The risk of unprovoked seizure occurrence after status epilepticus in adults

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Key Words: Status Epilepticus, Aetiology, Acute Symptomatic, Antiseizure medications

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Abstract

Objective: Status epilepticus (SE) may lead to long-term consequences. This study evaluated the risk and predictors of seizure occurrence after SE, with a focus on SE due to acute symptomatic aetiologies.

Methods: Prospectively collected data about adults surviving a first non-hypoxic SE were reviewed. The outcome was the occurrence of unprovoked seizures during the follow-up. Kaplan-Meier survival curves analysis and log-rank test were used to analyse the time to seizure occurrence and determine statistical significance between aetiological groups. Three subcategories within acute etiology were considered according to the presence of: *(i)* structural lesion (acute-primary); *(ii)* brain involvement during systemic disorders (acute-secondary); *(iii)* drug or alcohol intoxication/withdrawal (acute-toxic). Cox proportional hazards model was adopted to estimate hazard ratios (HRs) with the 95% confidence intervals (CIs).

Results: Two hundreds and fifty-seven individuals were included. Fifty-four (21.0%) subjects developed seizures after a median of 9.9 [4.3-21.7] months after SE. The estimated 1, 2, and 5-year rates of seizure occurrence according to acute SE aetiologies were: 19.4%, 23.4%, and 30.1% for acute-primary central nervous system (CNS) pathology; 2.2%, 2.2% and 8.7% for acute-secondary CNS pathology; 0%, 9.1% and 9.1% for acute-toxic causes. Five-year rates of seizure occurrence for non-acute SE causes were 33.9% for remote, 65.7% for progressive, and 25.9% for unknown aetiologies. In multivariate Cox regression model, progressive aetiology [adjusted HR ($_{adj}$HR)=2.27, 95% CI 1.12-4.58], SE with prominent motor phenomena evolving in non-convulsive SE ($_{adj}$HR 3.17, 95% CI 1.38-7.25), and non-convulsive SE ($_{adj}$HR=2.38, 95% CI 1.16-4.90) were independently associated with higher hazards of unprovoked seizures. Older people ($_{adj}$HR=0.98, 95% CI 0.96-0.99) and people with SE due to acute-secondary CNS pathology ($_{adj}$HR=0.18, 95% CI 0.04-0.82) were at decreased risk of seizure occurrence.

Significance: Status epilepticus carries a risk of subsequent seizures. Both the underlying cause and epileptogenic effects of SE are likely to contribute.

Key Words: Status Epilepticus, Aetiology, Acute Symptomatic, Antiseizure medications

Key Points

- The different causes of status epilepticus within the umbrella of 'acute aetiology' are associated with distinct risks of unprovoked seizures
- The risk is lower in status epilepticus due to acute-secondary than acute-primary insults of central nervous system
- Progressive causes of status epilepticus, younger age, and worse functional capacity also predict the occurrence of unprovoked seizures

1. Introduction

Status epilepticus (SE) is a neurologic emergency that may lead to long-term consequences. In animal models, SE results in anatomical changes of the brain and reorganization of neural networks that contribute to epileptogenesis.[1] In humans, data about brain changes and their clinical implications are limited to MRI studies[2-4] and translation of the experimental findings to the clinical scenario requires caution.

Clinical studies indicate that a not negligible proportion of people surviving a SE episode can develop epilepsy,[5] and it remains challenging to discern the roles of SE itself and the underlying aetiology.[1] The aim of this study was to evaluate the risk and predictors of unprovoked seizures in adults with a first episode of non-hypoxic SE, with a particular focus on SE due to acute symptomatic aetiologies. The current classification of SE aetiology, which provides a single category for all the different acute causes of SE,[6] might be implemented by considering different classes of acute aetiologies.[7,8]

2. Methods

2.1 Participants

Consecutive episodes of SE occurring in subjects ≥14 years old admitted at the Ospedale Civile Baggiovara (Modena, Italy) from September 1st, 2013 to June 30th, 2021 were reviewed. A prospective SE registry (Modena Status Epilepticus Registry – MoSER) exists at the centre since 2013. Subjects with SE following hypoxic-anoxic encephalopathy, SE in defined electroclinical syndromes, previous history of seizures or SE, and subjects who died within 30 days from SE onset or were not residing in Modena city district were excluded.

Before 2015, SE was considered as a continuous seizure that lasts ≥5 minutes or two or more discrete seizures between which there is not a complete recovery of consciousness.[9] After 2015, the definition proposed by the ILAE was adopted.[6] The SE episodes that occurred before 2015 were reviewed by two Authors, and all met the ILAE diagnostic criteria. The diagnosis of non-convulsive

status epilepticus (NCSE) was confirmed by applying the Salzburg EEG criteria.[10,11] As previously described,[12-14] a specific Status Epilepticus Form was used to collect data, including age, gender, place of residence, history of epilepsy prior to SE, consciousness before treatment initiation, aetiology, semiology of SE, Status Epilepticus Severity Score (STESS),[15] level of disability before SE and at discharge. The form was filled in by the first physician (in out institution always a neurologist or neuro-intensivist) taking care of the individual with SE. The aetiology of SE was classified as recommended by the ILAE into acute, remote, progressive, and "unknown" (i.e., cryptogenic).[6] For the acute aetiologies, we considered a recently proposed subclassification of acute SE into the following subcategories:[7] i) acute primary central nervous system (CNS) pathology, including cerebrovascular diseases, active CNS infections, or head trauma ("acute-primary CNS"); ii) 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 iii) drug or alcohol intoxication and withdrawal ("acute-toxic").[7]

Treatment responsiveness was defined as SE cessation after first-line therapy with benzodiazepines alone or followed by second-line treatment with one antiseizure medication (ASM). Refractory SE was defined as persistent SE despite administration of first-line therapy with benzodiazepines and one second-line treatment with ASMs. Super-refractory SE was defined as a status persisting or recurring despite treatment with anaesthetics for longer than 24 hours.[9]

The study outcome was the occurrence of unprovoked seizures during the follow-up.[16] Follow-up data were acquired by the computerized hospital chart review, outpatients' visits and telephone interviews, and were updated to March 1st, 2023.

2.2 Statistical analysis. Values were presented as median (interquartile range [IQR]) for continuous variables and as the number (percent) of subjects for categorical variables. Comparisons were made through Mann-Whitney test or chi-squared test. The Kaplan-Meier survival curves analysis and log-rank test were used to analyse the time to seizure occurrence during follow-up and determine

statistical significance between aetiological groups. Cox proportional hazards model was adopted to estimate hazard ratios (HRs) with the 95% confidence intervals (CIs). Age, sex, and baseline characteristics associated with a $p<0.10$ in the univariate analysis were entered into a multiple Cox regression model to identify factors independently associated with the study outcome. People who died were censored at the time of death and people lost to follow-up were censored at the time of their last medical contact unless they had previously experienced one unprovoked seizure. Competing-risk regression model was performed as sensitivity analysis to assess the impact of mortality as a competing event with the occurrence of seizures during the follow-up. The cumulative incidence function was used to estimate the risk of seizures over time considering mortality as a competing risk event. Results were considered statistically significant for p values <0.05 (two sided). Data analysis was performed using STATA/IC 13.1 (StataCorp LP, College Station, TX, USA). The study was reported according to the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[17]

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.

2.4 Data Availability. Anonymized data will be shared upon reasonable request of any qualified investigator.

3. Results

A total of 627 subjects were identified. After the exclusion of people with SE following hypoxic-anoxic encephalopathy (n=73), SE in defined electroclinical syndromes (n=4), or previous history of seizures or SE (n=156), and people who died within 30 days from SE onset (n=120) or who were not residing in Modena city district (n=17), 257 subjects with a first incident SE were included. Subjects had a median age at SE onset of 73 [63-80] years and 94 (36.6%) were men. The most common aetiology of SE episodes was acute-primary CNS pathology (27.6%), followed by remote

(22.2%) and progressive (21.8%) conditions. Demographic and clinical characteristics of participants are summarized in Table 1.

Fifty-four (21.0%) subjects developed seizures after a median of 9.9 [4.3-21.7] months from SE. People who experienced seizures during the follow-up were younger at time of SE and more commonly presented SE due to acute-primary CNS pathology and progressive conditions compared to people who did not experience seizures. The characteristics of participants according to the occurrence of seizures are shown in Table 1.

In the study cohort, treatment with ASMs was prescribed to 251 (97.7%) subjects. Treatment was prescribed to 91.1% of the subjects with SE due to acute-secondary CNS pathology, 87.5% of the subjects with SE due to acute-toxic causes and to all (100%) subjects with SE due to acute-primary CNS, remote, progressive, or unknown aetiologies. Subjects who were discharged without ASM treatment did not experience seizures during the study period. Among 251 subjects who received ASMs at discharge, the treatment was discontinued during the follow-up in 28 (11.2%) cases. The discontinuation of ASM treatment occurred in 9.9% of the subjects with SE due to acute-primary CNS pathology, 36.6% of the subjects with SE due to acute-secondary CNS pathology, 42.9% of the subjects with SE due to acute-toxic causes, and none of the subjects with SE due to remote, progressive, or unknown aetiologies. All the subjects who had their ASM treatment discontinued did not experience unprovoked seizures during the follow-up.

The estimated seizure occurrence rate was 15.3% [95% CI 11.0-21.0] in the first year, 21.8% [95% CI 16.6-28.4] in the second year, 28.2% [95% CI 22.0-35.7] in the third year, 29.2% [95% CI 22.8-36.9] in the fourth year, and 32.2% [95% CI 25.0-40.8] at 5 years. In 43 out of 54 (79.6%) subjects, seizures occurred during the first two years from SE onset, and no subjects experienced a first seizure later than 5 years after the index SE episode. The estimated probability of seizure occurrence in the study cohort is shown in Figure 1A.

3.1. Risk of unprovoked seizures according to aetiology and clinical variables

The estimated 1, 2, and 5-year rates of seizure occurrence were 19.4% [95% CI 11.5-31.8], 23.4% [95% CI 14.4-36.5], and 30.1% [95% CI 18.7-46.0] for acute-primary CNS pathology; 2.2% [95% CI 0.3-14.8], 2.2% [95% CI 0.3-14.8] and 8.7% [95% CI 1.9-35.2] for acute-secondary CNS pathology; 0%, 9.1% [95% CI 1.3-49.2] and 9.1% [95% CI 1.3-49.2] for acute-toxic causes; 13.9% [95% CI 6.9-27.1], 21.1% [95% CI 11.9-35.9], and 33.9% [95% CI 21.2-51.3] for remote; 28.9% [95% CI 16.5-47.4], 42.8% [95% CI 27.7-61.9], and 65.7% [95% CI 44.7-85.5] for progressive; and 16.7% [95% CI 4.5-51.8], 25.9% [95% CI 9.1-60.9], and 25.9% [95% CI 9.1-60.9] for unknown aetiologies ($p<0.001$) (Figure 1B).

In the univariate Cox regression analysis, progressive aetiology (HR=2.10, 95% CI 1.07-4.13; p=0.032), SE with prominent motor phenomena evolving in NCSE (HR=2.88, 95% CI 1.29-6.45; p=0.010), and higher mRS at baseline (HR=1.20, 95% CI 1.01-1.41; p=0.033) were associated with a higher, while the aetiology category of acute-secondary CNS pathology (HR=0.21, 95% CI 0.05-0.92; p=0.038) was associated with a lower risk of seizures during the follow-up (Table 2).

In the multivariate Cox regression model, progressive aetiology [adjusted HR ($_{adj}$HR)=2.27, 95% CI 1.12-4.58; p=0.023], SE with prominent motor phenomena evolving in NCSE ($_{adj}$HR=3.17, 95% CI 1.38-7.25; p=0.006), NCSE ($_{adj}$HR=2.38, 95% CI 1.16-4.90; p=0.018) and higher mRS before SE ($_{adj}$HR=1.29, 95% CI 1.09-1.54; p=0.004) were independently associated with higher hazards of seizures. In contrast, older people ($_{adj}$HR=0.98, 95% CI 0.96-0.99; p=0.004) and people with SE due acute-secondary CNS pathology ($_{adj}$HR=0.18, 95% CI 0.04-0.82; p=0.026) were at lower risk of presenting seizure during the follow-up (Table 2).

The results obtained in the analyses including only subjects (n=251) who were prescribed with ASM treatment at discharge and after the adjustment for the discontinuation of ASM treatment during the follow-up were consistent with the results obtained in the analyses of the full cohort (Table 3).

Finally, in the competing risks analysis adjusted with mortality as a competing outcome during follow-up, SE with prominent motor phenomena evolving in NCSE and NCSE were associated with increased risk of seizure occurrence, while older age and the aetiology of acute-secondary CNS conditions were associated with a lower risk of seizures during the follow-up (Table 4). The cumulative incidence functions for competing events according to the aetiology of SE are shown in Figure 2.

4. Discussion

The current study suggested that the risk of unprovoked seizures in adults with a first-ever episode of SE is influenced by a combination of clinical variables, including the aetiology and semiology of SE, the age at time of SE onset, and functional capacity before SE. Different aetiologies under the umbrella of 'acute SE' carried distinct risks for the occurrence of unprovoked seizure or post-SE epilepsy. People with SE due to progressive causes had the highest risk and people with SE due to acute-secondary CNS insults had the lowest risk of unprovoked seizures during the follow-up. Younger age and worse functional capacity at the time of SE were also predictors of the occurrence of unprovoked seizures.

Evidence has accumulated that the aetiology of SE significantly affects the risk of subsequent seizures. Hesdorffer et al. investigated the impact of SE in the development of subsequent epilepsy and found that the risk of unprovoked seizure among people with SE was increased 7.1-fold if SE was due to a structural cause and 3.6-fold if SE was due to a metabolic cause.[18] The 10-year risk of subsequent unprovoked seizure was 45% and 29% among people with SE associated with structural and metabolic causes, respectively.[18] Santamarina et al. looked at the occurrence of seizures among subjects with SE and no prior history of epilepsy.[19] After a median follow-up of 10 months, 58.7% of survivors presented seizures and the risk of epilepsy was markedly lower in people with SE due to toxic-metabolic causes.[19] Orlandi et al. also corroborated the pivotal role of aetiology in predicting the risk of unprovoked remote seizures after SE.[20] The risk of remote seizures was 2.7-

fold higher in people who experienced SE due to progressive compared to acute symptomatic disorders, and 2-fold higher in case of SE due to structural compared to non-lesional causes.[20] Recently, Rodrigo-Gisbert et al. performed a cross-sectional study of consecutive people with SE and no previous epilepsy and analysed the development of unprovoked remote seizures.[21] After the adjustment for identifiable confounders, the progressive symptomatic aetiology of SE was independently associated with a greater risk and the acute symptomatic aetiology with a lower risk of unprovoked seizure occurrence.[21] Although not considered individually in the multivariate analysis, the rates of remote seizures differed significantly within each subgroup of acute aetiologies being 0% in the case of alcohol abuse and sodium imbalance, 18.5% in presence of acute CNS infection, and 23.9% in the case of acute cerebrovascular disease.[21] Further, in a post-hoc analysis, 21.7% and 12.0% of all subjects with SE due to acute-primary and acute-secondary CNS pathology developed seizures during the follow-up, and the corresponding risks of unprovoked seizures in the first two years after SE were 22.4% and 14.4%.[8,22]

The relationship between progressive causes of SE and the increased hazard of seizure occurrence during the follow-up is not unexpected as subjects presenting with a first SE episode with underlying progressive symptomatic aetiologies meet the operational definition of epilepsy.[23]

In clinical practice, also the occurrence of remote symptomatic SE is usually considered as fulfilling the epilepsy definition and long-term ASM is prescribed. In this regard, the findings suggesting that remote SE carries a 10-year risk of seizure recurrence below 60% in our cohort could be explained by the prescription and continuation of ASM treatment in this group of participants during the study period. Conversely, the actual probability to develop a subsequent unprovoked seizure in people with SE due to acute symptomatic causes may be of paramount relevance to guide clinical practice. The category of acute symptomatic aetiology, however, encompasses a great variety of causes with distinct longitudinal risks. The findings of the current study suggested that the more granular classification of acute symptomatic aetiology, which includes different subcategories and

distinguishes between acute-primary and acute-secondary CNS pathology, may interpret better the different risk of seizure occurrence over time.

The semiology of SE also emerged as a predictor of unprovoked seizures suggesting the epileptogenic contribution of SE itself. Status epilepticus is a highly dynamic condition characterized by molecular and cellular processes in the brain and systemic homeostatic mechanisms aimed to compensate for the increased cerebral metabolism.[24,25] As ictal activity persists, compensatory mechanisms can break down and episodes of motor SE can evolve into non-convulsive. The non-convulsive phase in the semeiology sequence might, hence, be considered as a marker of disease severity and brain damage.[26,27] Experimental studies suggested that prolonged NCSE can have deleterious neuronal consequences.[1] Brain pathology was observed in rats that developed unprovoked spontaneous seizures (epileptogenesis), including altered levels of adhesion molecules and immune reaction extending outside the epileptic focus and into cortical tissue.[28] As the duration of SE was coded in our database in days, and not hours, we considered this variable coarse and not accurate enough to be included in the analyses. Therefore, we could not explore the potential impact of SE duration on the long-term risk of seizures, and whether and at which extent the association between NCSE and unprovoked seizure occurrence was mediated by the length of seizure activity. The duration of SE, indeed, has been already shown to significantly contribute to the risk of epileptogenesis[19,21] and, in this regard, it is worth noticing that NCSE can represent a challenging diagnosis and treatment initiation is often delayed.

Consistent with the existing literature, older age acted as a protective factor against the risk of unprovoked seizures.[21] Smooth neuronal plasticity with increasing age may result in reduced epileptogenicity and explain the lower risk.[29] The time-based Cox analysis based on the actual length of follow-up of participants and the competing-risk regression based on mortality as a competing risk event with the occurrence of seizures during the follow-up could account for the potential confounder effect of the reduced life expectancy in older people.

The baseline functional status can be a further modulator of the risk of unprovoked seizures. As a measure of disability and dependence, higher mRS may underpin a more compromised global status that may hamper the functional reserve capacity. Within the frame of the burden model for SE, the lower is the functional reserve, the higher is the risk of decompensation.[30] The extent of decompensation has a correlating impact of burden, which may lead to further structural damage and metabolic derangement and increase the risk of long-term consequences.[30]

4.1 Study strengths and limitations

This study built upon the current body of knowledge about the occurrence of unprovoked seizures after SE. The main strength included the adoption of the recently proposed and more granular aetiological classification of SE episodes,[7] which ultimately allowed to identify distinct risks of seizures among cases falling within the traditional category of acute symptomatic SE. The analysis based on a hospital-based cohort of subjects not limited to the intensive care unit, the long-term follow-up, and the sensitivity analysis based on the competing-risk regression model contributed to give robustness to the results. Although data collection in a real-world setting may have introduced potential sources of bias, all information were gathered prospectively by means of a consistent form over years. Some shortcomings need, however, to be acknowledged. Clinical variables associated with the risk of seizure occurrence after SE such as the time to first-line treatment initiation,[21] peri-ictal MRI abnormalities,[31] and fluid biomarkers of neurodegeneration and neuroinflammation[32] were not available for all subjects and were not included. One major flaw was the impossibility to explore in depth the potential impact of the treatment with ASMs, limiting the generalizability of the results. Treatment with ASMs was left at the discretion of the treating physician in the absence of any standardized protocol for starting, reducing, and discontinuing drugs. Prophylactic treatment with ASMs may have masked a condition of controlled epilepsy rather than no epilepsy. The lack of a statistically significant association between the discontinuation of ASM treatment during the follow-up and the outcome, however, played against a significant contribution of this variable to the

findings obtained in this study. The trend toward a higher propensity to discontinue ASMs in people with SE due to acute secondary-CNS and toxic-metabolic causes and to pursue treatment in people with SE due to acute primary-CNS, progressive and remote causes played in favour of the results and supported the existence of distinct intrinsic risks of unprovoked seizures. It is, however, worth to emphasize that the few cases of treatment discontinuation limited the power to identify meaningful associations and did not allow to draw definitive conclusions about the potential influence of ASM prescription on seizure occurrence across the different SE aetiologies. The results of this study could offer the background to set up specific studies aimed to address clinically relevant and still unanswered practices like the optimal duration of ASM prescription, the long-term epileptological follow-up, and the need of driving restrictions in people who presented with acute symptomatic SE. The categories of SE due to acute-toxic and unknown aetiologies were poorly represented, limiting the power to provide precise estimates about their association with outcome and differences versus other aetiologies. Heterogeneity exists within each aetiological category, and additional analyses, ideally prospective and based on larger, independent cohorts are warranted to externally validate the findings and stratify the risk across the individual causes of SE. The lack of any statistically significant association between responsive, refractory, and super-refractory SE with the study outcome both at uni- and multi-variate analyses was somewhat surprising. In this regard, the overwhelming role of the aetiology, the effect of SE duration, and the need of a more granular classification of treatment refractoriness may represent potential contributing factors and additional studies are warranted to address this issue.[33,34]

5. Conclusions

In summary, SE carries a risk of subsequent unprovoked seizures. Both the underlying cause and the epileptogenic effects of SE are likely to contribute, and the interplay of these factors is complex and difficult to ascertain. The development of multimodal scoring systems and predictive tools

might be useful to inform survivors of SE and provide guidance to clinicians for a tailored decision-making aimed to optimize treatment and follow-up.

Author contributions

Simona Lattanzi planned and designed the study, performed the statistical analyses, interpreted the data, 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.

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Disclosure of Conflicts of Interest

Simona Lattanzi has received speaker's or consultancy fees from Angelini Pharma, Eisai, GW Pharmaceuticals, Medscape, 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. Simona Lattanzi has received research grant support from the Italian Ministry of Health and Ministry of University and Research. Eugen Trinka has received consultancy fees from Arvelle Therapeutics, Argenx, Clexio, Celegene, UCB Pharma, Eisai, Epilog, Bial, Medtronic, Everpharma, Biogen, Takeda, Liva-Nova, Newbridge, Sunovion, GW Pharmaceuticals, and Marinus; speaker fees from Arvelle Therapeutics, Bial, Biogen, Böhringer

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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 and figure legends

Table 1: Characteristics of study participants and comparison according to the occurrence of unprovoked seizures during follow-up

Table 2: Association between demographic and clinical characteristics and the occurrence of unprovoked seizures

Table 3: Association between demographic and clinical characteristics and the occurrence of unprovoked seizures in subjects receiving antiseizure medications at discharge

Table 4. Competing-risk regression analysis for competing events (seizure occurrence/death)

Figure 1: Time to occurrence of unprovoked seizures

Figure 2: Comparative cumulative incidence functions for competing events (seizure occurrence/death)

Table 1. Characteristics of study participants and comparison according to the occurrence of unprovoked seizures during the follow-up

	Study participants (n=257)	Unprovoked seizures during the follow-up		p value
		No (n=203)	Yes (n=54)	
Sex, n (%)				0.578
Male	94 (36.6)	76 (37.4)	18 (33.3)	
Female	163 (63.4)	127 (62.6)	36 (66.7)	
Age, years	73 [63-80]	75 [64-81]	69 [56-78]	0.011
Semiology, n (%)				0.282
Prominent motor phenomena	74 (28.8)	63 (31.0)	11 (20.4)	
Non-convulsive	132 (51.4)	102 (50.3)	30 (55.6)	
Prominent motor phenomena with evolution in non-convulsive	51 (19.8)	38 (18.7)	13 (24.1)	
Consciousness, n (%)				0.933
Alert/somnolent	194 (75.5)	153 (75.4)	41 (75.9)	
Stuporous/comatose	63 (24.5)	50 (24.6)	13 (24.1)	
STESS score	3 [3-4]	3 [3-4]	3 [2-4]	0.360
Aetiology, n (%)				0.013
Acute-primary CNS	71 (27.6)	55 (27.1)	16 (29.6)	
Acute-secondary CNS	45 (17.5)	43 (21.2)	2 (3.7)	
Acute-toxic	16 (6.2)	15 (7.4)	1 (1.9)	
Remote	57 (22.2)	43 (21.2)	14 (25.9)	
Progressive	56 (21.8)	38 (18.7)	18 (33.3)	
Unknown	12 (4.7)	9 (4.4)	3 (5.6)	
mRS before status epilepticus	1 [0-3]	1 [0-3]	1 [0-3]	0.603
mRS at discharge	3 [1-5]	4 [1-5]	3 [1-4]	0.145
Response to treatment, n (%)				0.776
Responsive status epilepticus	208 (80.9)	166 (81.8)	42 (77.8)	
Refractory status epilepticus	26 (10.1)	20 (9.9)	6 (11.1)	
Super-refractory status epilepticus	23 (9.0)	17 (8.4)	6 (11.1)	
Antiseizure medications at discharge, n (%)	251 (97.7)	197 (97.0)	54 (100.0)	0.201

Data are mean (SD) or median [IQR] for continuous variables and n (%) for categorical variables.
Abbreviations: CNS=central nervous system, IQR=interquartile range, mRS=modified Rankin scale, SD=standard deviation, STESS=Status Epilepticus Severity Score.

Table 2. Association between demographic and clinical characteristics and the occurrence of unprovoked seizures

Dependent Variable	HR (95% CI)	p value	*Adjusted HR (95% CI)	p value
Age	0.99 (0.97-1.00)	0.051	0.98 (0.96-0.99)	0.004
Male sex	0.85 (0.48-1.50)	0.573	0.76 (0.43-1.35)	0.348
[a]Aetiology, n (%)				
Acute-secondary CNS	0.21 (0.05-0.92)	0.038	0.18 (0.04-0.82)	0.026
Acute-toxic	0.22 (0.03-1.66)	0.143	0.19 (0.02-1.42)	0.105
Remote	1.00 (0.49-2.05)	0.996	1.20 (0.56-2.55)	0.643
Progressive	2.10 (1.07-4.13)	0.032	2.27 (1.12-4.58)	0.023
Unknown	1.02 (0.30-3.50)	0.976	1.18 (0.34-4.07)	0.798
[b]Semiology				
Non-convulsive	1.69 (0.85-3.38)	0.135	2.38 (1.16-4.90)	0.018
Prominent motor phenomena with evolution in non-convulsive	2.88 (1.29-6.45)	0.010	3.17 (1.38-7.25)	0.006
[c]Consciousness				
Stuporous/comatose	1.33 (0.71-2.49)	0.367	-	-
STESS score	1.05 (0.86-1.28)	0.632	-	-
mRS before status epilepticus	1.20 (1.01-1.41)	0.033	1.29 (1.09-1.54)	0.004
mRS at discharge	1.05 (0.91-1.22)	0.477	-	-
[d]Response				
Refractory	1.20 (0.51-2.82)	0.681	-	-
Super-refractory	1.65 (0.70-3.89)	0.251	-	-

Values are from Cox regression model. *Adjustment for age, sex, aetiology, semiology, and mRS before status epilepticus. HR is for unitary increase of age, STESS, and mRS.

[a]Reference is acute-primary CNS. [b]Reference is prominent motor phenomena. [c]Reference is alert/somnolent. [d]Reference is responsive status epilepticus.

Abbreviations: CNS=central nervous system, CI=confidence interval, HR=hazard ratio, mRS=modified Rankin scale, STESS=Status Epilepticus Severity Score.

Table 3. Association between demographic and clinical characteristics and the occurrence of unprovoked seizures in subjects receiving antiseizure medications at discharge

Dependent Variable	HR (95% CI)	p value	*Adjusted HR (95% CI)	p value
Age	0.99 (0.97-1.00)	0.050	0.98 (0.96-0.99)	0.004
Male sex	0.85 (0.48-1.50)	0.576	0.76 (0.43-1.35)	0.349
[a]Aetiology, n (%)				
Acute-secondary CNS	0.23 (0.05-0.99)	0.049	0.19 (0.04-0.87)	0.032
Acute-toxic	0.24 (0.03-1.79)	0.163	0.19 (0.02-1.45)	0.109
Remote	1.00 (0.49-2.05)	0.996	1.20 (0.56-2.55)	0.644
Progressive	2.10 (1.07-4.13)	0.032	2.27 (1.12-4.58)	0.023
Unknown	1.02 (0.30-3.50)	0.976	1.18 (0.34-4.06)	0.799
[b]Semiology				
Non-convulsive	1.65 (0.83-3.29)	0.157	2.37 (1.15-4.88)	0.019
Prominent motor phenomena with evolution in non-convulsive	2.77 (1.24-6.20)	0.013	3.15 (1.38-7.21)	0.007
[c]Consciousness				
Stuporous/comatose	1.35 (0.72-2.53)	0.344	-	-
STESS score	1.06 (0.87-1.29)	0.585	-	-
mRS before status epilepticus	1.19 (1.01-1.40)	0.039	1.29 (1.08-1.54)	0.004
mRS at discharge	1.05 (0.91-1.22)	0.467	-	-
[d]Response				
Refractory	1.17 (0.50-2.76)	0.720	-	-
Super-refractory	1.61 (0.69-3.80)	0.273	-	-
Discontinuation of ASMs during the follow-up	5.07e^16	1.000	-	-

Values are from Cox regression model. *Adjustment for age, sex, aetiology, semiology, and mRS before status epilepticus. HR is for unitary increase of age, STESS, and mRS.

[a]Reference is acute-primary CNS. [b]Reference is prominent motor phenomena. [c]Reference is alert/somnolent. [d]Reference is responsive status epilepticus.

Abbreviations: ASM=antiseizure medication, CNS=central nervous system, CI=confidence interval, HR=hazard ratio, mRS=modified Rankin scale, STESS=Status Epilepticus Severity Score.

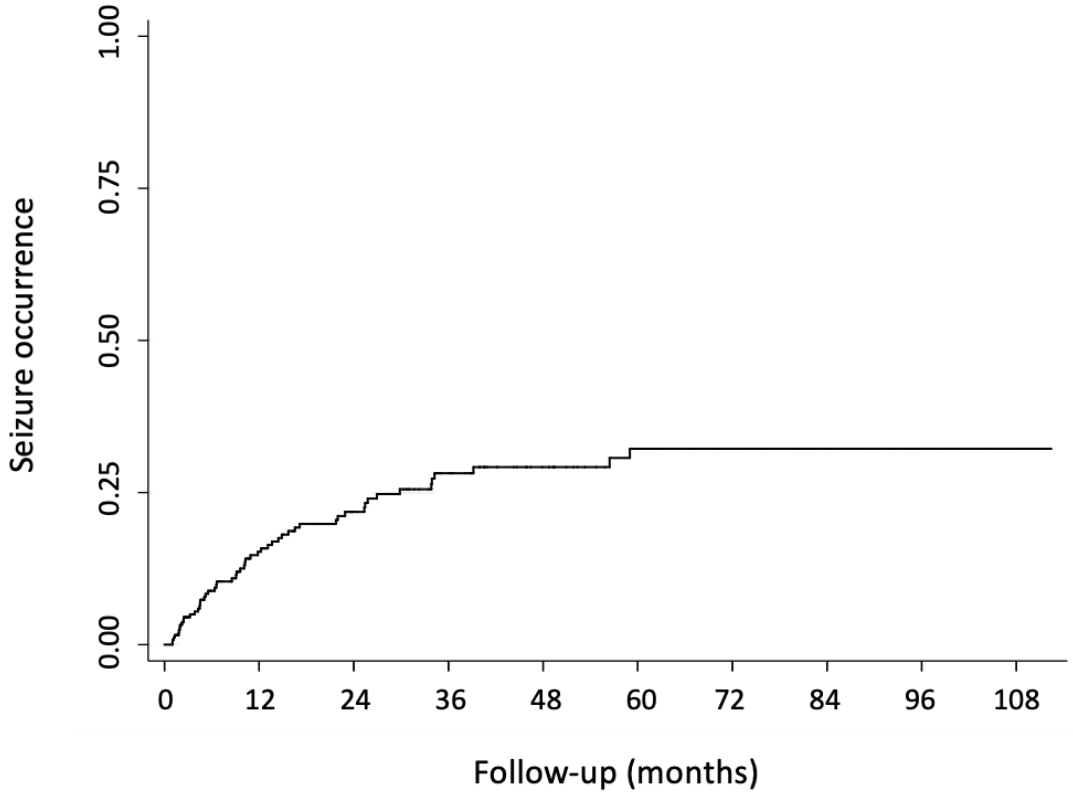
Table 4. Competing-risk regression analysis for competing events (seizure occurrence/death)

Dependent Variable	*SHR (95% CI)	p value
Age	0.97 (0.96-0.98)	<0.000
Male sex	0.77 (0.44-1.34)	0.350
[a]Aetiology, n (%)		
Acute-secondary CNS	0.17 (0.04-0.79)	0.023
Acute-toxic	0.21 (0.02-1.83)	0.159
Remote	1.31 (0.62-2.77)	0.486
Progressive	1.49 (0.73-3.02)	0.270
Unknown	1.25 (0.37-4.17)	0.719
[b]Semiology		
Non-convulsive	2.12 (1.08-4.13)	0.028
Prominent motor phenomena with evolution in non-convulsive	2.51 (1.14-5.55)	0.023
mRS before status epilepticus	1.19 (1.02-1.40)	0.028

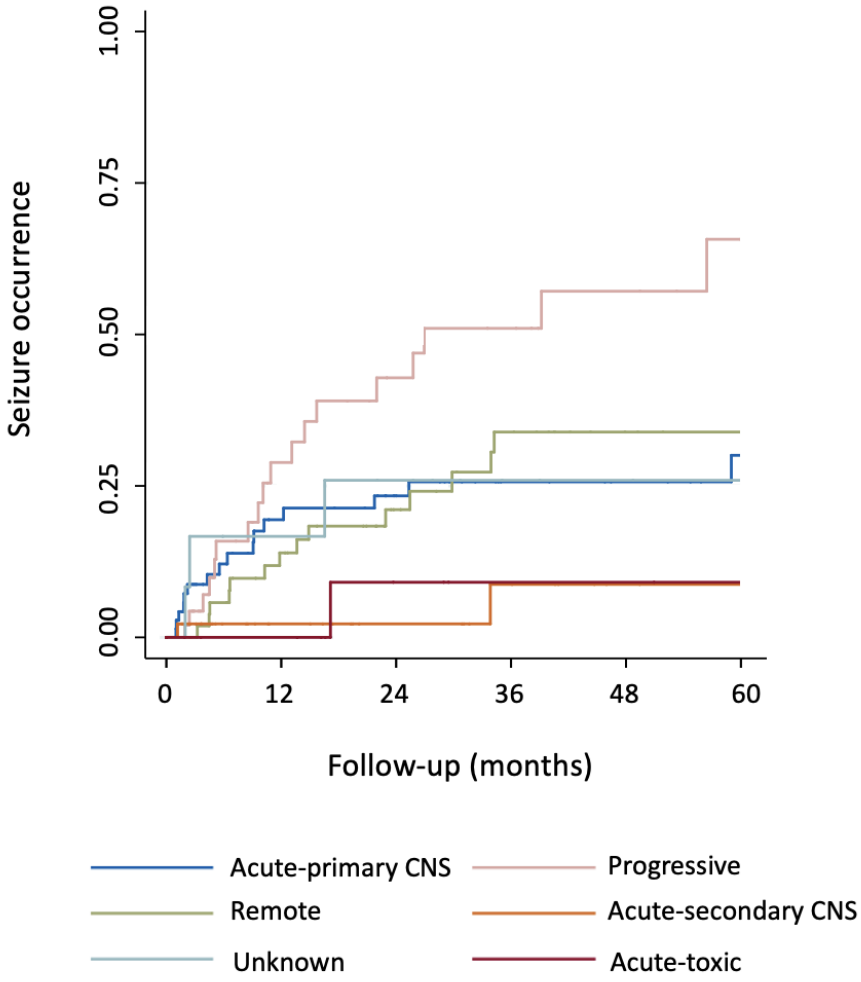
Values are from competing-risk regression analysis to assess the impact of mortality as a competing event with the occurrence of seizures during the follow-up. *Adjustment for age, sex, aetiology, semiology, and mRS before status epilepticus. SHR is for unitary increase of age, STESS, and mRS.
[a]Reference is acute-primary CNS. [b]Reference is prominent motor phenomena. [c]Reference is alert/somnolent. [d]Reference is responsive status epilepticus.
Abbreviations: CNS=central nervous system, CI=confidence interval, mRS=modified Rankin scale, SHR=subhazard ratio.

Figure 1. Time to occurrence of unprovoked seizures

A. Study cohort

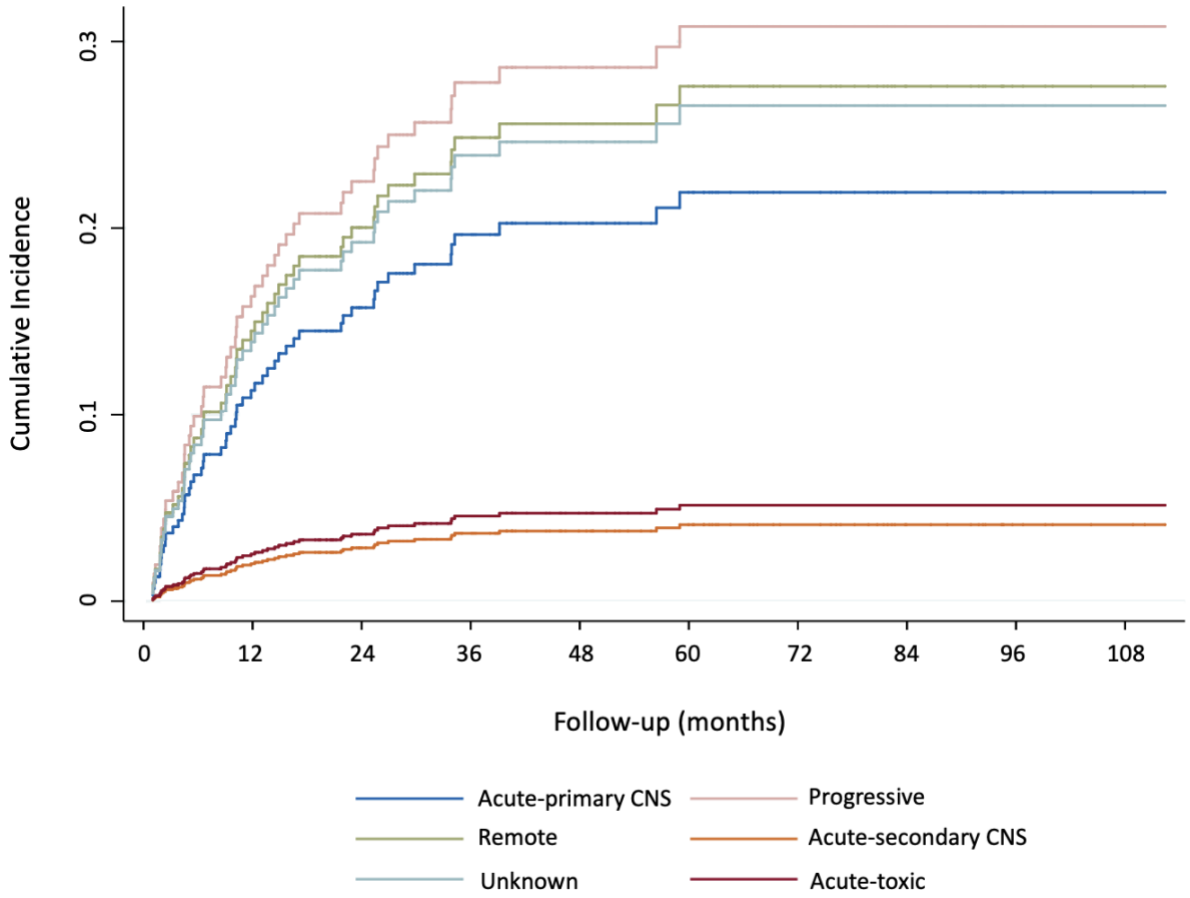


B. By the aetiology of status epilepticus



Kaplan-Meier estimates for the time to the occurrence of unprovoked seizures over 5-year follow-up in the whole study cohort (A) and according to the aetiology of status epilepticus (p for log-rank test <0.001) (B). Data are from 257 subjects with a total observation of 7362,133 person-years.

Figure 2. Comparative cumulative incidence functions for competing events (seizure occurrence/death) according to the aetiology of status epilepticus



Comparative cumulative incidence functions from competing-risk regression analysis to assess the impact of mortality as a competing event with the occurrence of seizures during the follow-up.