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Post-stroke seizure risk prediction models: a systematic review and meta-analysis

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ABSTRACT

Objective. Stroke is the commonest cause of epileptic seizures in older adults. Risk factors for post-stroke seizure (PSS) are well known, however, predicting PSS risk is clinically challenging. This study aimed to evaluate the predictive accuracy of PSS risk prediction models developed to date.

Methods. We performed a systematic review and meta-analysis of studies using MEDLINE and EMBASE from database inception to 28th December 2020. The search criteria included all peer-reviewed research articles, in which PSS risk prediction models were developed or validated for ischaemic and/or haemorrhagic stroke. Random-effects meta-analysis was used to generate summary statistics of model performance and receiver operating characteristic curves. Quality appraisal of studies was conducted using PROBAST.

Results. Thirteen original studies involving 182,673 stroke patients (mean age: 38-74.9 years; 29.4-60.9% males), reporting 15 PSS risk prediction models were included. The incidence of early PSS (occurring ≤one week from stroke onset) and late PSS (occurring >one week from stroke onset) was 4.5% and 2.1%, respectively. Cortical involvement, functional deficits, increasing lesion size, early seizures, younger age, and haemorrhage were the commonest predictors across the models. SeLECT demonstrated greatest predictive accuracy (AUC 0.77 [95% CI: 0.71-0.82]) for late PSS following ischaemic stroke, and CAVE for predicting late PSS following haemorrhagic stroke (AUC 0.81 [0.76-0.86]). Fourteen of 15 studies demonstrated a high risk of bias, with lack of model validation and reporting of performance measures on calibration and discrimination being the commonest reasons.

Significance. Although risk factors for PSS are widely documented, this review identified few multivariate models with low risk of bias, synthetising single variables into an individual prediction of seizure risk. Such models may help personalise clinical management and serve as useful research tools by identifying stroke patients at high risk of developing PSS for recruitment into studies of anti-epileptic drug prophylaxis.

Key words: cerebrovascular disorders, epilepsy, seizure, stroke, systematic review

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Stroke as a risk factor for the development of epileptic seizures has long been established. It is indeed the commonest cause of epileptic seizures in older adults, accounting for approximately 50% of acquired epilepsy in those over 60 years of age [1, 2]. Stroke affects more than one million individuals annually in the European Union, and stroke prevalence and the number of survivors are both projected to increase [3]. However, predicting post-stroke seizure (PSS) risk is complex and anti-epileptic drug (AED) prophylaxis remains

controversial. The lack of prognostic biomarkers for PSS further contributes to this clinical challenge.

In this review, we use the terms "post-stroke seizures" and "post-stroke epilepsy" in the strictest sense. We define post-stroke seizure as "single or multiple convulsive episodes after stroke, related to reversible or irreversible cerebral damage due to stroke regardless of time of onset following the stroke" and post-stroke epilepsy as "recurrent seizures following stroke with confirmed diagnosis of epilepsy" or a single late PSS [2].

PSSs are categorized as early (occurring ≤one week from stroke onset) or late (>one week). The International League Against Epilepsy categorises a single late PSS as structural epilepsy due to high risk of recurrence (>60%) within 10 years [4]. Contrastingly, early seizures do not qualify for the diagnosis of epilepsy, as aetiologically they are deemed to be provoked [5]. Depending on the population of stroke patients studied, early PSS and late PSS (post-stroke epilepsy) incidence rates range from 3.2%-6.3% and 1.3%-14.1%, respectively [6-12].

Pre-clinical models and treatment trials to prevent epileptogenesis have been unsuccessful in human stroke patients [13]. The identification of stroke patients at high risk of seizures and the need for long follow-up durations may be contributory factors to this. Trials in an unselected population would require large sample sizes to account for the relatively low incidence (<10%) of late seizures among ischaemic stroke patients [9, 14]. Such trials would prove costly and prognostic biomarkers may therefore provide useful tools for clinical research [15].

Risk factors for early PSS and late PSS (post-stroke epilepsy) have been extensively documented in the existing literature and various studies have attempted to derive prediction models of post-stroke seizure risk, with the aims of guiding early identification and appropriate management of high-risk patients. In this study, we aimed to better understand the predictive accuracy of these tools by conducting a systematic review and meta-analysis of various PSS prognostic indices developed to date. Although we are aware of a multitude of individual studies published among different settings, the comparative performance of these tools has yet to be summarised in a meta-analysis.

Methods

This systematic review and meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [16]. No review protocol was created or published. This review did not require ethical approval or patient consent as analyses were based on previously published data. All data not published in this article may be provided to qualified investigators on request to the corresponding author.

Search strategy

We aimed to identify all studies using EMBASE (embase.com) and MEDLINE (nlm.nih.gov/bsd/medline.html) from database inception to 28th of December 2020. Relevant key words and search terms for stroke, cerebrovascular disease, seizures, epilepsy and risk prediction or prognostic models were used, aided by Medical Subject Headings. Further details on the database and search terms used are shown in *supplementary table 1*. Following removal of duplicate results, two reviewers (SHL and KLA) independently screened for eligible abstracts. Any disagreements in abstract inclusion were discussed to reach a consensus.

After title and abstract screening, the full-text articles were independently assessed for eligibility by two reviewers (SHL and KLA). Any disagreements with study inclusion were discussed with further reviewers (SB and PKM). The reference list of relevant articles was also reviewed to identify additional studies.

Inclusion and exclusion criteria

Published full-text articles from peer-reviewed journals in the English language, including empirical studies and systematic reviews, were reviewed. Full-text research articles studying post-stroke seizure or post-stroke epilepsy following ischaemic or haemorrhagic strokes were assessed. Studies which derived or validated PSS risk prediction models, defined as: i) a multivariate set of defined single variables predictive of PSS risk; and ii) synthesis of single variables into an individual prediction of seizure risk, were included in the final selection and studies reporting sufficient data were included in quantitative meta-analysis. Included studies were categorized by stroke aetiology (ischaemic/haemorrhagic) and timing of seizure presentation (early PSS/late PSS).

Non-systematic reviews (*e.g.* narrative or literature reviews), editorials, opinions, letters, conference proceedings, and case reports were excluded. Studies with limited stroke data (>90% of the data for patients without stroke) and studies restricted to non-stroke cerebrovascular diseases (*e.g.* arteriovenous malformations, transient ischaemic attack) were also excluded. Pregnant and paediatric (<18 years) populations were also part of the exclusion criteria. There was no limit on study design. For studies with duplicate data published from the same cohort, the most recent and relevant results were included in quantitative meta-analysis.

Data extraction and appraisal of study quality

Data from eligible studies were extracted using standardized forms based on Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS). Data collection of stroke and seizure characteristics, sample size, and baseline patient characteristics were undertaken. Model performance measures on classification (sensitivity and specificity), discrimination (ability of a prediction model to distinguish between individuals who do or do not develop the outcome), and calibration (agreement between predictions from the model and observed outcomes) were extracted as recommended by the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines [17]. Other factors including follow-up method and duration, previous history of epilepsy, use of neuroimaging, interventions received during index stroke admission, and AED usage were also extracted (*supplementary table 2*).

Quality appraisal of included studies was conducted using Prediction Model Risk of Bias Assessment Tool (PROBAST), a tool for assessing risk of bias or applicability of studies addressing multivariable models deriving or validating risk prediction models [18]. Risk of bias assessment involved four domains. The domains were used to consider whether the enrolled participants were representative of the intended target population. The predictor and outcome domains indicate concerns with the definition and measurement of predictors (PSS/PSE risk factors) and outcomes (PSS/PSE), respectively. The analysis domain considers appropriate data handling and statistical analysis.

Statistical analysis

Pooled sensitivity analysis of PSS risk prediction models was conducted by calculating sensitivity, specificity, diagnostic odds ratios, and false-negative/false-positive rates using random-effects meta-analysis on Review Manager 5. Subgroup analysis was performed according to stroke aetiology (ischaemic or haemorrhagic) and timing of post-stroke seizure (early or late) to explore possible causes of heterogeneity. SROC curves were also constructed for indirect comparison of paired sensitivity and specificity. Publication bias was evaluated visually using funnel plots and statistically through Egger and Begg tests using ProMeta 3 [19, 20].

Results

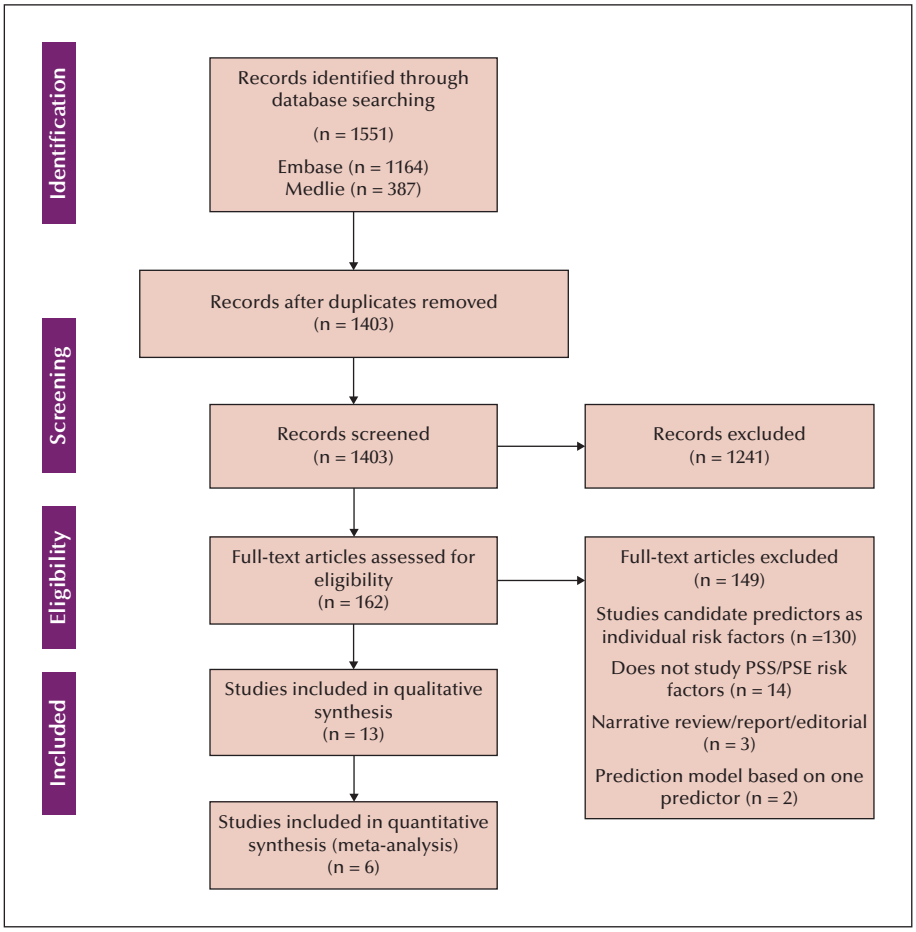
A total of 1,403 titles and abstracts were screened, of which 1,241 were excluded as they did not focus on PSS risk or prognostication. One hundred and sixty-two full-text articles were assessed for eligibility, of which 149 were excluded as they did not derive or validate multivariable PSS risk prediction models. Thirteen original studies were included in the systematic review, with six studies providing sufficient data for quantitative meta-analysis (*figure 1*). Although 13 studies were included, 12 cohorts were identified because there were two different studies published by Abraira *et al.* using datasets from the same cohort. Both studies were included in the qualitative systematic review, but only the most recent study was included in the quantitative meta-analysis [21].

The total sample size included 182,673 participants. The incidence rates for early PSS and late PSS (PSE) were 4.5% and 2.1%, respectively. Of the participants, 95.2% had ischaemic strokes, while 4.8% had haemorrhagic strokes (*table 1*). The mean age of participants ranged from 38 to 74.9 years, and 29.4-60.9% were males. Patients with early PSS were followed for a median duration of 1 to 14 days and patients with late PSS (PSE) for 1 to 4.8 years. The median stroke severity (NIHSS) ranged from $\leq$3 to 11. Patients with a previous history of epilepsy were excluded from six studies [21-26], whilst they were included in six other studies [27-32]. One study did not report how they accounted for prior epilepsy during analysis [33]. Patients prescribed AEDs were included in the analysis for eight studies [23-29, 33], and excluded in one study [32]. Four studies did not report how they accounted for patients on AEDs [21, 22, 30, 31]. Nine studies were conducted in western Europe, three in East Asia and one in North America (*supplementary table 2*).

Some studies validated more than one PSS risk prediction model. There were two studies each validating CAVE and PoSER. There was one study each for SeLECT, PSEiCARe, CAVS, and MESS. There were a further eight studies, each validating their own un-named multivariate risk prediction models. Six of these studies developed or validated PSS risk prediction models specifically in ischaemic stroke patient cohorts [24, 25, 27-29, 31, 33]. There were two studies involving only haemorrhagic stroke patients [23, 26]. Four studies involved both ischaemic and haemorrhagic stroke patients [21, 30, 32]. Masuhr *et al.* [32] specifically recruited stroke patients with cortical vein thrombosis. The study characteristics and summary statistics are shown in *tables 1, 2*.

Indirect comparisons of the ability to identify stroke patients at risk of seizures

Forest plots of the raw data and estimated sensitivities and specificities for each model are presented in *figure 2*. Pooled estimates of sensitivities, specificities, positive and negative predictive values, and



■ **Figure 1.** Flow chart of study selection.

diagnostic odds ratios for each model are shown in *table 2*. CAVE demonstrated the highest sensitivity for predicting late PSS following haemorrhagic strokes (0.97 [95% CI: 0.90-1.00]), while SeLECT demonstrated the highest sensitivity for predicting late PSS among ischaemic strokes (0.93 [95% CI: 0.81-0.99]). PoSERS demonstrated the highest specificity for predicting late PSS following both ischaemic and haemorrhagic strokes (0.996 [95% CI: 0.98-1.00]). Alme 2016 showed the highest specificity for predicting early PSS following ischaemic strokes (0.85 [95% CI: 0.84-0.86]) (*figure 2*). The paired sensitivities (proportion of patients correctly deemed 'high risk' who subsequently develop PSS) and specificities (proportion of patients correctly deemed 'low risk' who do not develop PSS) demonstrated that PoSERS showed the greatest discrimination for predicting late PSS following ischaemic strokes and CAVE for predicting late PSS following haemorrhagic strokes (*figure 3*). Negative predictive values for post-stroke seizures were similar between models, ranging from 0.74 [32] to 0.99 (SeLECT). Contrastingly, positive predictive values ranged from 0.036 (MESS) to 0.88 (PoSERS).

Neuroimaging (CT/MRI) and clinical examination were the commonest modalities used for determining predictors, each being used to determine 20 different predictors across the models (*table 3*). Past medical history and non-modifiable patient factors were used to determine 14 predictors. Novel blood test biomarkers were required for five of the predictors. Knowledge of iatrogenic treatment factors and EEG investigation were required for assessing three and one of the predictors, respectively. The commonest subtypes of predictors were based on anatomical location (*e.g.* cortical involvement, MCA involvement), functional deficits (*e.g.* mRS, mobility), and seizure characteristics (*e.g.* partial seizure, early/late seizure).

Galovic *et al*. demonstrated an overall low risk of bias based on the development and validation of the SeLECT model. Kim *et al*. showed an overall unclear

▼ **Table 1.** Study characteristics.

Study; setting	Sample size	Study design	Type of stroke	Outcome (early/ late seizure)	Development/ validation	Predictors in final model
Abraira *et al.* 2020; Spain [21]	895	Prospective longitudinal cohort study, the STROKE-CHIP study	Ischaemic/ haemorrhagic	Late	Development only	Endostatin >1.203; S100B <1.364; Hsc70 <2.496
Abraira *et al.* 2020; Spain [22]	895	Prospective longitudinal cohort study, the STROKE-CHIP study	Ischaemic/ haemorrhagic	Early	Development only	NIHSS, haemorrhagic stroke, TNF-R1 <0.013, NCAM >0.326
Kwon *et al.* 2020; USA [23]	2507	Retrospective analysis of the ERICH longitudinal study cohort	Haemorrhagic	Early/late	Development of CAVS; and external validation of CAVE	Cortical haemorrhage, age <65 years, haemorrhage volume >10 mL, surgical hematoma evacuation
Yamada *et al.* 2020; Japan [24]	436	Prospective analysis of a multicentre observational study, the INPOSE study	Ischaemic/ haemorrhagic	Late	Development only	Haemorrhagic stroke, cortical stroke location
Chi *et al.* 2018; Taiwan [27]	125757	Retrospective analysis of a population-based registry, the National Health Insurance Research Database (NIHRD) of Taiwan	Ischaemic	Late	Development of PSEiCARE; and internal validation of PSEiCARE	Prolonged hospital stay (>2 weeks), seizure on stroke admission, age ≥80 years, ICU admission, cognitive impairment (dementia), pre-existing atrial fibrillation, and respiratory tract infection (pneumonia) on stroke admission
Galovic *et al.* 2018; Europe [25]	1169	Prospective analysis of a regional post-stroke seizure registry	Ischaemic	Late	Development of SeLECT; internal and external validation of SeLECT	Stroke severity (NIHSS), large artery atherosclerosis, early seizure (≤7 days), cortical involvement, territory of MCA
Alme *et al.* 2016; Norway [28]	2598	Retrospective analysis of a regional longitudinal cohort, the Bergen NORSTROKE registry	Ischaemic	Early	Development only	Diabetes mellitus, NIHSS on admission, cortical involvement
Kim *et al.* 2016; South Korea [29]	3792	Retrospective analysis of a regional longitudinal cohort, all consecutive patients admitted to Ewha Womans University Hospital	Ischaemic	Early/late	Development of Score 3-1 and Score 4; internal validations of score 3-1 and score 4 with external validations of CAVE, PoSERS, and MESS	Score 3-1: male sex, atrial fibrillation, cortical involvement, partial seizure Score 4: age <65 years, male sex, larger lesion size, partial seizure MESS: mRS ≥1, abnormal EEG

▼ **Table 1.** Study characteristics (*continued*).

Study; setting	Sample size	Study design	Type of stroke	Outcome (early/ late seizure)	Development/ validation	Predictors in final model
Haapaniemi *et al*. 2014; Finland [26]	1089	Retrospective analysis of a national stroke cohort, with patients recruited consecutively	Haemorrhagic	Late	Development of CAVE; and external validation of CAVE	CAVE: cortical involvement, age >65, volume >10mL, early seizure (≤7 days)
Krakow *et al*. 2010; Germany [30]	37322	Retrospective analysis of a regional stroke registry	Ischaemic/ haemorrhagic	Early	Development only	Age <75 years, mRS 3-5, diabetes mellitus, acute infection, history of TIA
Strzelczyk *et al*. 2010; Germany [31]	264	Prospective analysis of consecutive patients admitted to the Department of Neurology of Philipps-University, Marburg	Ischaemic	Late	Development only (PoSERS)	PoSERS: Supratentorial stroke, ICH involving cortical areas, ischemia involving cortical or cortical-subcortical areas, ischemia + ongoing neurological deficit, stroke caused neurological deficit with mRS >2, seizure occurred up to 14 days after stroke, seizure occurred 15 days or later after stroke
Masuhr *et al*. 2006; Germany [32]	194	Prospective analysis of consecutive patients admitted to two neurology departments	Ischaemic/ haemorrhagic (Cerebral venous thrombosis)	Early	Development only	Motor deficits, intracranial haemorrhage, cortical venous thrombosis
Lamy *et al*. 2003; France [33]	581	Prospective analysis of a multicentre study (the PFO-ASA study)	Ischaemic	Late	Development only	Age (per year), early seizure, impairment of consciousness at stroke onset, cortical signs, Rankin score >2, haemorrhagic infarct, size > one-half hemisphere

NIHSS: National Institute of Health Stroke Scale; MCA: middle cerebral artery; mRS: modified Rankin Scale; TIA: transient ischemic attack; ICH: intracerebral haemorrhage.

risk of bias. Although Haapaniemi *et al*. demonstrated an overall high risk of bias based on their scoring system, they demonstrated a low risk of bias in all other domains regarding participant inclusion, predictor assessment, and outcome determination. Haapaniemi *et al*. demonstrated the lowest risk of bias among haemorrhagic stroke-PSS risk prediction models. Eleven studies were deemed to be at high risk of bias under PROBAST assessment, suggesting that the reported predictive performances were likely be lower in clinical practice (*table 4*). The funnel plot showed asymmetry, and the Egger (p=0.016) and Begg (p=0.186) tests demonstrated evidence of publication bias (*supplementary figure 1*).

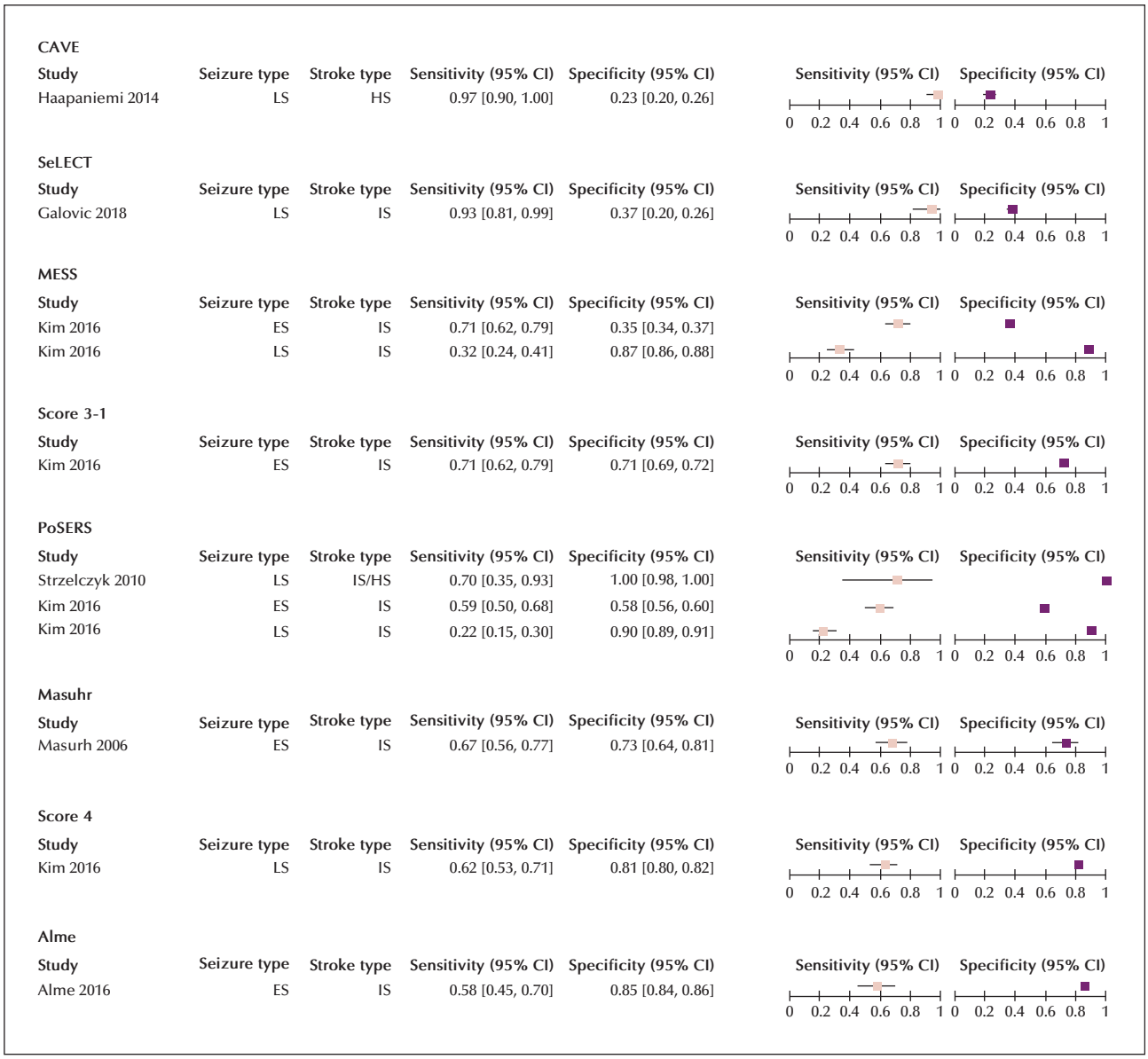
Discussion

In this systematic review and meta-analysis covering the comparative test performance of PSS multivariate

▼ **Table 2.** Summary statistics of model performance measures.

Study	C-statistic (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic OR (95% CI)
Abraira *et al*. 2020; Spain [21]	0.743 (0.652 – 0.833)	NI	NI	NI	NI	NI
Abraira *et al*. 2020; Spain [22]	0.735 (0.651 – 0.819)	NI	NI	NI	NI	NI
Kwon *et al*. 2020; USA [23]	0.76 (CAVS), 0.73 (CAVE)	NI	NI	NI	NI	NI
Yamada *et al*. 2020; Japan [24]	NI	NI	NI	NI	NI	NI
Chi *et al*. 2018; Taiwan [27]	0.759	NI	NI	NI	NI	NI
Galovic *et al*. 2018; Europe [25]	0.77 (0.71 – 0.82)	0.052 (0.048 – 0.057)	0.99 (0.98 – 1.00)	1.49 (1.35 – 1.63)	0.19 (0.06 – 0.56)	7.97 (2.45 – 25.93)
Alme *et al*. 2016; Norway [28]	0.8572	0.091 (0.075 – 0.11)	0.987 (0.983 – 0.990)	3.84 (3.06 – 4.81)	0.50 (0.38 – 0.66)	7.69 (4.66 – 12.67)
Kim *et al*. 2016; South Korea [29]	0.735 (0.588 – 0.852)[a], 0.734 (0.62 – 0.829)[b], 0.509 (0.361 – 0.657)[c], 0.576 (0.425 – 0.717)[d], 0.594 (0.475 – 0.705)[e], 0.532 (0.414 – 0.647)[f]	0.076 (0.068 – 0.086), 0.10 (0.087 – 0.115), 0.036 (0.032-0.04), 0.045 (0.039 – 0.052), 0.078 (0.061 – 0.10), 0.067 (0.048 – 0.092)	0.986 (0.982 – 0.990), 0.984 (0.981 – 0.988), 0.973 (0.965 – 0.980), 0.976 (0.971 – 0.981), 0.974 (0.971 – 0.977), 0.971 (0.969 – 0.974)	2.45 (2.16 – 2.77), 3.29 (2.82 – 3.83), 1.10 (0.98 – 1.23), 1.40 (1.21 – 1.61), 2.52 (1.92 – 3.29), 2.11 (1.49 – 2.99)	0.41 (0.31 – 0.54), 0.47 (0.37 – 0.59), 0.82 (0.62 – 1.08), 0.71 (0.57 – 0.88), 0.78 (0.69 – 0.88), 0.87 (0.79 – 0.96)	5.98 (4.03 – 8.87), 7.03 (4.85 – 10.2), 1.35 (0.91 – 1.99), 1.98 (1.38 – 2.85), 3.24 (2.20 – 4.78), 2.42 (1.56 – 3.76)
Haapaniemi *et al*. 2014; Finland [26]	0.81 (0.76 – 0.86)	0.113 (0.107 – 0.119)	0.9877 (0.953 – 0.997)	1.26 (1.19 – 1.34)	0.12 (0.03 – 0.49)	10.19 (2.47 – 42.03)
Krakow *et al*. 2010; Germany [30]	NI	NI	NI	NI	NI	NI
Strzelczyk *et al*. 2010; Germany [31]	NI	0.875 (0.487 – 0.981)	0.988 (0.970 – 1.00)	177.80 (24.12 – 1310.86)	0.30 (0.12 – 0.78)	590.33 (54.39 – 6407.35)
Masuhr *et al*. 2006; Germany [32]	0.797	0.67 (0.59 – 0.74)	0.74 (0.67 – 0.80)	2.51 (1.78 – 3.54)	0.45 (0.32 – 0.62)	13.86 (7.63 – 25.16)
Lamy *et al*. 2003; France [33]	NI	NI	NI	NI	NI	NI

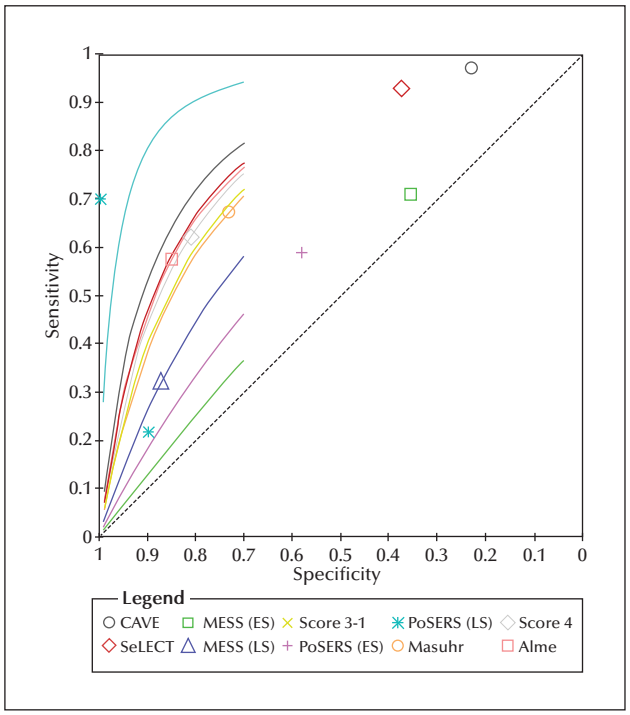
a = score 3-1; b = score 4; c = MESS (early post-stroke seizure); d = PoSERS (early post-stroke seizure); e = MESS (late post-stroke seizure); f = PoSERS (late post-stroke seizure); NI: no information.



■ **Figure 2.** Forest plots of sensitivity and specificity.IS: ischemic stroke; HS: haemorrhagic stroke; ES: early post-stroke seizure; LS: late post-stroke seizure.

risk prediction models, we identified 15 models involving 35 different predictors of PSS risk from 182,673 eligible patients. Four of these models were internally validated and three were externally validated (*table 1*). We identified two models, SeLECT and CAVE, demonstrating the greatest predictive accuracy in classification and discrimination in both internal and external datasets, with the lowest risk of study bias as per PROBAST. Eleven studies demonstrated high risk of bias and one study demonstrated unclear risk of bias due to the lack of validation and assessment of calibration, thereby increasing the risk of model overfitting (*table 4*). These models are likely to perform worse in practice than the performance measures reported in the studies and therefore provide potential as useful research tools requiring further external validation for full clinical implementation.

SeLECT is the most sensitive in predicting late PSS for ischaemic stroke patients with a low false-negative rate (AUC: 0.77; 95% CI: 0.71-0.82), thereby giving clinicians greater confidence in identifying patients at



■ **Figure 3.** SROC curves of PSS risk prediction models.ES: early post-stroke seizure; LS: late post-stroke seizure.

▼ **Table 3.** Predictor characteristics by subtype across the models.

Modality	Predictor	*n*
Neuroimaging	Anatomical location	12
	Lesion size	4
	Haemorrhage	3
	Cortical vein thrombosis	1
Clinical examination	Functional deficits	8
	Seizure characteristics	8
	Neurological co-morbidities	2
	Infection	2
Past medical history/patient factors	Vascular risk factors	6
	Age	5
	Sex	3
Other factors	Serum biomarkers	5
	Iatrogenic treatment factors	3
	EEG	1

lower risk of developing epileptic seizures and requiring AEDs. Conversely, PoSERS demonstrates a higher specificity and positive predictive value, meaning that a greater proportion of higher-risk patients are correctly classified as such. However, the poor sensitivity of PoSERS may lead to the incorrect classification of high-risk patients as low risk of late PSS. However, due to the relatively low proportion of seizures among study participants, the negative predictive values between these models are very similar, suggesting that clinical differences between models are likely to be insignificant (*table 2*). Although PoSERS demonstrates greater performance measures in discrimination (*figure 3*), it poses a high risk of bias due to the lack of validation and small number of outcome events.

CAVE demonstrates highest sensitivity in predicting late PSS among haemorrhagic stroke patients with a low false-negative rate (AUC: 0.81; 95% CI: 0.76-0.86). CAVE and CAVS were the only models developed specifically for use following haemorrhagic strokes. This distinction is appropriate considering differences in epileptogenic mechanisms between haemorrhagic and ischaemic strokes. Haemorrhagic strokes are associated with a higher risk of seizures, likely due to the mechanical effects of expanding haematomas and large volume of excitotoxic metabolites sequestrated [2, 34, 35]. In fact, ischaemic strokes with haemorrhagic transformation demonstrate greater epileptogenicity compared to ischaemic strokes alone [36].

PoSERS is the only validated model used to predict seizures following both haemorrhagic and ischaemic strokes. It too puts greater weight on haemorrhage as a predictor of PSS. However, our meta-analysis suggests that PSS risk prediction models should be categorized according to stroke aetiology, owing to heterogeneity in interventions and morbidity. For instance, surgical haematoma removal was shown to increase seizure risk in haemorrhagic stroke patients in one of the models [23]. Moreover, the lower prevalence of haemorrhagic strokes and its higher mortality means that statistical aspects concerning censoring and optimistic model performance are intrinsically different to those for ischaemic strokes.

The commonest predictors across all 15 models were cortical involvement [23-26, 28, 29, 31, 33], functional deficits [22, 25, 28-32], increasing lesion size [23, 26, 29, 33], and early seizures [25, 26, 31], reflecting the association between stroke severity and increased seizure risk (*table 1*). Cortical lesions and lesions affecting the middle cerebral artery territory demonstrated particular epileptogenic foci [23-26, 28, 29, 31, 37]. Indeed, this increased risk is also seen with subcortical strokes that expand cortically, but less so with subcortical strokes alone [36, 38]. Neuroimaging was the commonest tool used to

▼ **Table 4.** PROBAST assessment of risk of bias and applicability.

Study	ROB				Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
Abraira *et al.* 2020 [21]	+	+	-	-	+	+	?	-	?
Abraira *et al.* 2020 [22]	+	+	+	-	+	+	+	-	+
Kwon *et al.* 2020 [23]	?	-	-	-	-	-	-	-	-
Yamada *et al.* 2020 [24]	+	?	?	-	+	+	?	-	?
Chi *et al.* 2018 [27]	-	-	?	+	?	+	-	-	-
Galovic *et al.* 2018 [25]	+	+	+	+	+	+	+	+	+
Alme *et al.* 2016 [28]	-	?	-	+	+	+	+	-	+
Kim *et al.* 2016 [29]	+	?	?	?	+	+	+	?	+
Haapaniemi *et al.* 2014 [26]	+	+	+	-	+	+	+	-	+
Krakow *et al.* 2010 [30]	-	+	-	-	-	+	-	-	-
Strzelczyk *et al.* 2010 [31]	?	+	-	-	+	+	-	-	-
Masuhr *et al.* 2006 [32]	?	+	+	-	+	+	+	-	+
Lamy *et al.* 2003 [33]	-	+	+	-	-	+	+	-	-

ROB: risk of bias; + indicates low ROB/low concern regarding applicability; - indicates high ROB/high concern regarding applicability; and ? indicates unclear ROB/unclear concern regarding applicability.

ascertain predictors, to determine stroke aetiology and anatomical involvement of lesions (*table 3*). Two models, PSEiCARe and Krakow 2010, consisted of predictors, solely determined at the bedside through clinical examination and medical history [27, 30]. This provides an alternative model for clinicians in settings with limited access to neuroimaging, EEG, or clinical biochemical labs. However, these two models demonstrated high risk of bias and have not been validated.

Our meta-analysis also identified models incorporating novel biomarkers for late PSS. Abraira *et al.* demonstrated that greater sensitivity can be achieved when clinical variables (*e.g.* NIHSS) are combined with blood biomarkers, than with clinical variables alone. With blood samples obtained during the acute phase of stroke, their immunoassay analyses showed that upregulation in endostatin and NCAM, and downregulation in S100B, Hsc70, and TNF-R1 were associated with increased risk of late PSS among ischaemic and haemorrhagic stroke patients for a median follow-up period of five years [21, 22].

There were conflicting results on age as a risk factor for post-stroke seizures. Some models considered younger age as a risk predictor [23, 26, 29, 30], whereas one model classified older age as a risk predictor [27]. Models that included younger age as a risk predictor had varying cut-off values between <65 or <75 years of age. One model classifying older age as a risk predictor used >80 years of age as the threshold. However, current evidence in the literature leans towards younger age as a risk factor of PSS [39-42].

Eleven studies demonstrated high risk of bias as per PROBAST (*table 4*). The commonest reasons for this were lack of model validation and inappropriate data handling. Many studies did not report how missing data on predictors and outcomes were handled in statistical analysis, and were therefore likely to have used complete-case analysis. This was especially relevant for studies based on routine care databases, where participants were not recruited from predesigned study protocols and where data was originally collected for other purposes [21, 22, 27, 30]. Furthermore, some studies did not report performance measures of calibration or discrimination, making it difficult to ascertain the model's ability to provide individual probabilities. Even when reporting classification measures including sensitivity, specificity and predictive values, some studies did not report the C-statistic. Complexities in data (*e.g.* censoring and competing risks) were not taken into account using appropriate tools such as time-to-event analysis. Model overfitting and optimistic performance were also commonly overlooked during statistical analysis, placing studies with smaller sample sizes and lower events per variable at even higher risk of bias. Only CAVE, PoSERS, and SeLECT underwent external validation, and this systematic review identified only one research article externally validating each of these models. There were few studies overall for PSS risk prediction model development and even fewer validation studies. Further external validation studies are warranted if these models are to be adopted in wider clinical practice.

The presence of only one underpowered RCT does not provide reliable evidence for primary AED prophylaxis compared to no treatment in preventing early post-stroke seizures [43]. Moreover, observational studies show that in most stroke patients, the risk of developing early seizures is approximately 5% [44]. Consensus guidelines remain clear about primary AED prophylaxis - AEDs are not recommended for haemorrhagic strokes unless there has been a seizure. Despite this, prophylactic AED usage remains widespread and is increasing [45]. In fact, Naidech *et al*. found that almost 40% of haemorrhagic stroke patients were prescribed prophylactic AEDs.

The CHANT trial provides evidence of adverse neurological outcomes in haemorrhagic stroke patients receiving AEDs, particularly phenytoin [46]. Contrastingly, findings from the ERICH study do not report adverse outcomes with prophylactic AEDs, although most patients were treated with levetiracetam [47]. The AHA/ASA guidelines (1999) state that a brief one-month course of prophylactic AEDs, preferably phenytoin, may be considered for haemorrhagic stroke patients receiving a Class IIb, Level of Evidence C recommendation [48, 49]. More recently, the only RCT of AEDs for haemorrhagic stroke suggested early seizure prevention with valproic acid [43]. Although only approximately a tenth of haemorrhagic stroke patients develop PSS, many of these patients are given prophylactic AEDs; treatment they will not need.

The absence of randomised controlled trials makes it difficult in making a reliable recommendation for secondary AED prophylaxis. Only observational studies have been published in the current literature, which indicate high seizure recurrence (70%) following one unprovoked post-stroke seizure [50]. Thus, secondary AED prophylaxis needs to be considered, although the quality of evidence underlying these studies is still low due to significant risk of bias and imprecision [44, 51, 52]. PSS risk prediction models may provide a useful research tool for RCTs studying AED prophylaxis.

Our study was limited by the clinical heterogeneity of patients and limitations in study designs that increased the potential for bias. There was heterogeneity in ascertainment of outcome events; while some studies ascertained seizure occurrence through outpatient clinics or telephone follow-ups, others retrospectively analysed medical records or insurance healthcare claims. Follow-up durations were also variable across the studies, ranging from one day to 4.8 years. Moreover, some studies did not consider possible confounding factors for PSS such as interventions received during the index stroke admission, past medical history of epilepsy, or the usage of AEDs (*supplementary table 2*). Funnel plot asymmetry and Egger and Begg tests suggested evidence of publication bias, although this may have been due to heterogeneity of seizure ascertainment because patients experiencing minor or non-motor seizures were less likely to be detected [53]. It was not clear whether this introduced a greater proportion of higher-risk patients into assessed cohorts.

Many PSS risk prediction models demonstrate high risk of bias and model overfitting. SeLECT and CAVE demonstrate the greatest predictive accuracy with the lowest risk of bias in predicting ischaemic and haemorrhagic strokes, respectively. These models can help identify stroke patients at high risk of seizures, who otherwise need long follow-up periods to ascertain late PSS. This can facilitate patient recruitment into clinical trials and more importantly, guide and personalise clinical management. While the evaluated models provide useful research tools, further external validation studies are warranted for wider clinical implementation. ■

Supplementary material.
Supplementary data accompanying the manuscript are available at www.epilepticdisorders.com.

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TEST YOURSELF

(1) How do early post-stroke seizures and late post-stroke seizures differ?

(2) What is the incidence of early post-stroke seizures and late post-stroke seizures, respectively?

(3) What are the commonest risk factors for post-stroke seizures?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.