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Mortality and risk of epilepsy after acute symptomatic status epilepticus following ischemic stroke and an updated prognostic model (SeLECT 2.0)

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Key points

Question: Does mortality and the risk of post-stroke epilepsy differ between different types of acute symptomatic seizures occurring within 7 days after ischemic stroke?

Findings: This multicenter study included 4,591 adults with acute ischemic stroke. Acute symptomatic seizures presenting as status epilepticus had a higher 10-year mortality ($\geq 76\%$) and risk of post-stroke epilepsy in stroke survivors ($\geq 81\%$) compared to short seizures (30% and 40%, respectively) and individuals without acute symptomatic seizures (11% and 13%, respectively).

Meaning: Acute symptomatic status epilepticus is associated with an increased risk of mortality and epilepsy following ischemic stroke.

Abstract

Importance: Acute symptomatic seizures occurring within 7 days after ischemic stroke may be associated with an increased mortality and risk of epilepsy. It is unknown whether the type of acute symptomatic seizure influences this risk.

Objective: Compare mortality and risk of epilepsy following different types of acute symptomatic seizures.

Design: Multicenter cohort study, data acquired 2002-2018; replication in three separate cohorts, data acquired 2002-2019; final data analysis July 2022.

Setting: Nine tertiary referral centers.

Participants: The derivation cohort included adults from seven cohort and two case-control studies with neuroimaging-confirmed ischemic stroke and without a history of seizures. The replication cohort included adults with acute symptomatic status epilepticus following neuroimaging-confirmed ischemic stroke.

Exposure: Type of acute symptomatic seizures.

Main Outcome and Measures: All-cause mortality and epilepsy (at least one unprovoked seizure presenting > 7 days after stroke).

Results: We included 4,552 adults (2,005 female; median age 73 years) in the derivation cohort. Acute symptomatic seizures occurred in 226 (5%) individuals, of whom 8 (0.2%) presented with status epilepticus. 10-year mortality was 79% in those with acute symptomatic status epilepticus, compared to 30% in those with short acute symptomatic seizures and 11% in those without seizures. The 10-year risk of epilepsy in stroke survivors with acute symptomatic status epilepticus was 81%, compared to 40% in survivors with short acute symptomatic seizures and 13% in survivors without seizures. In a replication cohort of 39 individuals with acute symptomatic status epilepticus following ischemic stroke (24 female; median age 78 years) the 10-year risk of mortality and epilepsy was 76% and 88% respectively. We updated a previously described prognostic model (SeLECT_{2.0}) with the type

of acute symptomatic seizures as a covariate. SeLECT_{2.0} successfully captured cases at high risk of poststroke epilepsy.

Conclusions and Relevance: Individuals with stroke and acute symptomatic seizures presenting as status epilepticus have a higher mortality and risk of epilepsy compared to those with short acute symptomatic seizures or no seizures. The SeLECT_{2.0} prognostic model adequately reflects the risk of epilepsy in high-risk cases and may inform decisions on the continuation of antiseizure medication treatment and the methods and frequency of follow-up.

Introduction

Stroke has the largest contribution to the global burden and mortality (67% of all deaths) of neurological disorders.¹ Stroke is also the most common cause of acquired epilepsy in the elderly with an estimated incidence of 800,000 vascular epilepsy cases per year worldwide.^{1,2} It remains controversial whether seizures contribute to mortality after stroke.³⁻⁶

Post-stroke seizures are categorized into acute symptomatic, occurring within the first week following stroke onset, or remote symptomatic, which are unprovoked and occur more than 1 week after the insult.⁷ Distinguishing these two types of seizures reflects different underlying pathophysiological mechanisms and has important implications for medical management.

A single remote symptomatic seizure after ischemic stroke qualifies as post-stroke epilepsy due to the high recurrence risk (>60%) of unprovoked seizures within the next 10 years.^{3,8} In contrast, acute symptomatic seizures are considered provoked and do not qualify as epilepsy because of a substantially lower risk of subsequent unprovoked seizures.^{2,3,8} The overall incidence of acute symptomatic seizures ranges from 1 to 4% and long-term treatment with antiseizure medications (ASM) is usually not considered necessary.⁹

It is unknown whether the risk of post-stroke mortality or epilepsy differs between types of acute symptomatic seizures. In clinical practice, many physicians are particularly cautious if acute symptomatic seizures manifest as status epilepticus. There are no clear guidelines for the management of acute symptomatic status epilepticus given its low prevalence of 0.1% to 0.3% in individuals with stroke.¹⁰⁻¹²

Emerging evidence points towards higher mortality related to status epilepticus occurring in people with brain tumors and subarachnoid hemorrhage.^{13,14} It is unknown if acute symptomatic status epilepticus is associated with an increased risk of post-stroke mortality or epilepsy compared to short acute symptomatic seizures.¹⁵

We previously developed and validated a prognostic model, named SeLECT score, in a large multicenter study to predict unprovoked seizures after ischemic stroke.² The original model

did not distinguish between different types of acute symptomatic seizures. Here, we compared the risk of poststroke mortality and epilepsy between different types of acute symptomatic seizures. From a clinical perspective, we hypothesized that the risk of poststroke mortality and epilepsy would be highest following acute symptomatic status epilepticus.

Methods

Participants

We analyzed a derivation and a replication cohort of participants. The derivation cohort (n=4,552) consisted of nine international subcohorts participating in a registry assessing post-stroke seizures incepted as part of the SeLECT study,² see online supplement for detailed information. The replication cohort included participants with acute symptomatic status epilepticus following ischemic stroke from three subcohorts. We screened all participants who were diagnosed with status epilepticus at the University Hospital Zurich, Switzerland (from May 2002 to December 2019), the Vall d'Hebron University Hospital in Barcelona, Spain (from February 2011 to April 2017),¹⁵ and the Udine University Hospital, Italy (from 2011 to 2020), and included those with acute symptomatic status epilepticus following acute ischemic stroke. In all cohorts, eligibility criteria were being 18 years or older with neuroimaging-confirmed acute ischemic stroke. We excluded individuals with a transient ischemic attack, history of seizures or epilepsy, primary hemorrhagic stroke, re-infarction during follow-up or potentially epileptogenic comorbidities (i.e. intracranial tumors, cerebral venous thrombosis, history of severe traumatic brain injury, history of brain surgery) and those initially receiving palliative care.

All local ethical committees granted regulatory approval. Informed consent was obtained in written or verbal form (4 cohorts only written, 2 cohorts both) or consent was waived (3 cohorts) as described in detail in the online supplement.

Definitions

Seizures were classified as acute symptomatic (≤ 7 days after stroke) or remote symptomatic (spontaneous unprovoked seizures > 7 days after stroke).⁷ A single remote symptomatic seizure was classified as post-stroke epilepsy due to the high ($> 60\%$) recurrence risk.^{3,8} For the categorization into status epilepticus or short seizures (i.e. not fulfilling criteria for status epilepticus), we used the revised definition of the ILAE;¹⁶ non-convulsive status epilepticus was defined electroencephalographically according to the Salzburg criteria.¹⁷ Status epilepticus was only diagnosed in cases with clinical signs or symptoms suggestive of convulsive or non-convulsive status epilepticus. Other definitions are given in the online supplement.

Statistical Analysis

In the derivation cohort, we used multivariable Cox proportional hazards regression (**Table 1**) to evaluate the association between acute symptomatic seizure type with time to death or time to first remote symptomatic seizure, while adjusting for co-variables (age, sex, NIH Stroke Scale at admission, cortical involvement, involvement of the middle cerebral artery territory, stroke cause, reperfusion treatment, anti-seizure medication treatment after acute symptomatic seizure). In the replication cohort, we used univariable Cox proportional hazards regression to determine the association of clinical characteristics and acute symptomatic status epilepticus parameters with time to death or time to first remote symptomatic seizure. We did not perform a multivariable analysis in the replication cohort because there were few significant variables in univariable analysis. We censored cases at the time of death, first remote symptomatic seizure, or last follow up. We followed the STROBE reporting guideline.

SeLECT score update

We updated the original SeLECT score² to include the type of acute symptomatic seizure (status epilepticus vs. short seizure) as an additional parameter. We assigned an integer value to each parameter based on their adjusted hazards ratio (aHR).

We assessed model discrimination using the concordance (*c*) statistic. Prognostic models developed from multivariable regression can be optimistic and thereby overestimate predictions when applied to a new cohort of patients.¹⁸ To obtain realistic risk predictions, a shrinkage factor was estimated from 1000 bootstrapped random samples to correct the *c* statistic for over-optimism. This technique has been used previously to improve model generalizability.^{19,20}

Analyses were done with R statistical software version 4.0.3 and SPSS version 26 (IBM Corp.).

Results

The derivation cohort included 4,552 individuals from nine centers. Data on mortality was available in five cohorts (n=3,119). Baseline characteristics are displayed in **Supplemental Table 1**.

Acute symptomatic seizures occurred in 226 patients (5.0%). They were categorized as status epilepticus in 8 (0.2%) individuals, as short seizures in 182 (4.0%), and undetermined or unknown seizure-types in 36 individuals (0.8%). Short seizures were classified as focal aware in 58 (1.3%), focal with impaired awareness in 36 (0.8%), and focal to bilateral tonic-clonic in 88 (1.9%) subjects. The incidence of acute symptomatic status epilepticus was comparable across all cohorts (p=0.17, **Supplemental Table 2**). The association of patient characteristics with the occurrence of acute symptomatic status epilepticus is shown in **Supplemental Table 3**.

Mortality

Acute symptomatic status epilepticus (aHR 12.7, 95% confidence interval [CI] 3.0-52.7, $p < 0.001$) and short acute symptomatic seizures (aHR 3.0, 95% CI 1.8-4.8, $p < 0.001$) were independently associated with a higher all-cause mortality compared to patients without acute symptomatic seizures (**Table 1, Figure 1A**). Acute symptomatic status epilepticus had a higher mortality (aHR 8.2, 95% CI 3.8-17.9, $p < 0.001$) when directly compared with short acute symptomatic seizures. Acute symptomatic status epilepticus remained a significant predictor of mortality (aHR 8.1, 95% CI 1.9-35.1, $p = 0.005$) after additional correction for prestroke disability and comorbidities in a subcohort of participants with available data ($n = 1069$, **Supplemental Table 4**). We also replicated this finding in a subgroup with more recent data acquired after 2014 ($n = 1,334$; **Supplemental Table 5**).

The estimated all-cause mortality following acute symptomatic status epilepticus was 60% after 2 years and 79% after 10 years of the index stroke (**Figure 1A**). Mortality was lower following short acute symptomatic seizures (19% after 2 years; 30% after 10 years) and in individuals without acute symptomatic seizures (7% after 2 years; 11% after 10 years).

To corroborate our findings, we assessed a replication cohort of 39 adults with acute symptomatic status epilepticus following ischemic stroke that met eligibility criteria (Zurich, $n = 13$; Barcelona, $n = 21$; Udine, $n = 5$). Baseline characteristics of these individuals are displayed in **Supplemental Table 6**. Two and ten years after the index stroke 59% and 76% died respectively (**Figure 1B**). Characteristics of the status epilepticus were not associated with mortality (**Supplemental Table 6**). The causes of documented deaths were infection ($n = 11$, 48%), transition to palliative care ($n = 3$, 13%), cardiovascular ($n = 2$, 9%), other nonvascular causes ($n = 3$, 9%), or unknown ($n = 4$, 17%).

Risk of remote symptomatic seizures

Acute symptomatic status epilepticus was independently associated with an increased risk of remote symptomatic seizures (**Table 2**, aHR 4.3, 95% confidence interval [CI] 1.3-13.9,

p=0.02) compared to short seizures in the derivation cohort (**Figure 1C**). We found no significant association with other covariates (demographics, stroke severity, location, cause, and early treatment; **Table 2**). We replicated this finding in a subgroup with more recent data acquired after 2014 (**Supplemental Table 7**).

The risk of stroke survivors having remote symptomatic seizures following acute symptomatic status epilepticus was 46% after 2 years and 81% after 10 years of the index stroke (**Figure 1C**). This risk was lower following short acute symptomatic seizures (17% after 2 years; 40% after 10 years) and in individuals without acute symptomatic seizures (4% after 2 years; 13% after 10 years).

In the replication cohort 63% and 88% of stroke survivors had remote symptomatic seizures 2 and 10 years after stroke, respectively (**Figure 1D**). Characteristics of the status epilepticus were not associated with the risk of remote symptomatic seizures (**Supplemental Table 8**).

Modified prognostic model

The updated “SeLECT_{2.0}” score ranges from 0 to 13 points, awarding additional 4 points if an acute symptomatic status epilepticus occurs (**Table 3, Supplemental Table 9**). SeLECT_{2.0} had a comparable optimism-corrected discrimination (0.77) to the original model (SeLECT, 0.77). The lowest SeLECT_{2.0} value (0 points) predicts a 2% (95% CI 1-3) risk of remote symptomatic seizures within 5 years following stroke, compared to a 100% (95% CI 98-100) risk for the highest value (13 points, **Figure 2**). In contrast, the highest value (9 points) of the original SeLECT score predicts a 77% (95% CI 62-86) risk of remote symptomatic seizures within 5 years. The prediction charts of the original SeLECT score (**Supplemental Figure 1**) do not adequately capture very high-risk cases compared to the modified SeLECT_{2.0} score (**Figure 2**). We updated the “SeLECT score” web (<https://predictapps.github.io/select/>) and

smartphone applications available for iOS (<https://apps.apple.com/app/id1241429202>) and Android (<https://play.google.com/store/apps/details?id=sk.sasak.select>) to reflect these changes.

Example case

As an example, we considered a 65-year-old male admitted to hospital due to acute ischemic stroke of cardioembolic etiology affecting the posterior cerebral artery territory and involving the cortex with 6 points on NIH Stroke Scale (NIHSS) at admission, who suffered a focal to bilateral tonic clonic seizure developing into status epilepticus on the first day of admission. The original SeLECT score for this case is 6 points, predicting a 29% (95% CI 24-33) risk of remote symptomatic seizures within 5 years after stroke. In contrast, the updated SeLECT_{2.0} score is 10 points, predicting an 86% (95% CI 73-93) risk of remote symptomatic seizures within 5 years.

Discussion

Using data from nine international cohorts we show that acute symptomatic status epilepticus is associated with a high risk of post-stroke mortality and epilepsy. Acute symptomatic status epilepticus, albeit being rare, was the strongest and most robust predictor of mortality and epilepsy after stroke. We observed similarly high risks in an independent replication cohort. We implemented the type of acute symptomatic seizures into a previously described prognostic model. The updated model (SeLECT_{2.0}) more adequately captured cases at high risk of poststroke epilepsy.

Acute symptomatic status epilepticus following ischemic stroke is rare. In our multicenter dataset, 0.2% of individuals with stroke had acute symptomatic status epilepticus. This is similar to previous studies reporting a prevalence between 0.1% to 0.3%.¹⁰⁻¹² The pathophysiological mechanisms underlying acute symptomatic seizures include metabolic

dysfunction, blood-brain barrier disruption, inflammation, and the release of excitotoxic neurotransmitters secondary to ischemic brain damage.⁹ Status epilepticus following stroke may occur due to the failure of seizure-terminating mechanisms. It may point to a higher severity of neuronal or metabolic disruption or to a lower individual seizure threshold. In this study, acute symptomatic status epilepticus was the best indicator of poststroke mortality, which is in line with previous observations in people with brain tumors and subarachnoid hemorrhage.^{13,14} This association was independent from age, NIHSS, stroke location, stroke etiology, reperfusion treatment, and, in a subcohort, from prestroke disability and comorbidities.

We propose several potential explanations for the high mortality following acute symptomatic status epilepticus. Firstly, acute symptomatic status epilepticus may be an indicator of severe neuronal injury that is not adequately reflected by the NIHSS. Secondly, patients with acute symptomatic status epilepticus may be more prone to infections and other complications during hospital stay related to a prolonged impairment of consciousness due to status epilepticus or its treatment. The presence of dysphagia or medical installations, such as catheters, may increase the risk of infections after discharge from hospital. Accordingly, infections during hospital stay and after discharge were the most common cause of mortality in the replication cohort. Thirdly, patients with stroke and acute symptomatic status epilepticus may be more likely to transition to palliative care due to the perceived simultaneous impact of both conditions. Fourthly, status epilepticus or its treatment may interfere with early stroke rehabilitation, leading to worse long-term outcomes. We did not find a significant association of poststroke mortality with any single characteristic of status epilepticus. It is thus likely that a combination of the above mentioned factors, and possibly other unidentified factors, could be the cause of increased mortality in these cases. Additionally, an acute symptomatic status epilepticus may directly impair poststroke outcomes. This could be related to the well-described neurotoxic effects of prolonged

seizures.^{21,22} Prolonged seizure activity leads to an overactivation of NMDA receptors that may cause excitotoxicity and could mediate ischemic damage after stroke.^{23,24} Future studies should assess the molecular mechanisms underlying the poor outcome following poststroke status epilepticus. In contrast, short acute symptomatic seizures were a less robust predictor of poststroke mortality, and the association was not significant after correction for prestroke disability and comorbidities.

Acute symptomatic status epilepticus was independently associated with an increased risk of poststroke epilepsy when compared to short acute symptomatic seizures. A similar association was reported in a study that included individuals with cerebral venous thrombosis,²⁵ and in a population-based cohort that included individuals with acute symptomatic seizures due to different etiologies.²⁶ In our study, the increased risk of developing epilepsy following initial status epilepticus remained significant after the correction for demographic factors and the severity, location, and cause of stroke. Thus, more severe strokes are unlikely to explain the higher propensity for epileptogenesis in these cases. Status epilepticus was the only and major risk factor for epilepsy following an acute symptomatic seizure (**Table 2**), highlighting the important prognostic role of status epilepticus compared to other variables. In a previous study evaluating acute symptomatic status epilepticus following ischemic or hemorrhagic stroke, those with a status epilepticus duration > 16 hours had a higher risk of post-stroke epilepsy.¹⁵ We did not observe such an association in our study.

Several factors may contribute to epileptogenesis following acute symptomatic status epilepticus. A lower seizure-threshold or the failure of seizure-terminating mechanisms that contribute to the acute symptomatic status epilepticus may also affect the development of epilepsy. A large number of animal studies points to a direct pro-epileptogenic effect of prolonged seizures.²⁷ Status epilepticus may cause brain injuries, as demonstrated in animal²⁷ and small human^{21,22} studies. The additional structural or functional disruptions caused by prolonged seizures may contribute to epileptogenesis.

To provide realistic expectations of the risk of post-stroke epilepsy, we created an updated SeLECT_{2.0} prognostic model that incorporates the type of acute symptomatic seizures into the model prediction. The overall discrimination of the SeLECT_{2.0} model was not better than of the original SeLECT model, because acute symptomatic status epilepticus is a rare phenomenon and, thus, contributes only minimally to overall model performance. However, our prediction charts indicate that the novel SeLECT_{2.0} model may improve the ability to detect rare cases at very high risk of developing post-stroke epilepsy (**Figure 2** vs. **Supplemental Figure 1**). Eight or more points on the SeLECT_{2.0} model predict a >60% risk of unprovoked seizures over 10 years. The SeLECT_{2.0} model may, thus, influence treatment decisions in these high-risk cases.

Our results have several implications. First, acute symptomatic status epilepticus is an indicator of high mortality which is important for the information of relatives and healthcare providers about realistic outcome expectations. Second, the risk of unprovoked seizures in stroke survivors following a post-stroke acute symptomatic status epilepticus (81% in the derivation and 88% in the replication cohorts over 10 years) exceeds the 60% threshold outlined in the ILAE practical clinical definition of epilepsy.¹³ Thus, patients and caregivers should be informed about the high risk of post-stroke epilepsy and encouraged to report incidents that may be suspicious for seizures. Third, the high risk of unprovoked seizures may have an impact on the patients' ability to drive or work and influence their quality of life. Fourth, clinicians may consider to schedule follow up visits or to perform follow up electroencephalography to assess the risk of seizures and the need for treatment with antiseizure medications. Lastly, most patients with an acute symptomatic status epilepticus receive initial treatment with ASMs. ASMs were started in all cases with status epilepticus in our cohorts. Because of the high risk of unprovoked seizures, some clinicians may consider long-term ASM treatment in these cases. It is, however, unclear whether starting or

continuing ASMs following acute symptomatic status epilepticus is efficient to prevent further seizures and this will need to be addressed in prospective studies.

Improvements in stroke care led to a decrease in overall stroke-related mortality over the past decades.²⁸ In contrast, status epilepticus-related mortality seemed to be stagnating.²⁹ Future research will need to address potentially modifiable factors in people with acute symptomatic status epilepticus to reduce the impact of status epilepticus on post-stroke mortality.

Our study has several strengths. We evaluated one of the largest multicenter cohorts of post-stroke seizures. We replicated our findings in a separate cohort, supporting the robustness and generalisability of the results. We incorporated the findings into a simple and practical prognostic model, SeLECT_{2.0}, that may help guide follow-up and clinical decisions in these cases. We updated the “SeLECT score” smartphone app for iOS and Android to assist in calculations at bedside.

Our study has limitations. Firstly, the diagnosis of seizures in the SeLECT registry was largely based on clinical evaluation. An electroencephalogram (EEG) was not performed in all cases. This reflects differences in local protocols evaluating post-stroke seizures. Because it was practically not possible to perform continuous EEG monitoring in all cases in our large cohorts, the incidence of non-convulsive status epilepticus may have been underestimated. Thus, our results only apply to convulsive or non-convulsive status epilepticus with clinical signs or symptoms and cannot be generalized to status epilepticus without any apparent clinical symptoms. Secondly, the number of individuals having an acute symptomatic status epilepticus was low despite the large sample size of our multicenter cohorts. Thirdly, detailed status epilepticus parameters were not collected in the SeLECT registry. However, our replication cohorts provide information on the type, severity, duration, and treatment of status epilepticus and showed that these factors did not influence the risk of post-stroke epilepsy. Fourthly, all individuals with acute symptomatic status epilepticus received early ASM treatment. This may have altered our results and the risk of unprovoked seizures may be even

higher in an untreated population. Fifthly, data on causes of death or long-term disability were not collected in the SeLECT registry. Data on prestroke disability and comorbidities was only available in a subcohort (n=1069). Lastly, although we performed internal multicenter validation of the SeLECT_{2.0} model with correction for overoptimism, we did not validate the model externally. However, given a comparable model discrimination, we expect that SeLECT_{2.0} would have a similarly good performance as the original SeLECT model when applied to external cohorts.

To conclude, we showed that acute symptomatic status epilepticus following stroke is associated with a high risk of mortality and epilepsy. We provide an updated calculator (SeLECT_{2.0} model) to more adequately predict the individualized risk of poststroke epilepsy. The improved predictions using SeLECT_{2.0} may make a relevant difference for some stroke survivors at high risk of epilepsy. SeLECT_{2.0} will have a practical utility for physicians regarding the continuation of ASM treatment and the methods and frequency of follow-up.

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Authors Contributions

LS, LA, LI, DZ, MK, NS, GB, and MG conceptualized and designed the study. ND, BEC, AF, PS, NS, GB, JS, CFA, MK, NS, GB, LI, MK, LA, ES, JAS, MW, TJO, JNW, GLG, AS, FJ, GM, MV, GG, JC, SE, PL, FR, FB, CB, ARP, TPM, BT, MRK, JSD, JWS, BT, MJK, MG contributed to the acquisition and analysis of the data. LS, LA, and MG contributed to the interpretation of the data. LS and MG drafted the manuscript and figures. All co-authors revised the manuscript for intellectual content.

Potential Conflicts of Interest

LA has received personal fees and travel support from UCB Pharma, Eisai, Esteve and Bial and personal fees from Sanofi outside the submitted work. ES has received grants and personal fees from UCB Pharma, personal fees from Eisai, personal fees from Esteve, and grants and personal fees from Bial, outside the submitted work. MK received non-financial (in kind) support from ROCHE and BRAHMS Thermofisher Scientific outside the submitted work. SE received honoraria for consulting and for lectures from from Allergan/Abbvie, Lilly,

Lundbeck, Novartis, Perfood, Teva (past 3 years). FB received fees and travel support from Lusofarmaco, outside the submitted work. CB received a Grant from Sociedade Portuguesa do AVC (sponsor by Tecnifar), honoraria for lectures and support for scientific events from Bial, Eisae and Angelini outside the submitted work. MK received non-financial (in kind) support from ROCHE and BRAHMS Thermofisher Scientific outside the submitted work. MRK reports grants from UCB and Eisai, outside of the submitted work. BT reports personal fees from Biogen outside the submitted work. JWS reports grants and personal fees from UCB and grants from Netherland Epilepsy Funds and GW Pharma; and personal fees from Zogenix and Arvelle outside the submitted work. MG received fees and travel support from Arvelle, Advisis, Bial, Nestlé Health Science, and UCB outside the submitted work. All other authors declare no competing interests. JNW received fees from Boehringer Ingelheim and UCB as well as travel grants from ROCHE, outside the submitted work. TJO reports personal fees from Liva Nova, Indivior Austria GmbH, Philips, UCB Pharma, Almirall, Arvelle Therapeutics, GW Pharma, Zogenix GmbH, Angelini Pharma Österreich, Novartis Pharma GmbH, Bayer Pharma GmbH, grants from Merck, personal fees and non-financial support from gtec GmbH Austria, grants, personal fees and non-financial support from Boehringer-Ingelheim, grants and personal fees from Eisai outside the submitted work.

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Tables

Table 1: *Multivariable Cox regression model of time to death in the derivation cohort.*

Variable	aHR (95% CI)	P value
Demographics		
Age (<i>per 10 years</i>)	2.1 (1.9-2.4)	<0.001
Male sex	1.1 (0.9-1.4)	0.25
Stroke severity at admission		
NIHSS 4-10	1.9 (1.4-2.5)	<0.001
NIHSS \geq 11	3.3 (2.4-4.5)	<0.001
Stroke location		
Middle cerebral artery territory involvement	1.0 (0.8-1.4)	0.76
Cortical involvement	1.1 (0.9-1.5)	0.32
Stroke cause		
Small-vessel occlusion	0.5 (0.3-0.7)	<0.001
Larger-artery atherosclerosis	0.5 (0.4-0.8)	0.001
Cardioembolic	0.7 (0.6-0.9)	0.008
Treatment		
Acute reperfusion treatment	0.9 (0.7-1.2)	0.40
ASM treatment after acute symptomatic seizure	0.3 (0.1-0.6)	0.001
Acute symptomatic seizure type		
Short seizure	3.0 (1.8-4.8)	<0.001
Status epilepticus	12.7 (3.0-52.7)	<0.001

Data analyzed using a Cox proportional hazards model in the derivation cohort (n=4552).

Dependent variable was time to death of any cause.

aHR, adjusted hazard ratio; NIHSS, National Institutes of Healthy Stroke Scale; ASM, anti-seizure medication.

Table 2: Multivariable Cox regression model of time to first remote symptomatic seizure in stroke survivors with an acute symptomatic seizure in the derivation cohort.

Variable	aHR (95% CI)	P value
Demographics		
Age (<i>per 10 years</i>)	1.0 (0.8-1.3)	0.75
Male sex	1.0 (0.5-2.0)	0.92
Stroke severity at admission		
NIHSS 4-10	0.5 (0.2-1.2)	0.13
NIHSS \geq 11	0.7 (0.3-1.7)	0.40
Stroke location		
Middle cerebral artery territory involvement	0.9 (0.4-2.0)	0.86
Cortical involvement	1.9 (0.9-3.9)	0.08
Stroke cause		
Small-vessel occlusion	1.1 (0.2-5.2)	0.90
Larger-artery atherosclerosis	1.6 (0.7-3.8)	0.31
Cardioembolic	1.1 (0.4-2.7)	0.88
Treatment		
Acute reperfusion treatment	1.7 (0.8-3.6)	0.19
ASM treatment after acute symptomatic seizure	0.7 (0.4-1.4)	0.29
Acute symptomatic seizure type		
Status epilepticus (<i>vs. short seizures</i>)	4.3 (1.3-13.9)	0.02

Data analyzed using a Cox proportional hazards model in stroke survivors that had an acute symptomatic seizure with known seizure type (n=190). Dependent variable was time to first remote symptomatic seizure after stroke.

aHR, adjusted hazard ratio; NIHSS, National Institutes of Healthy Stroke Scale; ASM, anti-seizure medication.

Table 3: Comparison of the original SeLECT scoring system and the modified SeLECT score including acute symptomatic status epilepticus (SeLECT_{2.0}).

Original SeLECT		SeLECT_{2.0}	
NIHSS 4-10	1	NIHSS 4-10	1
NIHSS \geq 11	2	NIHSS \geq 11	2
Large-artery atherosclerosis	1	Large-artery atherosclerosis	1
Any acute symptomatic seizure	3	Short acute symptomatic seizure	3
		Acute symptomatic status epilepticus	7
Cortical involvement	2	Cortical involvement	2
Territory of MCA involvement	1	Territory of MCA involvement	1
MAXIMUM POINTS	9	MAXIMUM POINTS	13

Figures

Figure 1: *Risk of mortality or remote symptomatic seizures following acute symptomatic seizures after stroke.*

This figure displays Kaplan Meier plots of the time to death (**Panels A and B**) and time to first unprovoked remote symptomatic seizure (**Panels C and D**) following acute symptomatic seizures after ischemic stroke. The data according to the type of acute symptomatic seizure in the derivation cohort (n=4529) is displayed in **panels A and C**. The data following acute symptomatic status epilepticus in the replication cohort (n=39 patients with acute symptomatic status epilepticus) is shown in **panels B and D**. The tables below display the Kaplan Meier estimates of the risk of remote symptomatic seizures 1 to 10 years after index stroke according to the type of acute symptomatic seizure. All results were obtained after adjusting for co-variates (age, sex, NIH Stroke Scale at admission, cortical involvement, involvement of the middle cerebral artery territory, stroke cause, reperfusion treatment, anti-seizure medication treatment after acute symptomatic seizure). The grey dotted horizontal line denotes the 60% cut-off for the risk of unprovoked seizures used in the ILAE practical clinical definition of epilepsy.

FA, focal aware seizure; FIA, focal seizure with impaired awareness; FBTC, focal to bilateral tonic-clonic seizure; SE, status epilepticus; UD, undetermined or unknown seizure type; no ASS, no acute symptomatic seizures.

Figure 2: *Predicted risk of remote symptomatic seizures according to the updated SeLECT_{2.0} score.*

Panel A shows the predicted risk of unprovoked remote symptomatic seizures 0–96 months after stroke. Each curve represents the estimates for a SeLECT_{2.0} value, ranging from 0 to 13. Risk estimate charts of late seizures 1 year and 5 years after stroke according to SeLECT_{2.0} score values are displayed in **panels B and C** respectively. Vertical lines are 95% CIs.