

The Role of Electroencephalography in Predicting Post-Stroke Seizures and an Updated Prognostic Model (SeLECT-EEG)

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Objective: Seizures negatively impact stroke outcomes, highlighting the need for reliable predictors of post-stroke epilepsy. Although acute symptomatic seizures are a known risk factor, most stroke survivors who develop epilepsy do not experience them. Early electroencephalography (EEG) findings may enhance risk prediction, particularly in patients without acute symptomatic seizures, aiding in patient management and counseling.

Methods: We conducted a multicenter cohort study using data from 1,105 stroke survivors (mean age 71 years, 54% male) with neuroimaging-confirmed ischemic stroke who underwent EEG within 7 days post-stroke. Electrographic biomarkers, including epileptiform activity and regional slowing, were analyzed for their association with post-stroke epilepsy using Cox proportional hazards regression and Fine–Gray subdistribution hazard models, adjusted for differences in EEG timing and patient characteristics.

Results: Post-stroke epilepsy developed in 119 patients (11%), whereas 233 (21%) had acute symptomatic seizures. The 5-year epilepsy risk was 42% (95% confidence interval [CI]: 30–49%) in patients with epileptiform activity versus 13% (95% CI: 9–16%) in those without. Regional slowing doubled the 5-year epilepsy risk (23%, 95% CI: 17–30% vs 11%, 95% CI: 7–16%). Epileptiform activity (subdistribution hazard ratio: 2.3, 95% CI: 1.5–3.4, $p < 0.001$) and regional slowing (subdistribution hazard ratio: 1.7, 95% CI: 1.1–2.7, $p = 0.02$) were independently associated with post-stroke epilepsy. A novel prognostic model, SeLECT-EEG (concordance statistic: 0.75, 95% CI: 0.71–0.80), outperformed the previous standard (SeLECT_{2.0}; 0.71, 95% CI: 0.65–0.76, $p < 0.001$).

Interpretation: Electrographic biomarkers improve post-stroke epilepsy prediction beyond clinical risk factors. The SeLECT-EEG model enhances early risk stratification, particularly in patients without acute symptomatic seizures, informing management strategies and patient counseling.

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Additional supporting information can be found in the online version of this article.

Stroke is the leading cause of epilepsy in older adults, accounting for over half of new-onset epilepsy cases in individuals age 65 and above.¹ Post-stroke seizures increase the risk of mortality, poor functional outcomes, disability, and dementia.^{2–5} Identifying accurate early predictors of post-stroke epilepsy is crucial for developing individualized management strategies for stroke survivors.

Although acute symptomatic seizures (ASyS) significantly increase the risk of post-stroke epilepsy,⁶ they occur in only a minority of patients, making it crucial to develop better predictive models and explore additional modalities for the majority of stroke patients without ASyS who are still at risk of developing post-stroke epilepsy.

Although epilepsy is a multifaceted neurological disease, electroencephalography (EEG) provides one of the most established and accessible disease biomarkers. However, the role of early EEG findings in predicting post-stroke epilepsy remains underexplored. Known predictors primarily include clinical and neuroimaging parameters, such as acute symptomatic (≤ 7 days post-stroke) clinical seizures, seizure type and timing,^{4,5} stroke severity, large-artery atherosclerosis, cortical involvement, middle cerebral artery (MCA) territory involvement, and hemorrhagic conversion.^{6,7} These factors are incorporated into clinical scores like SeLECT, SeLECT_{2.0}, and SeLECT-ASyS prognostic models.^{4,8,9}

Use of EEG in managing patients with acute brain injuries like stroke is already prevalent in the United States (US) and is gaining popularity in Europe.¹⁰ Up to 12% of acute ischemic stroke survivors present with electrographic seizures (ESz), and 25% show rhythmic or periodic patterns (RPPs) on EEG during the acute phase.^{11–14} Risk factors for ESz and RPPs are similar to those for post-stroke epilepsy, suggesting they may herald post-stroke epilepsy.¹⁵ EEG is also sensitive to ischemic cortical injury and has been found to predict post-stroke epilepsy following other brain insults like traumatic brain injury (TBI).^{16–18} Continuous EEG (cEEG) monitoring has shown that highly epileptogenic RPPs are associated with the development of post-stroke epilepsy and can likely complement clinical risk factors.^{19,20}

This study aims to clarify whether electrographic findings on short, commonly used, and widely available scalp EEG, as well as cEEG during the acute phase of ischemic stroke, are associated with a higher risk of post-stroke epilepsy. It also seeks to determine if these EEG findings provide complementary prognostic information to clinical risk factors and help improve currently available prognostic models, particularly for patients without ASyS.

Methods

Participants

The derivation cohort included 980 participants from 5 international cohorts. The first external validation cohort from Germany included 125 stroke survivors. A second independent validation cohort from Italy consisted of 84 participants. All participants were adults with acute ischemic stroke who received EEG within the first 7 days after stroke. For inverse probability weighting (IPW), we additionally analyzed data from a multicenter registry of seizures after ischemic stroke established as part of the SeLECT study,⁸ (8 international cohorts comprising 3,711 participants). Individuals with transient ischemic attacks, a previous history of seizures or epilepsy, primary hemorrhagic stroke, re-infarction during follow-up, or potentially epileptogenic comorbidities (such as intracranial tumors, cerebral venous thrombosis, severe traumatic brain injury, or prior brain surgery) were excluded from the study. Detailed descriptions of the individual cohorts are provided in the online supporting information.

Informed consent was obtained either in written or verbal form. Four cohorts used written consent, whereas 2 cohorts used both written and verbal consent. In 5 cohorts, consent requirements were waived by the regulatory authorities, as detailed in the supporting information.

Definitions

Seizures were classified as ASyS if they occurred within 7 days of the stroke and remote symptomatic seizures (RSyS) if they were unprovoked and occurred more than 7 days after the stroke, in accordance with International League Against Epilepsy (ILAE) guidelines.²¹ The occurrence of RSyS was categorized as post-stroke epilepsy because of its high risk of seizure recurrence, exceeding the 60% risk required for the ILAE epilepsy definition.²² Status epilepticus was classified according to the revised ILAE definition,²³ and electrographic status epilepticus was defined based on the Salzburg criteria.²⁴

Short EEG recordings were defined as those lasting between 20 and 60 minutes, whereas cEEG recordings lasted at least 12 hours. Each cEEG was preceded by a 20-minute EEG screening. Epileptiform activity on EEG included ESz and electrographic status epilepticus (E-SE) based on Salzburg, American Clinical Neurophysiology Society (ACNS) criteria and the unified diagnostic framework for nonconvulsive status epilepticus,^{24–26} interictal epileptiform discharges (IEDs) based on International Federation of Clinical Neurophysiology criteria,²⁷ lateralized periodic discharges (LPDs), lateralized rhythmic delta activity (LRDA), and generalized periodic discharges (GPDs), following the ACNS nomenclature.²⁵ Focal and

generalized slowing was also analyzed as a possible risk factor. Detection rates of these patterns in short EEGs versus cEEGs were compared, and their contributions to the predictive performance of the SeLECT-EEG model were assessed.

Further definitions and EEG parameter characterizations are provided in the Supporting information.

Design and Methodology

The flowchart in Figure S1 details the selection process for the study population. A total of 1,261 post-stroke survivors from 7 centers were included based on the availability of EEG data, which included three cohorts specifically designed to assess EEG after stroke and 4 cohorts that routinely acquired EEG data as part of standard clinical practice. Among these, 1,189 had EEG performed within 7 days of stroke. This group was then divided into the derivation cohort ($n = 980$) and 2 validation cohorts. The first from Germany ($n = 125$) and the second from Italy ($n = 84$) and within the derivation cohort, 336 post-stroke survivors had cEEG data available.

Statistics

First, we used multivariable Cox proportional hazards regression in the derivation cohort to assess the relationship between clinical and electrographic findings and the time to post-stroke epilepsy while adjusting for known predictors of post-stroke epilepsy: National Institutes of Health Stroke Scale (NIHSS) score at admission, cortical involvement, involvement of the MCA territory, and large artery atherosclerosis.^{4,8} To account for the competing risk of death, Fine–Gray subdistribution hazard models were additionally applied using the same covariates. Time zero for the survival analysis was defined as the time of stroke onset, consistent with previous SeLECT models. This approach ensures comparability across models and reflects the biological onset of epileptogenesis, even in patients without acute symptomatic seizures. In survival analyses, the first occurrence of RSyS was treated as the event of interest, consistent with the ILAE definition of post-stroke epilepsy.²² Patients were censored only at the time of last follow-up or death without RSyS. Adjusted risk estimates for post-stroke epilepsy were obtained from these multivariable Cox regression models.

Given that electrographic findings demonstrated a higher prognostic value in stroke survivors without ASyS, as described in the results, we developed a novel predictive model, called SeLECT-EEG, specifically for this subgroup to enhance the prediction of post-stroke epilepsy. Variables previously reported in the SeLECT_{2.0} prognostic model⁴ were retained in the new SeLECT-EEG model. This was done to maintain consistency with previous

models and because these variables were repeatedly shown to be associated with post-stroke epilepsy in previous studies. We assigned integer values to the retained variables based on their adjusted hazard ratios (aHR) (see Table 1). To ensure comparability between the new SeLECT-EEG prediction model and the previous SeLECT_{2.0} model and to adjust for the higher propensity of receiving an EEG in those at greater risk of post-stroke epilepsy—that may have artificially inflated risk estimates—we performed IPW using 3,711 stroke survivors from the remaining cohorts in the SeLECT registry as a reference. IPW weights were derived using the WeightIt package in R (method = “ps”, estimand = “ATE”) and applied to a Cox proportional hazards model predicting post-stroke epilepsy. Only patients without early seizures were included. This approach allowed estimation of risk distributions and model performance representative of the entire SeLECT registry population.

Kaplan–Meier estimate plots were applied to compare the observed RSyS risk in those with versus without significant electrographic findings from the initial Cox proportional hazards regression model. For the estimation of absolute seizure risk up to 7 years in relation to these EEG predictors, cumulative incidence functions were additionally used to account for death as a competing event and provide more accurate long-term risk estimates in this older stroke population with non-negligible mortality. For predictions of the new SeLECT-EEG scores up to 10 years, we used the surv function in RStudio, aligning with the ILAE definition of epilepsy by identifying patients with a $\geq 60\%$ 10-year risk, supporting clinical decision-making and treatment strategies.

Model performance was evaluated by assessing discrimination and calibration in both the derivation and external validation cohorts. In the validation cohort from Germany, missing values for generalized and regional slowing were imputed using multiple imputation by chained equations (MICE) with logistic regression (R package mice). The imputation model included relevant clinical and EEG variables: sex, late seizure occurrence, NIHSS, time to seizure, macrovascular stroke etiology, MCA and cortical involvement, early seizures, and all epileptiform EEG patterns. To evaluate the novel model’s discrimination—the ability to distinguish between high and low-risk cases—we estimated the C-statistic (95% confidence interval [CI]). Recognizing that predictive models derived from multivariable regression may be optimistic and potentially overestimate predictions when applied to new cohorts, we introduced a shrinkage factor. This factor was estimated through 1,000 bootstrapped random samples to adjust the C-statistic for overoptimism, a technique previously used to enhance model generalizability.^{28,29} We also assessed model calibration—the agreement

TABLE 1. Comparison of the Original SeLECT_{2.0} Scoring System (in Stroke Survivors without Acute-Symptomatic Seizures) and the Modified SeLECT-EEG Score Including Electrographic Findings

Criteria	aHR (95% CI)	SeLECT-EEG (points)	SeLECT _{2.0} (points)
Severity of stroke			
NIHSS 4–10	1.1 (0.5–2.1)	1	1
NIHSS ≥11	2.9 (1.6–5.3)	2	2
Large-artery atherosclerosis			
No	–	0	0
Yes	1.3 (0.7–2.1)	1	1
Cortical involvement			
No	–	0	0
Yes	2.5 (1.4–4.7)	2	2
Territory of MCA involvement			
No	–	0	0
Yes	1.3 (0.7–2.7)	1	1
Electrographic biomarkers			
Regional slowing			
No	–	0	–
Yes	2.4 (1.4–4.4)	1	–
All epileptiform activity (IED, GPD, LPD, LRDA, ESei, E-SE)			–
No	–	0	–
Yes	2.0 (1.2–3.1)	1	–
Maximum points		8	6

To calculate an individual's SeLECT-EEG score, the points associated with each predictor (aHR <2.5 = 1 point and aHR >2.5 = 2 points) can be added to obtain the total risk score. The total score ranges from 0 to 8 points.

aHR = adjusted hazard ratio; EEG = electroencephalography; E-SE = electrographic status epilepticus; ESei = electrographic seizures; GPD = generalized periodic discharges; IED = interictal epileptic activity; LPD = lateralized periodic discharges; LRDA = lateralized rhythmic delta activity; MCA = middle cerebral artery; NIHSS = National Institutes of Health Stroke Scale.

between predicted and observed risks—using calibration plots (Fig S2). Because of limited number of remote symptomatic seizures in the external validation cohorts (Germany and Italy), calibration was performed on the combined dataset ($n = 193$). A 45° diagonal line represents perfect calibration, whereas deviations above or below this line reflect underprediction or overprediction. We used a leave-one-cohort-out strategy to cross-validate model performance (Table S7). Furthermore, mediation analysis was performed to assess the role of epileptiform activity as a mediator in the relationship between regional and generalized slowing and late seizure outcomes.

Finally, we calculated the change of occurrence of a seizure in the next year (COSY),³⁰ relevant for assessing driving fitness in individuals with seizures, using standard conditional risk definitions (Fig S4).³¹ Suggested COSY thresholds are <20 to 40% for private driving and <2% for professional driving, although these may vary by local regulations.^{32–34}

Results

The baseline characteristics and frequency of EEG parameters for the derivation cohort are shown in Table 2,

TABLE 2. Predictors of Post-Stroke Epilepsy: Univariate Time-To-Event Analysis Using Cox Regression (n = 980)

Variable	HR or MD (95% CI)	<i>p</i>
Total		
Age (yr)	−4 (−6.7 to −1.3)	0.004
Sex		
M	1.1 (0.7–1.6)	0.84
Time of follow-up (in mo)	−3.0 (−7.8–1.8)	0.22
NIHSS at admission		
≤3	0.5 (0.3–0.8)	0.002
4–10	0.5 (0.3–0.8)	0.005
≥11	3.3 (2.3–4.9)	<0.001
Stroke location		
Middle cerebral artery territory involvement	2.2 (1.3–3.7)	0.02
Cortical involvement	3.0 (1.8–5.0)	<0.001
Stroke cause		
Large-artery atherosclerosis	1.6 (1.0–2.4)	0.04
All other	0.6 (0.4–0.9)	0.02
Seizures		
Acute symptomatic seizures	4.1 (2.7–6.1)	<0.001
EEG parameters		
Normal	0.2 (0.1–0.5)	<0.001
Generalized slowing	2.7 (1.9–4.0)	<0.001
Generalized rhythmic slowing	1.0 (0.6–1.7)	0.98
Regional slowing	2.6 (1.7–4.0)	<0.001
Regional rhythmic slowing (LRDA)	1.6 (0.8–3.0)	0.16
Generalized periodic discharges	2.3 (1.0–5.4)	0.05
IED	3.2 (2.0–5.4)	<0.001
LPD	4.6 (2.8–7.7)	<0.001
IED or LPD	3.1 (2.1–4.9)	<0.001
IED or LPD or LRDA	2.9 (1.9–4.3)	<0.001
ES	6.6 (4.0–11.0)	<0.001
E-SE	4.5 (2.3–8.8)	<0.001
All epileptiform activity (IED, LPD, GPD, LRDA, ESz, E-SE)	3.5 (1.5–5.2)	<0.001

This table presents the HR and MD comparing patients with post-stroke epilepsy to those without in the derivation cohort (n = 980), calculated using univariate Cox regression. The HRs are derived from the perspective of PSE, emphasizing significant findings. MDs are provided for continuous variables such as age and follow-up duration. Values in bold indicate statistical significance ($p < 0.05$). Notable significant findings include an increased risk for IED (HR: 3.2, 95% CI: 2.0–5.4), LPD (HR: 4.6, 95% CI: 2.8–7.7), and ESz (HR: 6.6, 95% CI: 4.0–11.0). Additionally, both generalized slowing (HR: 2.7, 95% CI: 1.9–4.0) and regional slowing (HR: 2.6, 95% CI: 1.7–4.0) are strongly associated with the PSE, indicating a strong link between these EEG abnormalities and PSE. Descriptive proportions for each predictor stratified by PSE status are provided in Table S10 for clinical context only; these are not adjusted for follow-up time and should not be used for inference.

CI = confidence interval; EEG = electroencephalography; E-SE = electrographic status epilepticus; ESz = electrographic seizures; HR = hazard ratio; IED = interictal epileptic discharges; LPD = lateralized periodic discharges; LRDA = lateralized rhythmic delta activity; M = male; MD = mean differences; mo = month; NIHSS = National Institutes of Health Stroke Scale; PSE = post-stroke epilepsy; yr = year.

Clinical/ Electrographic Findings

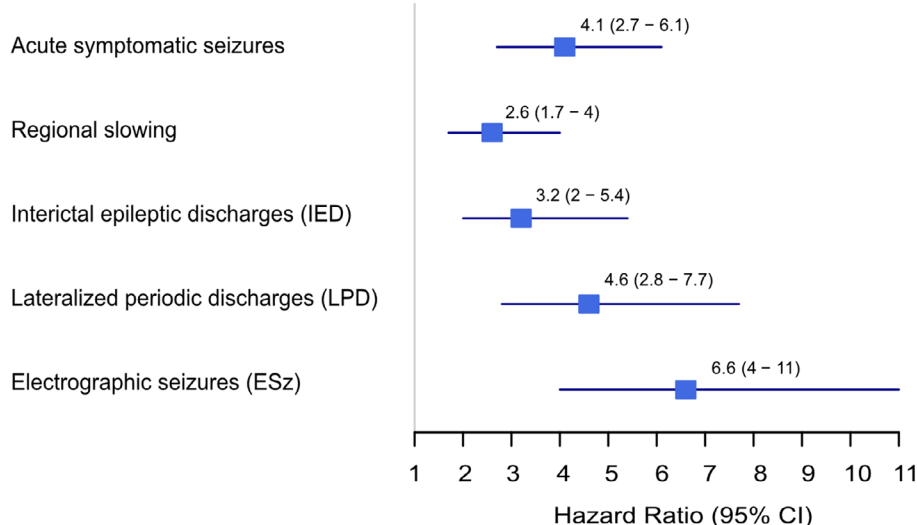


FIGURE 1: Forest plot of clinical and electrographic findings associated with post-stroke epilepsy risk. This forest plot illustrates the hazard ratio (HR) and 95% confidence interval (CI) from Table 1 for various clinical and electrographic findings in relation to the development of post-stroke epilepsy (PSE). Acute symptomatic seizures (ASyS) are shown alongside electrographic biomarkers such as regional slowing, interictal epileptiform discharges (IED), lateralized periodic discharges (LPD), and electrographic seizures (ESz). Each of these variables significantly increases the risk of PSE, with odds ratios (ORs) ranging from 2.6 to 6.6. Interestingly, ESz exhibited an HR comparable to clinical seizures (ASyS).

Tables S1, and S2. In univariable analysis, epileptiform activity (including IED, LPD, GPD, LRDA, ESz, E-SE; RR: 3.5, 95% CI: 1.5–5.2, $p < 0.001$), regional slowing (hazard ratio [HR]: 2.6, 95% CI: 1.7–4.0, $p < 0.001$) and generalized slowing (HR: 2.7, 95% CI: 1.9–4.0, $p < 0.001$) were associated with post-stroke epilepsy (Fig 1). In multivariable analysis, epileptiform activity (aHR: 2.0, 95% CI: 1.3–3.0, $p = 0.001$) and regional slowing (aHR: 1.9, 95% CI: 1.2–2.9, $p = 0.004$) were independently associated with post-stroke epilepsy (Table S3). This was confirmed using Fine–Gray subdistribution hazard models, which yielded consistent results (epileptiform activity SHR: 2.3, $p < 0.001$; regional slowing SHR: 1.7, $p = 0.02$) (Fig 2). Generalized slowing, however, did not show a significant independent association in the multivariable analysis (Table S3).

Stroke survivors with epileptiform activity had a 42% risk (95% CI: 30–49%) of developing post-stroke epilepsy 5 years after stroke, compared to a 13% risk (95% CI: 9–16%) in those without (see Fig 2A). Additionally, the 5-year risk of post-stroke epilepsy was twice as high in those with regional slowing (24%, 95% CI: 18–29%) compared to those without it (11%, 95% CI: 5–15%) (see Fig 2B).

Prognostic Modeling in Stroke-Survivors without ASyS

Besides already known predictors of post-stroke epilepsy, we performed a multivariate Cox-regression model in

stroke survivors (Table S4) to find new electrographic biomarkers. Variables retained in the final model were stroke severity at admission (NIHSS), stroke location with MCA territory and cortical involvement, large-vessel atherosclerotic stroke etiology, epileptiform activity, and regional slowing. The calculation of the new model termed SeLECT-EEG and ranging from 0 to 8 points, is shown in Table 1. The full results of the multivariable model and other variables independently associated with post-stroke epilepsy (stroke severity and location) in stroke survivors are shown in Table S4.

The SeLECT-EEG model demonstrated better discrimination for time to post-stroke epilepsy compared to the original SeLECT_{2.0} model in stroke survivors without ASyS (C-statistic: 0.75 [95% CI: 0.71–0.80] vs 0.71 [95% CI: 0.65–0.76], $p < 0.001$) (Table S5). For stroke survivors with ASyS, the C-statistics were not significantly different between the SeLECT_{2.0} and SeLECT-EEG models (both 0.59, $p = 0.97$) (Tables S5 and S6). Because of these findings and the low number of late seizure events in the ASyS group, we developed the model only in stroke survivors without ASyS. SeLECT-EEG demonstrated a near-optimal calibration for outcomes, although lacking data for lower probability outcomes (see Fig S2).

We cross-validated the results using a leave-one-cohort-out strategy (Table S7). The lowest score SeLECT-EEG value (0 points) predicts a 2.5% risk (95% CI: 0.5–4.4%) of post-stroke epilepsy 10 years following stroke,

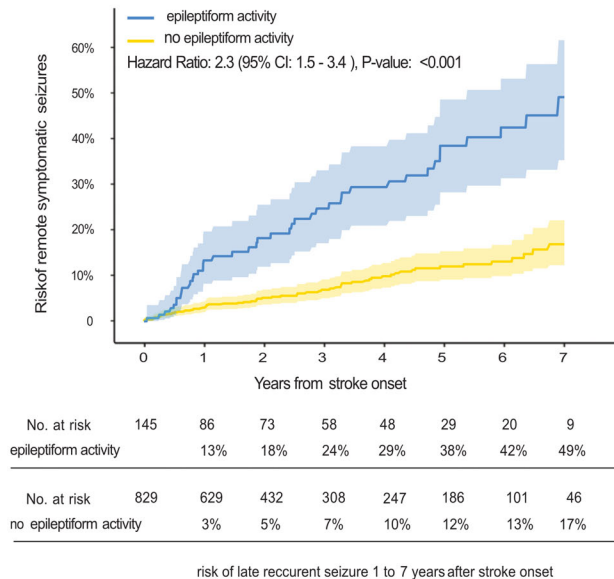
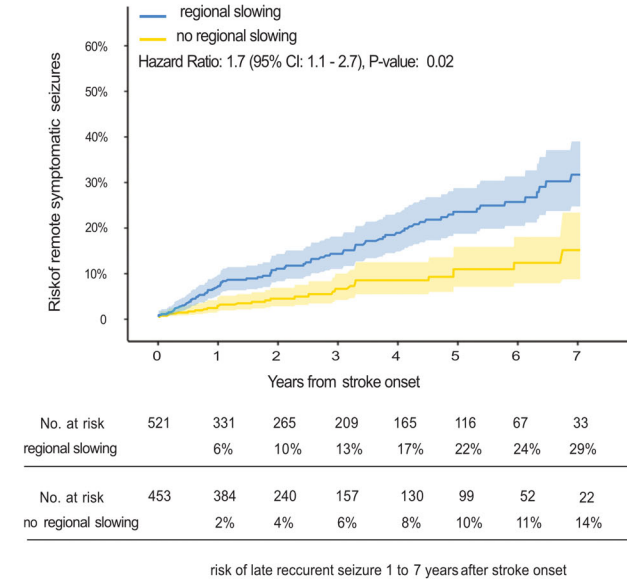
A Epileptiform activity**B** Regional slowing

FIGURE 2: Risk of epilepsy in individuals with or without regional slowing or any epileptiform activity. Cumulative incidence functions for the time to post-stroke epilepsy are presented, comparing individuals with any epileptiform activity (A) or regional slowing (B). Separate survival curves are illustrated for those with (blue) and without (yellow) epileptiform activity (A) or regional slowing (B). After adjusting for age, sex, National Institutes of Health Stroke Scale (NIHSS) score at admission, cortical involvement, middle cerebral artery (MCA) territory involvement, large artery atherosclerosis, and generalized slowing, individuals exhibiting epileptiform activity or regional slowing demonstrated a significantly higher risk of developing post-stroke epilepsy, indicating a higher likelihood of remote symptomatic seizures compared to those without these conditions (epileptiform activity: $p < 0.001$; regional slowing: $p = 0.02$).

compared with a 95% risk (95% CI: 67–99%) for the highest value (8 points; Fig 3 and Fig S5; comparison with SeLECT_{2.0} model).

Performance was further confirmed in 2 external validation cohorts from Germany ($n = 125$) and Italy ($n = 84$), where SeLECT-EEG showed higher discrimination than SeLECT_{2.0}, significantly so in the Italian cohort (C-statistic: 0.94 vs 0.84, $p = 0.008$) (Table S5). Joint calibration for both cohorts at 12 months showed strong agreement between predicted and observed risks, with a trend toward lower Brier scores for the SeLECT-EEG model (see Fig S2).

In addition, we updated the values for COSY (see Fig S4), a parameter that may be helpful for assessing the risks of safe driving.³¹ The new SeLECT-EEG model was implemented in the “SeLECT score” smartphone applications available for iOS and Android and in the web-based calculator.

Length of EEG Recording

Longer EEG recordings had a higher yield of electrographic findings (Table S8 and Fig S3). Overall, some findings, such as normal patterns (short vs cEEG counts: 207/199, 104%) and generalized (318/348, 91%) and regional

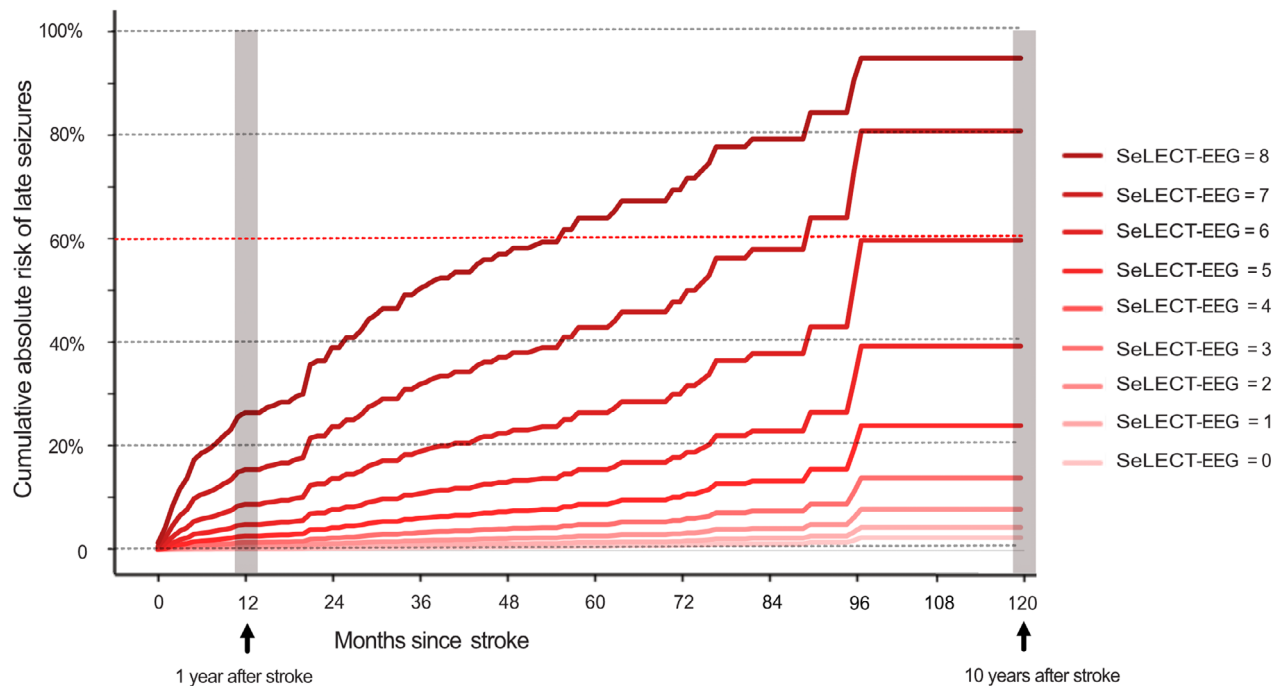
(470/526, 89%) slowing, had high detection rates in short EEGs, comparable to cEEGs. However, other findings, such as epileptiform activity (105/146, 72%), particularly IED (44/67, 66%) and rhythmic patterns (eg, LRDA; 16/40, 40%), showed lower detection rates in short EEGs. The increased detection rate of regional slowing and epileptiform activity enhanced the discrimination of the SeLECT-EEG model (C-statistics for short vs continuous recordings: 0.72 [95% CI: 0.66–0.77] vs 0.75 [95% CI: 0.71–0.80], $p < 0.001$) (Table S5).

Mediation analysis showed that epileptiform activity accounted for 30% of the total effect of both regional and generalized slowing on late seizure outcomes (Table S9). Furthermore, generalized slowing was more prevalent in severely affected stroke survivors (NIHSS ≥ 11) undergoing cEEG recordings (Table S8).

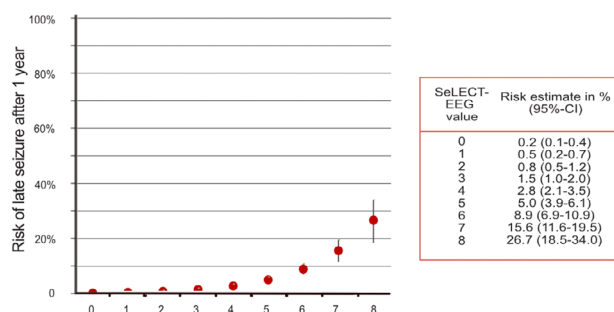
Case Example

As an example, we considered a 65-year-old male patient admitted to the hospital with an acute ischemic stroke of cardioembolic etiology, affecting the MCA territory and involving the cortex, with 16 points on the NIHSS at admission. On day 2 after the stroke, a routine EEG was performed, which showed IEDs. The SeLECT_{2.0} score for

A Prediction plot



B Risk estimate chart after 1 year of stroke



C Risk estimate chart after 10 years of stroke

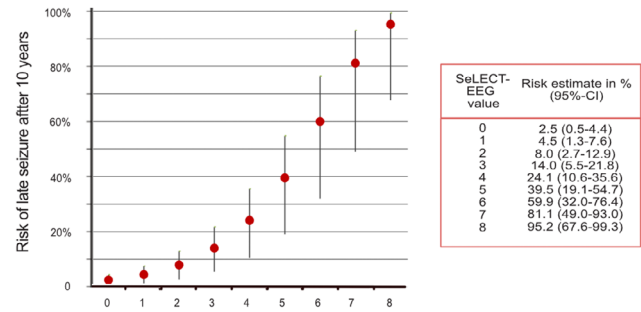


FIGURE 3: Predicted risk of post-stroke epilepsy according to a new prognostic model in stroke survivors without acute symptomatic seizures including electrographic findings. A illustrates the predicted risk of unprovoked remote symptomatic seizures occurring 0–120 months post-stroke. The red curves represent different SeLECT-EEG values for stroke survivors including electrographic findings. Each curve corresponds to SeLECT-EEG values ranging from 0 to 8 (in red). B and C present risk estimate charts for late seizures at 1 year and 10 years post-stroke, respectively, based on the SeLECT-EEG. Vertical lines denote the 95% confidence intervals.

this case is 5 points, predicting a 30% risk (95% CI: 14–44%) of post-stroke epilepsy within 10 years after stroke. In contrast, the new model developed specifically for those without acute symptomatic seizures and available EEG data (SeLECT-EEG) (Table 1) is 7 points, predicting 81% (95% CI: 49–93%) risk of post-stroke epilepsy within 10 years.

Discussion

In this study, we examined the predictive value of electrographic biomarkers detected on EEG within the first 7 days after ischemic stroke for post-stroke epilepsy.

Our results show that specific EEG abnormalities, such as regional slowing and epileptiform activity (including IED, LPD, GPD, LRDA, ESz, and E-SE), are significantly associated with an increased risk of post-stroke epilepsy, particularly in stroke survivors without ASyS.

The question of how EEG findings can serve as predictors of post-stroke epilepsy is rooted in their ability to detect early signs of cortical hyperexcitability, a key factor in epileptogenesis.^{35–37} ESz and RPPs, which are observed in as many as 15% of acute ischemic stroke survivors, are not merely markers of current neural dysfunction, but also indicators of underlying processes that may lead to

epilepsy.^{11–14} These EEG abnormalities share risk factors with post-stroke epilepsy, such as cortical involvement and stroke severity, suggesting that they can act as early warning signs of future seizures.¹⁵

Beyond epileptiform discharges, regional slowing emerged as a robust independent predictor of post-stroke epilepsy, even after adjusting for stroke severity (Table S8) and co-occurring epileptiform activity (Table S9), suggesting it may reflect focal cortical dysfunction simply rather than being an indicator of more severe strokes.^{19,38–41}

Furthermore, EEG sensitivity to ischemic cortical injury enables it to detect subtle, preclinical changes that contribute to the development of epilepsy. This is particularly important because such changes might not yet be apparent through clinical symptoms alone. The predictive value of EEG is also supported by similar findings in TBI, where EEG abnormalities like IEDs and RPPs are consistently linked to an increased risk of post-traumatic epilepsy.^{42–44} Notably, the prognostic value of EEG abnormalities in the derivation cohorts were more pronounced in patients with lower SeLECT_{2.0} scores, as demonstrated by a significant interaction effect (β : -0.29 , HR: 0.75 , 95% CI: 0.57 – 0.98 , $p = 0.037$) (Table S5), suggesting that EEG may be particularly useful in identifying otherwise “hidden” risk in individuals deemed to be low-risk individuals based on clinical variables. These insights underscore the importance of incorporating EEG findings into seizure prediction models, as they provide a critical layer of prognostic information that complements clinical risk factors.

Building on this understanding, we developed the SeLECT-EEG model specifically for stroke survivors without ASyS. This model not only accurately captures the heightened risk of post-stroke epilepsy in this subgroup, but also significantly outperforms the SeLECT_{2.0} model (C-statistic: 0.75 [95% CI: 0.71 – 0.80] vs 0.71 [95% CI: 0.65 – 0.76], $p < 0.001$) (Table S5). In contrast, for stroke survivors with ASyS, the predictive accuracy of the SeLECT_{2.0} and SeLECT-EEG models did not differ significantly (both C-statistics: 0.59 , $p = 0.97$). Given these findings and the likely distinct pathophysiological mechanisms in stroke survivors with ASyS,⁹ we focused the SeLECT-EEG model on those without ASyS.

This approach complements and expands on our recent work,^{4,9} which focused on subclassifying the timing and type of ASyS (SeLECT_{2.0} and SeLECT-ASyS),^{4,9} but did not include EEG findings. In contrast, the present study integrates early electrophysiological biomarkers and shows that findings such as epileptiform activity and regional slowing on EEG help identify individuals at high risk of developing post-stroke epilepsy even in the

absence of clinical ASyS. In other words, the new SeLECT-EEG model is particularly helpful in those without ASyS.

Translating these findings into clinical practice, the SeLECT-EEG model emerges as the preferred tool for prognostication in stroke survivors without ASyS. The case example presented illustrates the notable differences in risk estimation when using SeLECT-EEG compared to SeLECT_{2.0}, which could be clinically relevant and may influence treatment decisions and follow-up strategies. The model risk estimates offer a more nuanced assessment of post-stroke epilepsy risk, supported by its favorable calibration (see Fig S2). To guide clinical application, we provide diagnostic performance metrics for different SeLECT-EEG thresholds (Fig S7), showing that higher scores are associated with high specificity and positive predictive value. These findings support the model’s potential use for enriching future antiepileptogenesis trials by identifying high-risk individuals most likely to benefit from early intervention.⁴⁵

In addition to these findings, cEEG monitoring demonstrated a higher detection rate of epileptiform activity compared to short EEG recordings, significantly improving the predictive accuracy of the SeLECT-EEG model (C-statistics: 0.75 vs 0.72 , $p < 0.001$) (Table S5). Although short EEGs effectively detected generalized and regional slowing (Tables S8–S10 and Fig S3), they performed poorly in stroke survivors with higher NIHSS scores (group 2 with cEEG) (Table S8), where generalized slowing was more prevalent. This generalized slowing likely complicated the detection of focal slowing, whereas the short duration of the recording made it more challenging to detect epileptiform activity, underscoring the importance of continuous monitoring for identifying critical findings such as IEDs (see Fig S3).^{19,20} Mediation analysis demonstrated that epileptiform activity accounted for approximately 30% of the effect of both regional and generalized slowing on late seizure outcomes, indicating that epileptiform activity is unlikely without the presence of either focal or generalized slowing (Table S9). However, the optimal length of EEG monitoring remains unanswered, as cEEG offers benefits in certain high-risk subgroups, whereas normal short EEGs show high specificity in identifying stroke survivors unlikely to develop post-stroke epilepsy, reducing the need for extended monitoring (Table S8 and Fig S3).

A key finding of this study is that stroke survivors without ASyS who have SeLECT-EEG scores of 7 or more face a greater than 60% 10-year risk of developing epilepsy. This risk level aligns with the ILAE’s definition of epilepsy.²² Although this definition traditionally requires an unprovoked seizure, some clinicians might

consider preemptive treatment or extended follow-up, including EEGs for these high-risk stroke survivors, even in the absence of a seizure.^{5,46} However, the efficacy of such prophylactic treatment remains uncertain.

In a previous smaller analysis of the SeLECT registry,⁴⁷ we did not find significant associations between EEG findings and post-stroke epilepsy, likely because of the limited sample size and individual analysis of electrographic biomarkers. However, by expanding the dataset to include additional cohorts^{19,20} and refining our approach to combine biomarkers and focus on stroke survivors without acute symptomatic seizures, we now demonstrate significant associations.

Our study has several strengths. To our knowledge, this is the largest multicenter cohort study of post-stroke seizures assessing the predictive power of electrographic biomarkers. We translated our findings into a clinical model and user-friendly prognostic tool accessible via both smartphone and web applications. The novel model outperforms the current state-of-the-art model.

However, our study has several limitations. First, the indication for EEGs and their analysis varied across the 11 international cohorts included in this study, spanning from 2002 to 2022. In some earlier cohorts, primarily those performing short EEGs (group 1), the detection of certain rhythmic and periodic patterns may have been limited because of retrospective EEG assessments and differing criteria definitions. To correct for these variations and ensure comparability between the new SeLECT-EEG prediction model and the previous SeLECT_{2.0} model, IPW was applied using data from the broader SeLECT cohort ($n = 3,711$). Additionally, we performed a leave-one-cohort-out cross-validation analysis to explore site-specific variability, which showed only minor differences in model performance across cohorts (Table S7). The heterogeneity between cohorts included in the current analyses reflects real-world variability and reinforces the external validity of the SeLECT-EEG model. Future studies could further reduce indication bias by applying formal causal inference methods, such as G-computation.⁴⁸

Second, we grouped various EEG abnormalities, which may have obscured more specific prognostic factors. For example, generalized slowing was not consistently defined by a specific frequency, potentially leading to interpretational differences between cohorts. Similarly, regional slowing was treated as a unified category, although distinct subtypes (eg, rhythmic vs arrhythmic,¹⁹ accompanying attenuation,¹⁹ persistent vs transient^{39,41}) may differ in prognostic value—an important consideration for future studies using standardized EEG interpretation frameworks.

Third, the SeLECT-EEG model was developed specifically for stroke survivors without ASyS because the

event number in stroke survivors with ASyS was too low to improve on the existing SeLECT_{2.0} prognostic model. Additionally, the C-statistics for the SeLECT-EEG and SeLECT_{2.0} models in the ASyS group were not significantly different from each other, and some clinical parameters necessary to adapt the model to the recently published SeLECT-ASyS framework⁹ were missing.

Fourth, although NIHSS at admission was used across all cohorts for consistency, it may not fully capture post-treatment functional impairment relevant to epileptogenesis. In stroke survivors who underwent reperfusion therapies such as thrombectomy or thrombolysis, stroke severity assessed after treatment may offer improved prognostic value in this subgroup.⁴⁹

Fifth, the overall post-stroke epilepsy rate in our study was relatively high at 11%, likely influenced by the stringent selection criteria for cEEG monitoring in certain cohorts, particularly those from Belgium¹⁹ and the United States²⁰ (Table S7). We also used IPW to account for these differences and ensure the new SeLECT-EEG model was comparable to the SeLECT_{2.0} model. Despite the use of IPW to address potential bias from varying EEG indications across cohorts, some degree of ascertainment bias may persist, particularly as EEGs were performed based on clinical suspicion or routine care in certain cohorts.

Last, in the external validation cohorts, the number of post-stroke epilepsy (PSE) events was limited. In the German cohort, missing values for regional and generalized slowing were addressed using multiple imputation. Sensitivity analyses showed consistent discrimination in both imputed and non-imputed datasets. Although the German cohort showed a non-significant trend toward improved performance of SeLECT-EEG over SeLECT_{2.0}, the Italian cohort demonstrated significantly higher discrimination (Table S5). Calibration was strong across both cohorts, as reflected by the combined calibration analysis at 12 months (Fig S2).

Conclusions

Our study demonstrates that electrographic abnormalities detected on EEG during the acute phase of ischemic stroke, particularly regional slowing and epileptiform activity, are significant predictors of post-stroke epilepsy. The SeLECT-EEG model, developed specifically for stroke survivors without ASyS, outperforms the existing SeLECT_{2.0} model in predicting post-stroke epilepsy risk. cEEG monitoring, especially in selected stroke survivors with higher NIHSS scores and more severe generalized slowing, further enhances the detection of critical abnormalities, improving the model's predictive accuracy.

Notably, certain SeLECT-EEG risk scores exceed a 60% 10-year risk of developing epilepsy, aligning with the ILAE's definition of epilepsy.²² This finding suggests the potential for pre-emptive treatment or extended follow-up for high-risk stroke survivors, although the effectiveness of such approaches remains uncertain. Integrating these EEG-based insights into clinical practice could refine risk stratification in stroke survivors and help identify enriched cohorts for studies focused on preventive strategies for the development of post-stroke epilepsy.

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Author Contributions

K.M.S., M.G., and C.B. contributed to the conception and design of the study; K.M.S., V.D., A.L.O., C.T., G.N., N.G., A.S., G.M., M.V., V.P., C.B., and M.G. contributed to the acquisition and analysis of data; K.M.S. and M.G. contributed to drafting the manuscript and preparing the figures.

Potential Conflicts of Interest

N.G. reports institutional grant support from the Fonds de la Recherche Scientifique and Fonds Erasme pour le Recherche Médicale for the present work. All other authors declare nothing to report. Disclosures unrelated to the submitted work have been provided in the ICMJE conflict of interest forms.

Data Availability

De-identified participant data and supporting documentation, including statistical and analytic code, will be made available on reasonable request following publication. Access will be granted to qualified investigators, contingent on approval by the lead investigator and the respective local cohort contributors, as well as evidence of appropriate ethical approvals. Requests should be directed to marian.galovic@usz.ch. Data may be used for any purpose deemed scientifically sound and ethically approved.

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