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Authors: Delaj L, Novy J, Ryvlin P, Marchi NA, Rossetti AO

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Refractory and super-refractory status epilepticus in adults: a 9-year cohort study.

Laureta Delaj [1,2], MD, Jan Novy [1], MD, PhD, Philippe Ryvlin [1], MD, Nicola A. Marchi MD[1], Andrea O. Rossetti [1], MD

[1] Service de neurologie, Département des neurosciences cliniques, CHUV and University of Lausanne, Lausanne Switzerland

[2] Unità operativa di Neurologia, Dipartimento Emergenza-Urgenza, Medicina Generale e Specialistica, Azienda Ospedaliero-Universitaria di Parma, Italy.

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Address correspondence to:

Dr Andrea Rossetti

Neurologie, CHUV BH07

CH-1011-Lausanne

andrea.rossetti@chuv.ch

SUMMARY

Objective: While status epilepticus (SE) persisting after two antiseizure agents is called refractory (RSE), super-refractory status epilepticus (SRSE) defines SE continuing after general anesthesia. Its prevalence and related clinical profiles have received limited attention, and most studies were restricted to intensive care facilities. We therefore aimed at describing RSE and SRSE frequencies, and identifying associated clinical variables.

Methods: Between 2006 and 2015, consecutive adult SE episodes were prospectively recorded in a registry. Occurrence of RSE and SRSE and their relationship to clinical variables of interest, including outcome, were analysed.

Results: Of 804 SE episodes 268(33.3%) were RSE, and 33(4%) SRSE. Coma induction for SE treatment occurred in 79 (9.8%) episodes. Severe consciousness impairment (OR 1.67; 95%CI 1.24–2.46; p=0.001), increasing age (OR 1.01, 95%CI 1.01-1.02), and lack of remote symptomatic SE aetiology (OR 0.48; 95%CI 0.32–0.72) were independently associated with RSE, while severe consciousness impairment (OR 4.26; 95%CI 1.44-12.60) and younger age (OR 0.96; 95%CI 0.95-0.99) correlated with SRSE; however, most SRSE episodes were not predicted by these variables. Mortality was 15.5% overall, higher in RSE (24.5%) and SRSE (37.9%) than in non-refractory SE (9.8%) ($p<0.001$).

Significance: SRSE appears clearly less prevalent in this cohort than previously reported, probably since it is not restricted to intensive care unit. SRSE emerges in younger patients with marked consciousness impairment, pointing to the underlying severe clinical background, but these variables do not predict most SRSE developments. There is currently a knowledge gap for prediction of SRSE occurrence that needs to be filled.

INTRODUCTION

Status epilepticus (SE) is a potentially severe neurological emergency, with an annual incidence in Europe of 10–16 per 100.000 population, carrying a risk of major morbidity and mortality [1,2]. Its persistence despite first and second-line administration of antiepileptic drugs (AED), referred to as "refractory" SE (RSE), occurs in 14 – 46% of cases [3-14]. Super-refractory SE (SRSE) was recently defined as a refractory episode continuing despite 24 hours of general anaesthesia [15], and has been reported to occur in 12 – 26% of SE and in 13 – 42% of RSE [4,6,7,9,16,17]. Available estimations of both RSE and SRSE incidence primarily rely on retrospective studies conducted in Intensive Care Units (ICUs) [3,6,16,18,19] or in developing countries [9,10,17], with heterogeneous designs accounting for their variability. Only one prospective hospital-based study from Argentina reports a lower SRSE rate (5%) [8].

Management of RSE and SRSE is challenging, as it requires balancing the benefit and risks of treatment used to rapidly control seizures [20]. Recent data reported that drug-induced coma may be associated with a poorer outcome [6,21,22]. However, other studies challenge this view, considering that inadequate or delayed treatment could represent an independent risk of mortality [23,24]. Short-term SE mortality in Europe ranges between 11-37% in hospital-based studies, including ICU-limited settings [3,4,6,12,14]. The main predictors of fatal SE are older age, life-threatening aetiologies, and possibly the degree of impairment of consciousness and SE duration [3,12,13]. Mortality rates increase up to 15 – 54% among patients with RSE and SRSE [3-6,9,11,13,19,24], stressing the severity of these conditions.

A refined knowledge of RSE and SRSE epidemiology may help individualizing therapy according to the episode prognosis. Therefore, our primary aim was to determine the frequency of RSE and SRSE in a large hospital-based cohort population, not limited to the ICU, and subsequently, to identify clinical variables, including outcome, associated with their occurrence.

METHODS

Study design and setting

This is a retrospective analysis of prospectively collected data from a registry of consecutive adult patients (≥16 years old) with SE treated in our hospital (CHUV) between 1st April 2006 and 31st July 2015 (112 months). The CHUV represents the primary facility for the urban area of Lausanne (about 250'000 population) and a tertiary referral centre for a population of about 1'000'000. The registry is approved by the Commission cantonale d'éthique de la recherche sur l'être humain (CER-VD), a member of the Swiss Association of Ethics Committees; given its purely observational nature, informed consent is waived. The study was conducted according to the ethical principles of the Helsinki Declaration. Personal data were coded .

Patients and SE definition

All patients aged ≥16 years with SE are prospectively enrolled in our registry, the only exclusion criteria being a postanoxic aetiology, as previously described [12]. SE was defined as the occurrence of continuous or repetitive seizures, between which there is incomplete recovery of baseline clinical conditions for at least 30 minutes (until 2008) or 5 minutes (since 2008) [25]. SE episodes were diagnosed clinically by board certified neurologists, and confirmed, whenever necessary, with electroencephalography (EEG). RSE was defined if first- and second line antiepileptic treatments failed to control seizures, without a given time span, implying the need to prescribe an additional specific treatment [12]; for the purpose of this study, RSE does not include SRSE if not otherwise specified. SRSE was defined as continuous or recurrent seizures lasting 24 hours or more following administration of a first course of anesthetics for therapeutic coma induction [15].

Variables definition

The following items were prospectively recorded: demographics (gender and age, treated as a continuous variable), previous seizures, time to first SE treatment start and other relevant clinical data were noted on admission. Aetiology was classified according to the International League Against Epilepsy (ILAE) criteria, as acute symptomatic, remote symptomatic, progressive symptomatic, and idiopathic/cryptogenic [26]. SE causes were further categorized as potentially fatal aetiology or not, according to a previously established list of aetiologies known to be associated to death independently from SE [27]. Moreover, we defined inflammatory SE as caused by proven acute inflammation of the brain parenchyma, with or without involvement of meninges, associated with neurologic dysfunction, as previously reported [32]. Level of consciousness before treatment was classified as alert, confused or somnolent (arousable towards clear clinical contact), versus stuporous (arousable, but without contact), or comatose. The latter two were grouped as “severe impairment of consciousness”. SE semiology was defined by the worst clinical seizure in the given episode, and classified as simple partial (focal without impairment of consciousness), absence, myoclonic (related to genetic generalized epilepsy), complex partial (focal with impairment of consciousness), generalized convulsive (GCSE), or non-convulsive SE in coma (NCSEC). For each episode, the validated SE severity score (STESS) was calculated on admission, and categorized as < 3 versus ≥3 [28]. Prescribed AEDs (including anaesthetic drugs), load dosages and sequence of drug’s administration, including anaesthetics used for therapeutic coma induction, were recorded. The latency between onset of SE and treatment (time to treatment, TTT) was categorized as < 1 h versus ≥1 h. SE duration was categorized as lasting less or more than 30 min. Three possible outcomes were retrieved at hospital discharge: return to baseline clinical condition, new neurological disability (as compared to pre-SE clinical status), or death. The only retrospectively assessed variable was the Charlson Comorbidity Index (CCI, 17-item version) [29] and categorized in two groups: CCI = 0 versus CCI ≥ 1.

Procedures

Routine practice included complete electrolytic, metabolic, and hematologic work-up. Brain imaging (computed tomography and/or magnetic resonance) was performed in the vast majority of patients. All

subjects had at least one EEG recorded within the first 18 hours following hospital admission, while all those undergoing pharmacologically induced coma had continuous EEG monitoring. Follow-up studies, including infectious or inflammatory panels and lumbar puncture, were performed as clinically required. SE treatment followed the in-house protocol, and included following intravenous administrations: as first line, a slow bolus of lorazepam 0.1 mg/kg, clonazepam 0.015 mg/kg, or midazolam 0.15 mg/kg; as second line, phenytoin 20 mg/kg, or valproate 20-30 mg/kg, levetiracetam 20-30 mg/kg, or lacosamide 400 mg; as third line, propofol 2 mg/kg followed by 2–5 mg/kg/h and/or midazolam 0.2 mg/kg followed by 0.2–1.0 mg/kg/h, or thiopental 2-5 mg/kg followed by 1–5 mg/kg/h (see also [30]). The third line was monitored by continuous EEG, with seizure suppression or burst suppression as target, and maintained for at least 24 h before weaning off the anaesthetics over 6–12 hours. Additional treatments, such as oral topiramate and pregabalin, intravenous ketamine, ketogenic diet, immunomodulation, or hypothermia, were prescribed in selected cases. Patients were managed in intermediate care units, or in ICU if they needed coma induction.

Review of the literature

We searched for articles and abstracts on refractory and super-refractory status epilepticus. The search strategy was part of an ongoing systematic review, recently registered at PROSPERO International prospective register of systematic reviews with registration number CRD4201603334. Data on study design, setting, length of study period, as well as RSE and SRSE frequencies were reported in a table, including the present study.

Statistical analyses

We performed exploratory univariable analyses using Pearson χ^2, two-tailed Fisher's exact, Student t-test or Mann-Whitney U tests, as appropriate. Stepwise multivariable logistic regression analyses including variables associated with $p < 0.15$ in univariable analyses were then conducted. The final models were validated using the Hosmer-Lemeshow test. We estimated the 95% confidence intervals (CI) on RSE and SRSE frequencies using an exact binomial distribution. Calculation were performed with the STATA software (version 12) (StataCorp LP, College Station, TX, U.S.A.).

RESULTS

Patients and demographics

Eight hundred and four SE episodes (affecting 664 patients) were consecutively recorded in the registry during the study period; 323 (48.6%) occurred in women, while 286 patients (43.0 %) had suffered previous seizures; mean age was 61 ±18.6 years (range: 16 – 95 years). SE lasted <30 minutes in only 59 (7.3%) cases. SE aetiology was acute symptomatic in 454 episodes (56.5%), and categorized as potentially fatal in 380 (47%). Fifty-five SE episodes were related to an acute inflammatory aetiology. Two-hundred-sixty-eight (33.3%, 95% CI 30 – 37) episodes were classified as RSE (not including SRSE) and 33 (4.1%, 95% CI 2.5 –

5.7) as SRSE. A coma induction with mechanical ventilation was necessary in 83 (10.3%) SE, including all SRSE (100%), 46 RSE (17%), and four non-refractory SE (0.8%, due to SE treatment protocol violation) (**Figure 1**). While SRSE developed in 11% of refractory SE, its frequency raised to 40% among the subset of intubated patients.

Clinical variables

Comparisons between NRSE and RSE (including SRSE), and between RSE and SRSE are shown in **Tables 1 and 2**. Stepwise multiple logistic regressions showed that a severe consciousness impairment before treatment, increasing age, and the lack of remote symptomatic aetiology were independently associated with RSE. Overall, episodes in patients aged ≥65 years, with a severe impairment of consciousness and an aetiology other than "remote symptomatic" showed a likelihood of 49% (95% CI: 41 – 56%) to develop RSE, while episodes without these three variables had a likelihood of 87% (95% CI: 70 – 96%) to be non-refractoy. SRSE was independently associated to severe impairment of consciousness and younger age. The likelihood to develop SRSE was 23% (95% CI: 15-33%) for patients < 65 years old presenting a severe impairment of consciousness at SE onset.

Considering the 55 SE episodes related to an acute inflammatory aetiology (infectious or autoimmune), a higher proportion was found among SRSE episodes: 28 (6%) non-refractory SE, 21 (8%) RSE and 6 (18%) SRSE episodes ($p= 0.01$, $\chi 2$). Also, mean age of SE episodes related to acute inflammatory aetiology was significantly lower than that of episodes due to other aetiologies, respectively 54±19.9 and 61.5±18.5 years old ($p=0.005$, t-test).

Outcome at hospital discharge

Of the 664 incident patients, 103 (15.5%) died during their hospital stay; 37 of them (5.6%) during ongoing SE. Mortality among RSE (249 incident patients, including SRSE), at hospital discharge or during ongoing SE, was significantly higher when compared to non-refractory episodes (Table 1). At hospital discharge, return to baseline occurred less often in RSE (38%) and SRSE (8%) ($p<0.001$, $\chi 2$), and a new disability was also more frequent after RSE (28%) and SRSE (43.7%) ($p<0.001$, $\chi 2$), as compared to non-refractory SE.

Previously published data, addressing RSE and SRSE, are summarized in **table 3.**

DISCUSSION

This study, conducted on a large adult cohort not restricted to ICU, shows that while RSE developed in 33.3% (37% including SRSE), which appears in line with previous estimations, SRSE occurred in only 4.1%, which is clearly lower than the majority of recent data from other settings. Severe impairment of consciousness, lack of a remote symptomatic aetiology and increasing age were independently associated with SE refractoriness, whereas super-refractory episodes tended to occur more frequently in younger patients.

Our findings on RSE prevalence are in line with recently reported studies not limited to ICU [4,5,7,8,13] (**table 3**); yet, only 11% of RSE episodes fulfilled SRSE criteria. This contrasts with the few surveys addressing the frequency of SRSE, reporting a range of 12-26% [6,7,16,17], with wide confidence intervals due to small samples (**table 3**). Some of these studies were conducted in ICUs [6,16], while others in developing regions [9,17] where underlying infections are very frequent, implying possible selection biases. Our low SRSE prevalence might also reflect the relatively conservative therapeutic approach used in our centre, with a stepwise escalation of additional antiepileptic drugs (AEDs) and coma-induction in only a selected subgroup of RSE, in line with several expert opinions and recommendations [20,31]. To date, only one hospital-based study from Argentina reported a similarly low frequency of SRSE (5%, 95%CI 2.7%-7.3%) [8], supporting the finding that SRSE is a relatively uncommon condition in unselected cohorts.

We observed that short-term mortality was significantly higher in refractory SE episodes, respectively 24.5% and 37.9% among RSE and SRSE patients, broadly in line with most published data [4,5,18,19,24]. However, these figures are considerably higher than those recently reported from Finland, with respectively 6% and 10% short-term mortality in RSE and SRSE [16]. This might result from a mortality assessment performed before an early transfer to another hospital in this last study. In our cohort, one-third of deaths occurred during SE, but this rose to 73% in SRSE, suggesting greater severity of the conditions underlying SRSE. Nearly half of surviving RSE patients had a new handicap at discharge, and again disability was more frequent among RSE and SRSE patients, in line with previous studies [4,12,14].

Multivariable logistic regressions showed an independent association between a severe impairment of consciousness on admission and refractory SE. This finding is comparable to previous series [3,5,12,14], and likely reflects the severity of the underlying brain insult. Acute symptomatic aetiologies as a whole were not independently associated with RSE, in contrast with previous studies [3,12], probably because this category encompasses a wide spectrum of causes, including relatively benign metabolic disturbances or AED withdrawal. Remote symptomatic causes were found to be protective for RSE, suggesting that a static remote brain injury is less likely to trigger the process of SE refractoriness than acute brain insults.

Some previous data imply that young subjects may be at higher risk for very severe SE episodes [9,14], a finding confirmed in our analysis. How younger age leads to severe refractoriness is unclear, but recent studies suggest that this may represent a surrogate of inflammatory auto-immune causes that may be relatively frequently associated with SRSE [14,24,32]. Accordingly, a post-hoc analysis in our study showed that inflammatory aetiologies were significantly more frequent amongst SRSE episodes and younger subjects.

The variables identified in the logistic regressions allow a prediction of about one in two patients who will develop an RSE episode, but only one in five developing SRSE. It is thus striking that relatively few clinical differences are observed on admission between patients developing RSE or SRSE as compared to non-refractory episodes, suggesting that important biological substrates of SE refractoriness remain undetected.

Recent studies have stressed the epileptogenic effect of neuroinflammation and its dependence on genetically mediated mechanisms [33,34], this is supported by experimental models [35]. Also, a low serum albumin level at SE onset was recently shown to be a predictor of RSE [3]. The search for further biomarkers could open up perspective in the identification of new therapeutic targets. While co-morbidities were not considered in predictive models of SE refractoriness so far, we did not find any significant role.

Our study has some limitations. Firstly, it was a retrospective analysis of prospectively collected data. Therefore, only associations and not causation can be inferred from our findings. However, all clinical variables, except co-morbidities, were chosen a priori and collected prospectively, following a consistent protocol over years. While co-morbidities were not considered in predictive models of SE refractoriness so far, we did not find any significant role. Secondly, our cohort reflect the recruitment of a tertiary centre, potentially concentrating more severe SE episodes, and accounting for a higher short-term mortality (15.5%) than that reported in European population-based studies (i.e. 7.6-9.3%) [1,2]. Moreover, an survival bias could influence the demographics in the different subgroups, if patients with extremely severe SE would die prior to their admission; however, in our experience, SE patients very rarely die out of hospital. Thirdly, accordingly to the observational design of our study, decision on coma induction for SE treatment relied on patient's caregiver. Previous studies including this cohort confirm a similar low rate of coma-induction, implying generally accepted guidelines amongst CHUV clinicians on a step-wise SE treatment [22, 12, 28]. Thus, these findings may be applied to hospital settings with an analogous therapeutic approach of SE. Fourth, the database for the present study lacked data on treatment compliance towards recommendations, and therefore we did not analyze this aspect; of note, a subgroup analysis of this cohort showed that treatment appropriateness did not influence clinical outcome [30]. Finally, continuous EEG was not performed systematically after electro-clinical resolution of SE, potentially resulting in undetected non-convulsive SE recurrence. However, we believe this risk to be low since most patients underwent repetitive EEGs and all SRSE patients were monitored with continuous EEG.

In conclusion, to our knowledge this represents by far the largest cohort of adult SE patients prospectively collected over more than a 9-year period, not restricted to an ICU environment or to settings in developing regions labelled with very high proportions of infections. One-third of SE episodes became refractory to first and second line treatments, while SRSE remained relatively rare, affecting only 4% of all SE episodes. SE refractoriness is likely to be multifactorial with still largely unknown mechanisms. Further studies are needed in order to refine a predictive model of SE super-refractoriness, ideally delineating plausible biological and genetic biomarkers; this may prove very useful for patient care in this conditions, still hampered by considerable morbidity and mortality.

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DISCLOSURE OF CONFLICTS OF INTERESTS

None of the authors has any conflict of interest to disclose.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1. Demographics and clinical features in non-refractory and refractory SE (with super-refractory SE included)

	Univariate analysis						Multiple stepwise logistic regression**		
	NRSE episodes (n=503)		RSE episodes (n=301)		p-value	Test	OR	95% CI	P-value
Demographics*									
Incident SE patients (nr, %)	415	62.5%	249	37.5%					
Age (years) (mean, SD)	60	±19	62	±19	0.13	Student t	**1.01**	**1.01-1.02**	**0.039**
Female gender (nr, %)	206	49.6%	117	47.0%	0.508	Pearson $\chi 2$			
Earlier seizures (nr, %)	192	45.9%	94	37.9%	0.097	Pearson $\chi 2$			
Charlson Comorbidity Index (CCI) (median [range])	1	0-12	1	0-12	0.13	U-test			
CCI 0 (nr, %)	210	41.7%	103	34.2%					
CCI ≥1 (nr, %)	293	58.3%	198	65.8%	**0.034**	Pearson $\chi 2$			NS
Etiology according to ILAE (nr, %)									
Acute symptomatic	278	55.3%	176	58.5%					
Remote symptomatic	113	22.5%	38	12.6%			**0.48**	**0.32 – 0.72**	**<0.001**
Progressive symptomatic	79	15.7%	63	20.9%					
Cryptogenic/idiopathic	33	6.5%	26	8.6%	**0.001**	Pearson $\chi 2$			NS
Potentially fatal etiology (nr, %)	223	44.3%	160	53.2%	**0.015**	Pearson $\chi 2$			NS
Consiousness at SE onset (nr, %)									
Alert, confused or somnolent	239	47.4%	108	35.9%					
Stuporous or comatose	264	52 %	193	64.1%	**<0.001**	**Pearson $\chi 2$**	**1.67**	**1.24 – 2.46**	**0.001**
SE types (nr, %)									
Simple partial	99	19.7%	41	13.6%					
Absence	7	1.4%	1	0.3%					
Complex partial	159	31.6%	77	26.6%					
Generalized myoclonic	2	0.4%	0						
Generalized convulsive	227	45.1%	156	51.8%					
Nonconvulsive SE in coma	9	1.8%	26	8.6%	**<0.001**	Fisher			NS
STESS ≥ 3 (nr, %)	242	48%	172	57.1%	**0.013**	Pearson $\chi 2$			
Time to treatment > 1 h (nr, %)	303	60.2%	192	63.8%	0.317				
Intubation for treatment (nr, %)	4	0.8%	79	26.2%	**<0.001**	Pearson $\chi 2$			
Outcome at discharge (nr, %)									
Returned to baseline	321	63.8%	106	35.2%					
New handicap	141	28.0%	133	44.2%					
Death**	41	9.8%	62	25.0%	**<0.001**	Pearson $\chi 2$			
Death during SE (nr, %)	9	22%	28	45.2%	**<0.001**	Fisher			

SD, standard deviation; CI, confidence interval; SE, status epilepticus; STESS, status epilepticus severity score.
*** Demographics and mortality frequency was calculated according to the number of the incident patients.**
**** Hosmer–Lemeshow goodness-of-fit test for the final model, p = 0.58**
Bold values indicate significant results

Table 2. Demographics and clinical features in refractory and super-refractory SE

	Univariate analysis						Multiple stepwise logistic regression**		
	RSE episodes (not becoming SRSE) (n=268)		SRSE episodes (n=33)		p-value	Test	OR	95% CI	P-value
Demographics*									
Incident SE patients (nr, %)	220	33.1%	29	4.4%					
Age (years) (mean, SD)	64	±18	52	±19	**<0.001**	Student t	**0.96**	**0.95 – 0.99**	**0.002**
Female gender (nr, %)	104	47.3%	13	44.8%	0.804	Pearson $\chi 2$			
Earlier seizures (nr, %)	128	47.8%	16	48.5%	0.937	Pearson $\chi 2$			
Charlson Comorbidity Index (CCI) (median [range])	0	0-8	1	0-12	0.15	U-test			
CCI 0 (nr, %)	86	32%	17	51.5%					
CCI ≥1 (nr, %)	182	68%	16	48.5%	**0.026**	Pearson $\chi 2$			NS
Etiology according to ILAE (nr, %)									
Acute symptomatic	157	58.6%	19	57.6%					
Remote symptomatic	33	12.3%	5	15.2%					NS
Progressive symptomatic	57	21.2%	6	18.2%					
Cryptogenic/idiopathic	21	7.8%	3	9.0%	0.943	Pearson $\chi 2$			NS
Potentially fatal etiology (nr, %)	138	51.5%	19	57.6%	0.509	Pearson $\chi 2$			NS
Consiousness at SE onset (nr, %)									
Alert, confused or somnolent	104	38.8%	4	12.1%					
Stuporous or comatose	164	61.2%	29	87.9%	**0.003**	Pearson $\chi 2$	**4.26**	**1.44 – 12.60**	**0.001**
SE types (nr, %)									
Simple partial	40	14.9%	1	3.0%					
Absence	1	0.4%	0						
Complex partial	98	36.6%	10	30.3%					
Generalized myoclonic	0		0						
Generalized convulsive	110	41.0%	15	45.5%					
Nonconvulsive SE in coma	19	7.1%	7	21.2%	**0.007**	Fisher			NS
STESS ≥ 3 (nr, %)	152	56.7%	20	60.6%	0.670	Pearson $\chi 2$			
Time to treatment > 1 h (nr, %)	171	63.8%	21	63.6%	0.958	Pearson $\chi 2$			
Intubation for treatment (nr, %)	46	16.0%	33	100%	**<0.001**	Pearson $\chi 2$			
Outcome at discharge (nr, %)									
Returned to baseline	100	37.8%	6	18.0%	**0.030**	Pearson $\chi 2$			
New handicap	117	43.7%	16	48.5%	0.598	Pearson $\chi 2$			
Death**	51	24.5%	11	37.9%	0.084	Pearson $\chi 2$			
Death during SE (nr, %)	20	37%	8	72.7%	0.053	Fisher			

SD, standard deviation; CI, confidence interval; SE, status epilepticus; STESS, status epilepticus severity score.
***Demographics and mortality frequency was calculated according to the number of the incident patients.**
****Hosmer–Lemeshow goodness-of-fit test for the final model, p = 0.49**
Bold values indicate significant results

Table 3. RSE and SRSE frequency in literature and their 95% CI estimation

Location (Study)	Design	Study years	No. of SE	RSE frequency nr (%)	Estimated 95% CI	SRSE frequency nr (%)	Estimated 95% CI
Italy ([4])	Hospital based, prospective	2013 – 2014	83	12 (14%)	7.7– 23.8	14 (17%)	9.5 – 26.7
China ([17])	Hospital based, retrospective	2009 – 2012	98	20 (20.4%)	12.9 – 29.7	12 (12.2%)	6.5 – 20.4
Sweden ([7])	Hospital based, retrospective	2008 – 2012	103	59 (57%)	47.0 – 67.0	26 (25%)	17.2 – 34.7
Argentina ([8])	Hospital based, prospective	2007 – 2012	311	109 (35%)	29.8 – 40.6	15 (5%)	2.7 – 7.3
Switzerland ([6])	ICU-based, retrospective	2005 – 2011	171	63 (37%)	29.6 – 44.5	45 (26%)	19.9 – 33.6
India ([9])	ICU-based, retrospective	2005 – 2013	177	42 (23.7%)	17.7 – 30.7	30 (16.9%)	11.7 – 23.3
Switzerland (present study)	Hospital based, retrospective	2006 – 2015	804	268 (33.3%)	30.0 – 37.0	33 (4.1%)	2.5 – 5.7

95% Confidential Interval (95% CI)

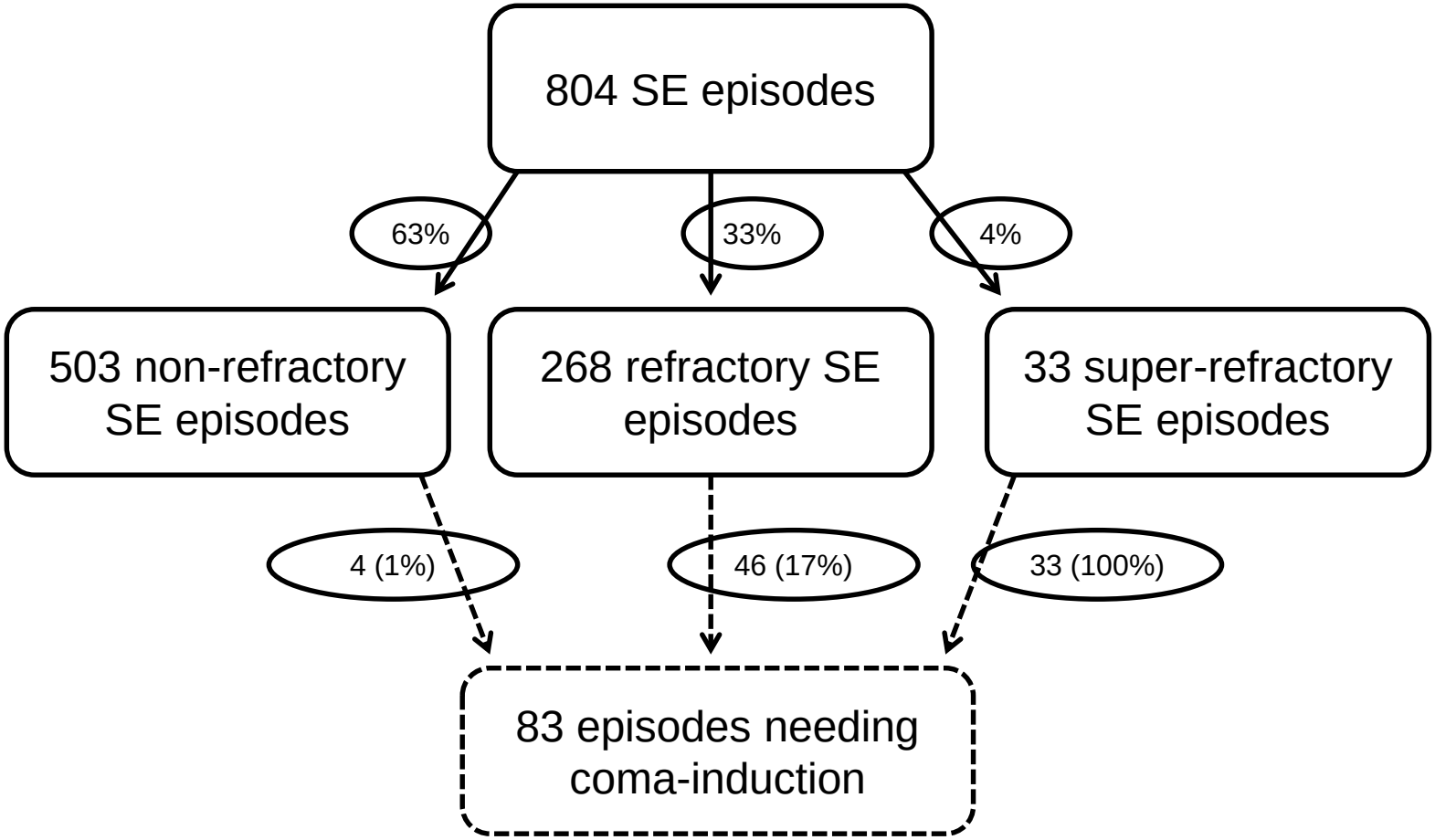

Figure 1: illustration of the distribution of Status epilepticus (SE) episodes according to their refractoriness and need of mechanical ventilation.