Received: 11 February 2023 | Accepted: 8 May 2023

DOI: 10.1002/epd2.20071

Epileptic Disorders

ORIGINAL ARTICLE

Electrographic seizure duration and inter-seizure intervals in focal status epilepticus

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Abstract

Objective: To characterize the duration of seizures and inter-seizure intervals in focal status epilepticus (SE).

Methods: We reviewed consecutive scalp EEG recordings from adult patients who were admitted for a first episode of focal status epilepticus. We identified electrographic seizure duration and inter-seizure intervals in the first diagnostic pretreatment EEG. We also reviewed isolated focal self-limiting seizures in epilepsy patients, as a comparison group for seizure duration.

Results: We recorded 307 focal seizures in 100 consecutive focal SE episodes, with a median seizure duration of 107 s (IQR: 54–186), and 134 isolated focal self-limiting seizures in 42 epilepsy patients, with a median duration of 59 s (IQR: 30–90; $p < .001$). The only clinical feature of SE that significantly increased seizure duration was acute symptomatic etiology. In SE, 15% and 7% of seizures lasted longer than 300 and 600 s, respectively (t1 of the actual definition for tonic–clonic and focal SE), while only 1% of self-limiting seizures lasted longer than 300 s, and none lasted longer than 600 s. The analysis of inter-seizure intervals in SE with multiple seizures showed that 50% of the inter-seizure periods were shorter than 60 s, and 95% were shorter than 540 s (9 min). Patients who had an increase in seizure duration (last versus first) of at least 1.4 times showed an increased 30-day mortality.

Significance: Focal seizures within a SE episode showed a wide range of duration, partly overlapping with the duration of focal self-limiting seizures but with a longer median duration. Inter-seizure intervals within an episode of SE were shorter than 1 min in 50% of the seizures and never lasted more than 10 min. Finally, an increase in seizure duration could represent an "electrophysiological biomarker" of a more severe SE episode, which may require more aggressive and rapid treatment.

KEYWORDS
epilepsy, ictal, inter-seizure intervals, seizure duration, status epilepticus

1 | INTRODUCTION

Status epilepticus (SE) is neurological emergency, characterized by high morbidity and mortality.[1] Conceptually, SE is defined as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures."[2] The diagnostic classification system endorsed by the International League Against Epilepsy (ILAE) distinguishes SE with prominent motor symptoms from nonconvulsive SE and proposes a framework for clinical diagnosis, investigation, and therapeutic approach.[2] Remarkably, SE represents a heterogeneous condition rather than a single disease entity, and considerable variability exists with regard to etiology, semiology, electroencephalographic correlates, and response to treatment.

The current definition of SE pays particular attention to the length of the ictal discharge. When this duration is longer than a predefined interval (called t1), the patient's condition is defined with high probability as SE. Currently, t1 is set at 300 s for tonic–clonic SE and at 600 s for focal SE with impaired awareness. The data leading to the current definition are based on studies that analyzed seizure durations in patients admitted to epilepsy monitoring units or to elective video-EEG recordings.[3–5] As recently reported, the duration of various epileptic seizure types is an important information, with high clinical relevance.[5] Knowing the upper limit of seizure duration for different seizure types is critical for the early identification of patients at risk for SE.[2,5]

However, although several studies have quantified the duration of self-limiting seizures to infer the risk of SE,[3–5] no studies have directly quantified the duration of seizures in status epilepticus episodes. Furthermore, no studies have directly compared repetitive focal seizures within an episode of SE with isolated self-limiting focal seizures.

Therefore, the objective of this study was to quantify focal seizures' duration and other seizure features within a SE episode. This knowledge could improve our understanding of the mechanisms underlying status epilepticus.

Key points

- We measured the duration of focal seizures and inter-seizure intervals in the pretreatment EEG of 100 episodes of status epilepticus.
- Focal seizures in status epilepticus had a median duration longer than focal self-limited seizures recorded in epilepsy patients.
- 15% and 7% of seizures in status epilepticus had a duration longer than 300 and 600 s, respectively, which are the thresholds for defining tonic–clonic and nonconvulsive status epilepticus.
- Inter-seizure periods were shorter than 60 s in 50% of the pairs, and in 95% of the pairs, they were shorter than 540 s (9 min).
- In cases with multiple recorded seizures, seizures tended to become longer in the absence of treatment, and this was associated with increased short-term mortality.

2 | METHODS

This is a retrospective analysis of adult SE episodes that were prospectively collected at Modena Academic Hospital in Italy from September 1, 2015, to August 31, 2019. We used an ad hoc case report form to prospectively collect all consecutive SE episodes in patients aged 14 years or older, and we have previously reported on the modalities of this form elsewhere.[6] We retrieved clinical information from medical reports in the hospital informatics database, as well as from clinical files such as therapy sheets and vital parameter graphics.

2.1 | Patients' selection and adopted definitions

For the purposes of this study, we included consecutive patients with (1) a diagnosis of focal SE, both with prominent motor or nonmotor (NCSE) features; (2) EEG characterized by separate repetitive electrographic/electroclinical seizures with a clear spatiotemporal evolution in frequency, morphology, and location of the ictal discharge according to American Clinical Neurophysiology Society (ACNS) and Salzburg EEG criteria[7–9]; (3) for whom one or more seizures were recorded in the diagnostic pretreatment EEG.

Status epilepticus was defined accordingly to the latest ILAE definition as a continuous seizure or two or more discrete seizures between which there is no complete

recovery of consciousness that lasts 5 min for convulsive SE (CSE) and 10 min for nonconvulsive Status Epilepticus (NCSE).[2] Patients presenting two or more SE episodes during the study period were considered only for the first episode. SE in the context of postanoxic encephalopathies was excluded from the study.

In cases of SE without prominent motor semiology, the diagnosis of nonconvulsive status epilepticus (NCSE) was reviewed according to Salzburg EEG criteria.[8–10]

According to the 2015 proposed classification of SE,[2] etiology was defined as acute symptomatic, remote symptomatic, and progressive symptomatic. When it was not possible to identify a clear etiology, SE was classified as cryptogenic. Moreover, SE was classified as multifactorial when more than one of the categories was simultaneously present and judged equally important in SE determination.

A specific dataset was used to collect demographic and clinical information, including age, gender, STESS (Status Epilepticus Severity Score),[11] EMSE (Epidemiology-based Mortality score in Status Epilepticus)[12] scores, and mortality occurring within 30 days from the SE. The form was filled in by the physician (neurologist or neurointensivist) taking care of the patient.

Treatment followed an internal protocol (publicly available at http://salute.regione.emilia-romagna.it/percorso-epilessia/PDTASE_AOU.pdf) based on the recommendations of international guidelines.[13–15] SE persisting after the administration of a benzodiazepine trial and one adequate trial of antiseizure medication (ASM) was classified as refractory (RSE) and SE that persisted or reappeared after 24 h of anesthetic therapy was defined as super-refractory SE (SRSE).

2.2 | Definition of seizure's features

For each included patient the diagnostic pretreatment EEG recording was evaluated. This choice was determined to avoid, as much as possible, the effects of intravenous administration of ASMs on the EEG measures of outcomes. EEG was recorded with the EBNeuro EEG system (EBNeuro, Italy), using the 10–20 scalp EEG electrode array. Recordings were carried out by certified, experienced EEG technicians. All the included EEGs were reviewed in monopolar and bipolar montages.

2.2.1 | Seizure duration

For each seizure, the duration was calculated by EEG visual inspection and defined as the time between the first EEG modification and the end of ictal activity. In particular, EEG seizure duration was defined as the time between the initial transition from background activity to focal ictal activity and the cessation of that activity/initiation of postictal EEG activity (suppression or slowing).[5] Examples of recorded seizure onset patterns are shown in Figure S1. Therefore, seizure durations in this study refers to electrographic parameters, not to clinical sign, even in seizures that were accompanied by clinical or behavioral changes.

Two epileptologists experienced in SE (SM and GT) independently reviewed all EEGs while blind to patients' clinical information. The concordance between the two raters was excellent (k = .8) as measured by Cohen's kappa coefficient (k). Discrepancies were resolved by discussion and by the evaluation of the EEG by a third expert (GG), who was blind to the evaluation of the first two raters.

2.2.2 | Last versus first seizure duration

For SE episodes in whom we recorded more than one seizure in the pretreatment EEG, we calculated the difference (delta time) between the duration of the last and the first recorded seizure. The rationale for this computation is that if we hypothesize that during impending SE untreated seizures tend to become longer, we should observe in the majority of the cases positive delta time (>0 s).

2.2.3 | Inter-seizure interval

We also calculated the intervals between each pair of seizures for SE episodes in which we recorded more than one seizure in the pretreatment EEG. Information on this metric has never been investigated, but it could be of great clinical relevance in estimating the critical interval between two subsequent seizures for the development and maintenance of recurring noninterrupting seizures.

2.3 | Comparison group

The duration of focal isolated self-limiting seizures recorded in patients with epilepsy admitted to the epilepsy monitoring unit (EMU) either for epilepsy surgery workup or for diagnostic/treatment reasons from January 2020 to August 2021 were reviewed and served as comparison group for seizure duration. None of these patients developed SE during their stay in the EMU.

Table S1 reports the demographic and clinical information of these patients. At admission, 11 patients were on monotherapy, 15 were on bi-therapy, and 16 were on poly-therapy with ASM. Down titration was performed in 30 out of 42 patients during their stay in the EMU. No patient was ASM-free during recorded seizures.

The EEGs of this group of patients were reviewed by certified neurophysiologists of the epilepsy monitoring unit (MP, AEV) following the same rules as for SE patients.

2.4 | Statistical analysis

The statistical analysis was conducted using the SPSS program (IBM SPSS Statistics version 26). The association between categorical variables was calculated by chi-squared test and, if necessary, the Fisher correction was applied. The *t*-test and Mann–Whitney *U*-test were used for the analysis of continuous variables in relation to their distribution. Linear regression models were created to define risk factors for increased seizures' duration. Comparisons and correlations were considered significant when the applied test presented a p value $<.05$. Considering that the population of SE and epilepsy patients differed for age distribution (median 75 in SE vs. 35 years in epilepsy group; $p < .001$) and gender (males 43% in SE vs. 71% in epilepsy group; $p = .002$), we analyzed in each dataset the correlation between median seizures' duration, age, and gender.

We evaluated the following EEG parameters on short-term mortality (30-day death): (1) the presence of at least one seizure lasting ≥300 s; and (2) a ratio ≥2 between the duration of the last recorded seizure and the duration of the first one. Finally, based on the ROC analysis and the Youden index (J) calculation we found the most suitable cut-off of the duration's increment between the first and the last recorded seizure, and we evaluated its effect on 30-day mortality.

2.5 | Standard protocol approvals, registrations, and patient consents

The Ethics Committee approved the study (prot. 556/2018 AOUMO) and informed consent was obtained from all participants included in the study. Anonymized data will be shared upon request by any qualified investigator.

3 | RESULTS

Based on the study's inclusion criteria, seizure duration was analyzed in 307 seizures for 100 patients/SE episodes (mean age: 70 years; Figure 1). The mean number of analyzed seizures per patient was 3 (1–5 seizure/patient). The demographic and clinical characteristics of this population are reported in Table 1. One-hundred and thirty-four isolated focal self-limiting seizures were recorded

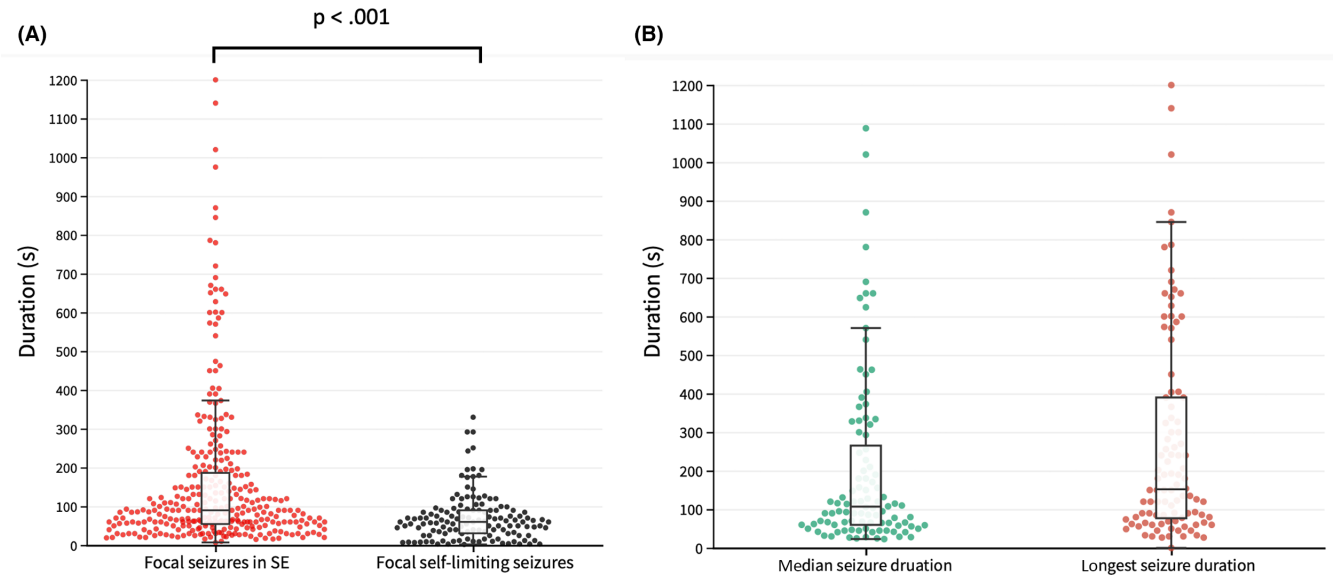


FIGURE 1 Seizure durations. Panel A shows the seizure duration distribution in the status epilepticus group (red dots; $n = 307$) and in the epilepsy group (gray dots; $n = 134$). Statistical comparison according to the Mann–Whitney *U*-test. Panel B shows the median seizure duration (green dots) and the longest seizure duration (pink dots) per patient in the SE group ($n = 100$). The white box represents interquartile ranges (IQR). Horizontal line indicates the median value. SE, status epilepticus.

TABLE 1 Demographics and clinical variables of the patients with status epilepticus.

Clinical characteristics of patient population	*n* (%)
Total	100
Gender	
Female	57 (57%)
Age (years)	
Range	17–98
Average	70
Median	75
Etiology	
Cerebrovascular	35 (35%)
Brain tumors	14 (14%)
Precipitating factors in previously epileptic patients / epileptic encephalopathies	19 (19%)
Others	32 (32%)
Etiology classification	
Acute symptomatic[a]	49 (49%)
Progressive symptomatic	18 (18%)
Remote symptomatic	19 (19%)
Multifactorial	11 (11%)
Cryptogenic	1 (1%)
In defined epilepsy syndrome	2 (2%)
Semiology	
NCSE	
All NCSE	75 (75%)
NCSE only	50
GCSE → NCSE	11
FMSE → NCSE	14
CSE	
GCSE, FMSE, MSE	25 (25%)
30-day mortality	19 (19%)
30-day functional outcome	
Worsening of clinical conditions compared with those existing before SE	62 (62%)
1-year mortality	51 (51%)
Response to treatment	
Responsive SE	39 (39%)
RSE and SRSE	61 (61%)

Abbreviations: CSE, convulsive status epilepticus; FMSE, focal motor status epilepticus; GCSE, generalized convulsive status epilepticus; MSE, myoclonic status epilepticus; NCSE, nonconvulsive status epilepticus; RSE, refractory status epilepticus; SE, status epilepticus; SRSE, super-refractory status epilepticus.

[a]Cerebrovascular disorders: 22; post-traumatic: 4; encephalitis: 2; metabolic: 3; sepsis: 4; precipitating factors in patients with epilepsy: 11; toxic: 3.

in 42 epilepsy patients (focal epilepsy group; mean age: 35 years).

Overall, the median duration of focal seizures was 107 s (IQR: 54–186 s) in the SE group, while it was 59 s (IQR: 30–90 s) in the epilepsy group ($p < .001$; Figure 1). The longest seizure in SE was 1200 s, while it was 340 for self-limiting seizures. Since it is known that focal seizures with a bilateral tonic–clonic evolution (FBTC) have a longer duration compared with seizure without,[3,4] we repeated this comparison after excluding 33 seizures in the SE group and 11 seizures in the epilepsy group that had FBTC. The aforementioned differences in seizure duration were confirmed. No significant correlations were found between median seizures' duration and age distribution (Kendall's tau correlation: −.042, $p = .541$ in epilepsy patients; −.027, $p = .8$ in SE patients) and with gender (Kendall's tau correlation: −.092, $p = .268$ in epilepsy patients; .040, $p = .759$ in SE patients).

Finally, the comparison of the median seizure duration was repeated in a selected subgroup of 12 young SE patients (median age 40 years) matched for age and gender distribution with the epilepsy group. Again, seizures in patients with SE were significantly longer (median 90 s: IQR 40–140 s) compared with those of epilepsy group (median 59 s: IQR 37–81 s; $p = .02$).

The median seizure duration in focal SE and in epilepsy obtained in this study and in previous studies investigating scalp EEG recording in epilepsy patients is shown in Figure 2.[3–5,16] Although the purposes of the examined studies were different from our study, seizure durations were comparable to the ones observed in our epilepsy control group and were shorter compared with the ones observed in our cohort of electrographic seizures in SE.

Figure 3 displays seizure duration distribution across 60-second intervals in the two populations of seizures. In focal self-limiting seizures, only one event lasted longer than 300 s, and none exceeded 600 s (the time point t1 that defines convulsive and focal nonmotor SE, respectively), whereas in SE, 15% (45 seizures) and 7% (20 seizures) of seizures lasted longer than 300 and 600 s, respectively.

We analyzed etiology classification, STESS and EMSE scores, and semiology (motor, nonmotor SE) as potential determinants of seizure duration in SE. Using linear regression, we found that only acute symptomatic etiology significantly increased seizure duration (B = .256, 95% CI .123–.883, $p = .01$).

Figure 4 shows the results of the difference in duration between the last and first seizure and the interseizure intervals (ISI) for SE episodes in whom we recorded more than one seizure in the pretreatment EEG (70 patients; 278 seizures). As expected, in 74% of SE episode, the last seizure had a duration longer than the first (Figure 4A), while the opposite trend was observed in a minority of episodes ($n = 12$). Furthermore, in 25 cases (36%), the last seizure lasted more than twice as long as the first, with extreme cases ($n = 3$) in which the last seizure was more than 10 times longer

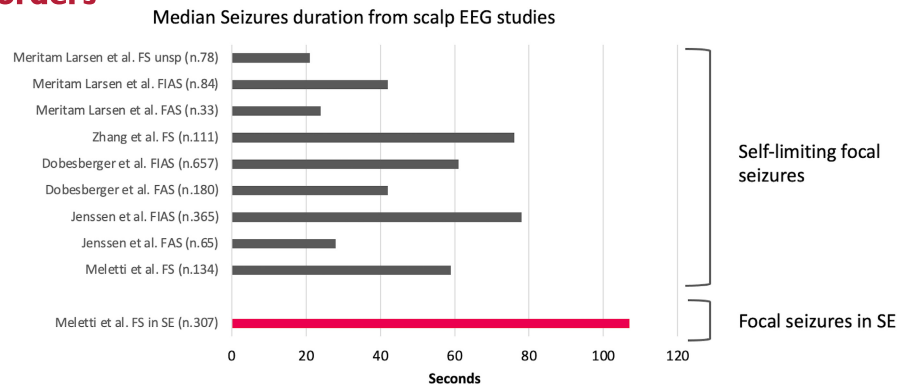
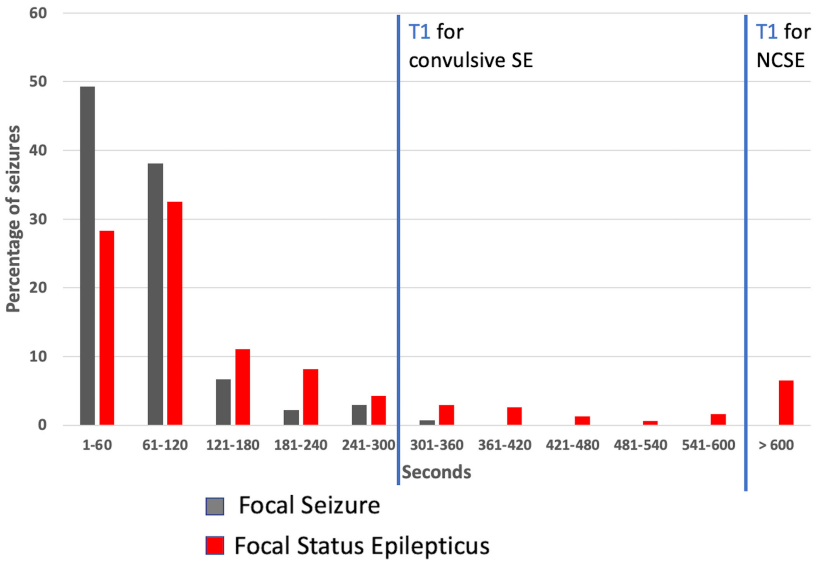


FIGURE 2 Focal seizure duration in SE compared with seizure duration in epilepsy patients. This picture reports the duration (median) of focal seizures in status epilepticus (bottom red bar; this study) and in isolated seizures observed in epilepsy patients in this and previous studies (gray bars). FAS, focal aware seizures; FIAS, focal impaired awareness seizures; FS, focal seizures. On the left are reported the names of the first author of each study (see ref.). In brackets is reported the number of analyzed seizures.

(A)



(B)

	n	%
Focal self-limited seizures (n=134 in 42 pts)		
Seizures > 300s	1	0,7
Patients wth seizures > 300s	1	2
Seizures > 600s	0	0,0
Patients wth seizures > 600s	0	0
Focal seizures in SE (n=307 in 100 pts)		
Seizures > 300s	45	14,7
Patients wth seizures > 300s	32	32
Seizures > 600s	20	6,5
Patients wth seizures > 600s	17	17

FIGURE 3 Seizure duration distribution. Panel A shows the distribution of seizure duration across 1-min bins in SE and focal self-limiting seizures. Panel B reports the number and percentages of seizure duration outlasting the threshold of 300 (t1 for motor SE) and 600 s (t1 for nonmotor SE).

than the first event. The analysis of inter-seizure periods (median 55 s) showed a skewed trend, with 50% of inter-seizure intervals lasting between 1 and 60 s, while 95% of inter-seizure periods were shorter than 540 s (9 min; Figure 4B). We examined the possible correlation between seizure duration and inter-seizure intervals but found no significant association between the two variables.

Finally, we investigated whether seizure duration impacted clinical outcomes. We analyzed short-term mortality in patients with seizure duration longer than 300 s compared to patients with seizures of shorter duration and found no significant difference. However, we found an increased 30-day mortality rate in patients with a ratio >2 between the duration of the last recorded seizure and that of the first one (36% vs. 11%, $p = .02$). ROC analysis indicated that an increase of at least 1.4 times between the duration of the first and last recorded seizures was associated with a significant increment of 30-day mortality (35% vs. 5%, $p = .001$; OR 10.64, 95% CI 2.18–51.93; Figure S2).

4 | DISCUSSION

Our findings confirm the hypothesis that focal seizures in SE have distinct and longer durations compared with

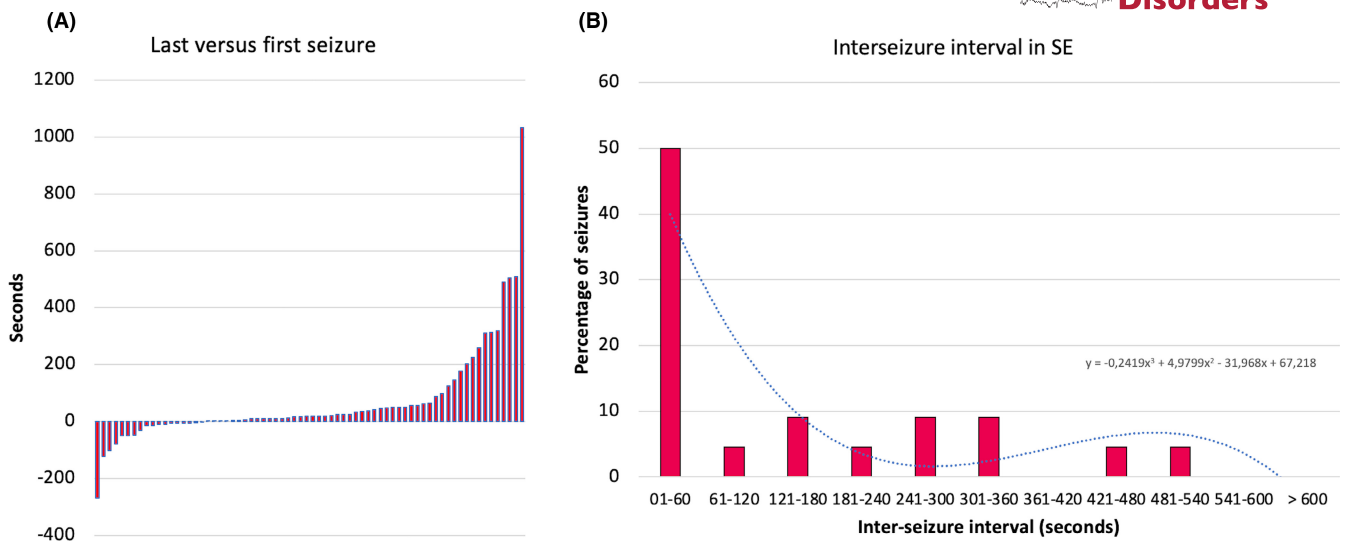


FIGURE 4 Seizures measures of outcome in cases with multiple recorded seizures. Panel A report the difference between the duration of the last- and the first-recorded seizure before ASM treatment in patients in whom more than one focal seizure was recorded. A positive value means that the last seizure was longer than the first. The delta times are ordered from left to right. In the majority of the patients, the delta time was positive. Panel B reports the inter-seizure intervals showing that for most of the patients, the interval between two subsequent seizures was shorter than 1 min.

those observed in focal self-limiting seizures in epilepsy patients.

The longer duration of seizures in SE compared with isolated seizures is likely due to the failure of the mechanisms responsible for seizure termination, which leads to abnormally prolonged ictal discharges, as emphasized in the most recent definition of SE.[2] In a previous study exploring the influence of clinical and demographic factors on isolated seizures' duration, a positive association between age and duration was found, theorizing that aging could impair the mechanisms responsible for seizure termination.[17] However, although the SE group was significantly older than the epilepsy group, we did not find a correlation between age and seizure duration within the SE group. The only significant association we found was with an acute etiology (focal acute brain damage/dysfunction). This finding is clinically relevant and suggests that acute local changes at both cellular (inhibitory and excitatory neurons balance) and molecular levels (receptor trafficking) are prominent factors determining seizure length.

Consistent with a recent previous study, our results support the idea that when a seizure exceeds a certain threshold of duration, the risk of developing SE increases.[5] However, our study also shows that a significant proportion of focal seizures within an episode of SE has a duration that is short or at least comparable to that observed in self-limiting seizures (see Figures 1 and 2). Although our results clearly show that seizures in focal SE are longer than self-limiting seizures, they also highlight that seizure duration alone is not the only seizure metric that can help us understand what is happening in status epilepticus. Our findings support the notion that focal SE is not just a matter of "longer" seizures but is a more complex condition.

From this perspective, the analyses of the other two outcome measures in this study are interesting. The difference in duration between the last and the first seizure, which we observed to be positive (>0 s) in more than 70% of cases, underscores the fact that in SE, seizures tend to become longer. This finding is clinically relevant and further supports the concept of SE as a time-dependent emergency, in which, in the absence of appropriate treatment, the mechanism underlying ictogenesis and seizure termination tends to fail progressively, leading to longer seizures. In 29% of cases with multiple recorded seizures, the last seizure was more than twice as long as the first recorded one. Importantly, the increase in seizure duration was associated with an increased 30-day mortality, and in our population, the threshold was set at a seizure length increase of at least 1.4 times. This finding could have high clinical relevance since it could be considered an early "electrophysiological biomarker" of a more severe SE condition needing more intensive and fast treatment.

Regarding the inter-seizure interval feature, the results of our study show that in most cases of SE seizures, this interval was less than 120 s. This finding raises the question of whether there is a time interval between two seizures below which the development of status epilepticus is highly likely. To our knowledge, there are no studies that have addressed this issue, and it would be of

great clinical relevance to investigate this parameter extensively, as has been done in the last 10 years regarding seizure duration. It would be interesting to perform such an analysis in a study focused on seizure clusters evolving into definite SE.

5 | STUDY LIMITATIONS

Several points must be considered carefully. First, our findings are limited to patients with focal SE characterized by spatiotemporal evolution in EEG discharge and cannot be generalized to status epilepticus with other underlying EEG patterns. Second, a limitation concerns the possible bias and errors due to visual analysis and coding of EEG. However, this can be considered an unlikely event in relation to estimating the duration of electrographic seizures. In fact, seizure duration in our view is a hard measure and not very prone to coding errors. A third point relates to the retrospective nature of the study. Our study has the limitation associated with such retrospective analyses. An important inclusion criterion for SE episodes/patients was to evaluate the first diagnostic EEG obtained before any ASMs treatment. We cannot be completely sure that some patients have received unreported treatments before the EEG recording, especially for the SE episodes with an out-of-hospital onset. However, even if this had happened in some cases, the results obtained would not lose their validity as the duration of the seizures in these cases could have been even longer than the ones recorded. Finally, a limitation inherent in the epilepsy control group relates to the ASM therapy of the patients. Indeed, even in down-titrated patients, there could still be some seizure-shortening effect by the ASM. However, it should be noted that seizures' length in our epilepsy group is in line with data reported from previous studies[3–5] (see Figure 2).

6 | CONCLUSIONS

Human and experimental evidence suggests that the mechanism underlying the seizure onset and termination are functionally distinct in SE compared with isolated seizures. Although the mechanisms determining different seizures' appearance are probably shared between isolated seizures and repetitive seizures within SE, a shift toward the downregulation of inhibitory mechanisms and upregulation of excitatory ones is probably responsible for the appearance of seizures with longer duration and shorter inter-seizure intervals in status epilepticus. We believe that the analysis of these seizures' features is of utmost importance for understanding the mechanisms of interictal to ictal transition. To further increase our understanding, it could be important to replicate and expand these findings through external validation studies and to consider other seizure characteristics (i.e., the pattern of seizure onset and termination), as well as analyze continuous patterns to improve our understanding of seizure generation and hopefully develop new therapeutic targets and strategies.

ACKNOWLEDGMENTS

This research received funding from the Italian MOH: Status epilepticus: improving therapeutic and quality-of-care intervention in the Emilia-Romagna region. Project code: RF-2016-02361365. And by the MIUR: grant "Dipartimenti di eccellenza 2018-2022" to the Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia.

CONFLICT OF INTEREST STATEMENT

G. Giovannini, G. Turchi, N. Orlandi, and M.C. Cioclu report no disclosures. S. Meletti received research grant support from the Ministry of Health (MOH) and has received personal compensation as scientific advisory board member for UCB and EISAI. A.E. Vaudano has received personal compensation as a scientific advisory board member for Angelini.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Meletti S, Turchi G, Orlandi N, Vaudano AE, Cioclu MC, Pugnaghi M, et al. Electrographic seizure duration and inter-seizure intervals in focal status epilepticus. Epileptic Disord. 2023;25:519–527. https://doi.org/10.1002/epd2.20071

Test yourself

1. Which of the following statements is correct?
   A. Focal seizures in an episode of status epilepticus have a significantly longer duration than isolated focal seizures, but they show great variability and in part have durations comparable to isolated seizures
   B. Focal seizures in a status epilepticus episode always have much longer durations than self-limiting isolated seizures
   C. Focal seizures tend to shorten as the status epilepticus continues
   D. Only 5% of focal seizures in status epilepticus have a duration longer than 300 s
2. Which of the following clinical variables is associated with seizures of longer duration?
   A. Female gender
   B. A STESS score > 3
   C. An acute symptomatic etiology
   D. A remote symptomatic etiology
3. In focal status epilepticus with repeated seizures, the intervals between two successive seizures:
   A. have a length of less than 60 s in 50% of the cases
   B. have a length between 120 and 240 s
   C. have a length of less than 30 s in 80% of cases
   D. have a length of more than 5 min in 50% of cases

Answers may be found in the supporting information.