H., Gueye P, Lefort H, Peigne V. Management of status epilepticus in the prehospital setting, in the emergency department and in intensive care unit. *RFE Etats de mal épileptiques 2018 – SRLF/SFMU/GFRUP CV/CI93 (srlf.org)*
- [12] Reznik ME, Berger K, Claassen J. Comparison of Intravenous Anesthetic Agents for the Treatment of Refractory Status Epilepticus. *J Clin Med* 2016;5.
<https://doi.org/10.3390/jcm5050054>.
- [13] Marchi NA, Novy J, Faouzi M, Stähli C, Burnand B, Rossetti AO. Status epilepticus: impact of therapeutic coma on outcome. *Crit Care Med* 2015;43:1003–9.
<https://doi.org/10.1097/CCM.0000000000000881>.
- [14] Adnet F, Lapostolle F. International EMS systems: France. *Resuscitation* 2004;63:7–9.
<https://doi.org/10.1016/j.resuscitation.2004.04.001>.
- [15] Legriel S, Lemiale V, Schenck M, Chelly J, Laurent V, Daviaud F, et al. Hypothermia for Neuroprotection in Convulsive Status Epilepticus. *N Engl J Med* 2016;375:2457–67.
<https://doi.org/10.1056/NEJMoa1608193>.
- [16] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015;56:1515–23.
<https://doi.org/10.1111/epi.13121>.
- [17] Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;270:2957–63.
- [18] Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. *J Neurol* 2008;255:1561–6. <https://doi.org/10.1007/s00415-008-0989-1>.
- [19] Rossetti AO, Milligan TA, Vulliémot S, Michaelides C, Bertschi M, Lee JW. A randomized trial for the treatment of refractory status epilepticus. *Neurocrit Care* 2011;14:4–10.
<https://doi.org/10.1007/s12028-010-9445-z>.
- [20] DeLorenzo RJ, Waterhouse EJ, Towne AR, Boggs JG, Ko D, DeLorenzo GA, et al. Persistent Nonconvulsive Status Epilepticus After the Control of Convulsive Status Epilepticus. *Epilepsia* 1998;39:833–40.
<https://doi.org/10.1111/j.1528-1157.1998.tb01177.x>.
- [21] Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. *Epilepsia* 2010;51:251–6.
<https://doi.org/10.1111/j.1528-1167.2009.02323.x>.
- [22] Giovannini G, Monti G, Tondelli M, Marudi A, Valzania F, Leitinger M, et al. Mortality, morbidity and refractoriness prediction in status

epilepticus: Comparison of STESS and EMSE scores. *Seizure* 2017;46:31–7.

<https://doi.org/10.1016/j.seizure.2017.01.004>.

[23] Delaj L, Novy J, Ryvlin P, Marchi NA, Rossetti AO. Refractory and super-refractory status epilepticus in adults: a 9-year cohort study. *Acta Neurol Scand* 2017;135:92–9.

<https://doi.org/10.1111/ane.12605>.

[24] Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J Neurol Neurosurg Psychiatry* 2005;76:534–9.

<https://doi.org/10.1136/jnnp.2004.041947>.

[25] Vooturi S, Jayalakshmi S, Sahu S, Mohandas S. Prognosis and predictors of outcome of refractory generalized convulsive status epilepticus in adults treated in neurointensive care unit. *Clin Neurol Neurosurg* 2014;126:7–10.

<https://doi.org/10.1016/j.clineuro.2014.07.038>.

[26] Rossetti AO, Alvarez V, Januel J-M, Burnand B. Treatment deviating from guidelines does not influence status epilepticus prognosis. *J Neurol* 2013;260:421–8. <https://doi.org/10.1007/s00415-012-6644-x>.

[27]... Kellinghaus C, Rossetti AO, Trinka E, Lang N, May TW, Unterberger I, et al. Factors predicting cessation of status epilepticus in clinical practice: Data from a prospective observational registry (SENSE). *Ann Neurol* 2019;85:421–32.

<https://doi.org/10.1002/ana.25416>.

[28] Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N*

Engl J Med 2001;345:631–7.

<https://doi.org/10.1056/NEJMoa002141>.

[29] Sutter R, Marsch S, Fuhr P, Kaplan PW, Rüegg S. Anesthetic drugs in status epilepticus: risk or rescue? A 6-year cohort study. *Neurology* 2014;82:656–64.

<https://doi.org/10.1212/WNL.000000000000009>.

[30] McKay J, Feyissa A, Sener U, D'Souza C, Smelick C, Spaulding A, et al. Time Is Brain: The Use of EEG Electrode Caps to Rapidly Diagnose Nonconvulsive Status Epilepticus. *Journal of Clinical Neurophysiology* 2019;36:460–6.

<https://doi.org/10.1097/WNP.0000000000000603>.

[31] Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. *N Engl J Med* 2019;381:2103–13.

<https://doi.org/10.1056/NEJMoa1905795>.

[32] Patel M, Bagary M, McCorry D. The management of Convulsive Refractory Status Epilepticus in adults in the UK: No consistency in practice and little access to continuous EEG monitoring. *Seizure* 2015;24:33–7.

<https://doi.org/10.1016/j.seizure.2014.11.005>.

[33]..Seblova J, Cimpoesu D, Khoury A, Revue E, Trenkler S. Prehospital emergency care systems in Europe - EuSEM prehospital section survey 2016. *Eur J Emerg Med* 2018;25:446–7.

<https://doi.org/10.1097/MEJ.0000000000000553>.

[34] Navarro V, Dagrón C, Elie C, Lamhaut L, Demeret S, Urien S, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus

(SAMUKeppra): a randomised, double-blind, phase 3 trial. *Lancet Neurol* 2016;15:47–55.

[https://doi.org/10.1016/S1474-4422\(15\)00296-3](https://doi.org/10.1016/S1474-4422(15)00296-3).

Supplementary data:

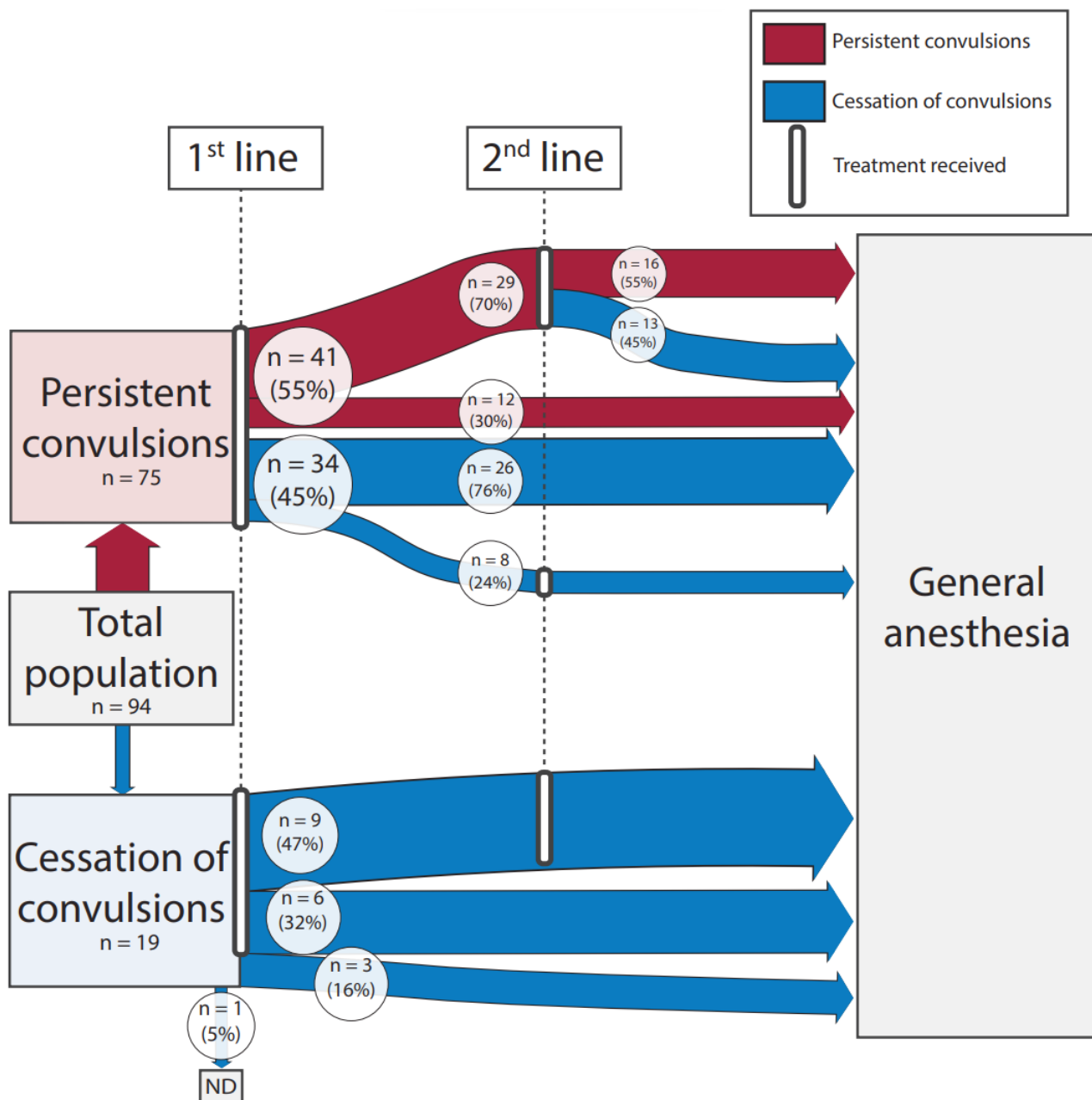


Figure A.1: Pre-hospital management according to the persistence of convulsions (n = 94, missing data: n = 4)
 Notes: ND: detailed treatment strategy not determined owing to missing data

	Functional deficit (n = 29)	Return to baseline (n = 65) ^a	p
Age (years)	66 [53–75]	48 [35–62]	< 0.001
Sex (male)	20 (69.0%)	47 (72.3%)	0.807
Alcoholism	8 (27.6%)	15 (23.1%)	0.903
STESS	4 [3–5]	2 [2–3]	< 0.001
SAPS II	55.8 (± 14.6)	48.5 (± 13.8)	0.027
Etiology			
Acute	15 (51.7%)	22 (33.8%)	0.115
Remote	3 (10.3%)	27 (41.5%)	0.004
Progressive	9 (31.0%)	5 (7.7%)	0.009
SE in electroclinical syndromes	0 (0.0%)	0 (0.0%)	NA
Unknown	0 (0.0%)	1 (1.5%)	1.000
Refractory GCSE	2 (6.9%)	11 (16.9%)	0.332
Complications during ICU stay	21 (72.4%)	39 (60.0%)	0.353

Table A.1: Characteristics of the patients according to the persistence of functional deficits on discharge from the ICU

^aTwo patients died, and two patients had missing data regarding functional state on discharge from the ICU.

Notes: Data are expressed as medians [first quartile to third quartile] for the continuous variables, except for the SAPS II, which is expressed as mean (± standard deviation), and as numbers (percentages) for the categorical variables.

Abbreviations: GCSE, generalized convulsive status epilepticus; ICU, intensive care unit; SAPS, simplified acute physiological score; SE, status epilepticus; STESS, status epilepticus severity score

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2
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