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Research progress on the prediction of post-stroke epilepsy

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Abstract

Epilepsy is a common neurological disease that not only causes difficulties in the work and life activities of patients, but also brings complex social problems. Cerebrovascular disease is currently the main cause of epilepsy in the elderly. With the increased survival rate of patients after stroke, the incidence of epilepsy after stroke has also increased. Effective prediction of epilepsy after stroke is extremely crucial for the prognosis of patients, the initiation of antiepileptic therapy and the reduction of epileptic seizures. In this review, we summarize and compare the current models for the prediction of epilepsy after stroke, including the SeLECT prediction model, Post-Stroke Epilepsy Risk Scale (PoSERS), CAVE score, electroencephalogram (EEG) prediction model, and Scandinavian Stroke Scale (SSS) score, in order to provide reference for clinical practice and future research. Prediction models can be selected based on the clinical classification of cerebrovascular events. The SeLECT score prognostic model is a better choice for ischemic stroke, especially for the exclusive prediction of mild post stroke epilepsy. The CAVE score model is suitable for intra-cerebral hemorrhage patients. It is simple and offers high correlation between the risk factors and epilepsy. The PoSERS score simultaneously predicts ischemic and hemorrhagic stroke, and is superior to other methods in specificity as well as positive and negative prediction rate. The SSS score, which only measures stroke severity, is not strictly considered as a mature predictor, but it can be used as a first step screening tool. A growing number of large studies are under the way to identify risk factors of poststroke epilepsy (PSE) and to improve the inclusion of predictive indicators. New and advanced findings by EEG recordings may further improve the prediction of PSE.

Keywords: Post-stroke, Epilepsy, SeLECT, PoSERS, CAVE, Scandinavian stroke scale score, Electroencephalogram

Background

Epilepsy is a common neurological disease with about 70 million patients in the world. According to the epidemiological survey in 2015, the incidence of epilepsy in China is 7.15%, which can be divided into primary epilepsy, symptomatic epilepsy and cryptogenic epilepsy [1]. Epilepsy not only affects the lives and work of patients, but also has complex psychosocial consequences. A retrospective cohort study in China has shown that the epileptic patients have an increased risk of stroke. The relationship between epilepsy and stroke risk is significant in every age group, irrespective of the gender [2]. On the one hand, cerebrovascular disease is also the main cause of epilepsy in advanced age group, accounting for nearly 50% of epilepsy patients over 60 years old. On the other hand, studies have suggested that the secondary epilepsy after stroke accounts for about 3–30% of cerebrovascular diseases [3]. The cerebrovascular diseases have wide occurrence in China, and the burden of stroke has increased over the past 30 years, especially in the underdeveloped rural areas and central and western regions. According to a newly published systematic analysis of mortality, morbidity and risk factors in China and its provinces, stroke is the leading cause of death in China [4, 5]. With the improvement in medical treatment, the survival rate of patients after stroke is improved, resulting in an increased incidence of stroke-related epilepsy. Moreover, as stroke patients tend to be

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younger these years, they demand heavily for a high quality of life after stroke. However, the recovery of damaged brain function often faces problems of unsatisfactory seizure control and repetitive seizures, which can cause temporary or even permanent neurological symptoms, leading to anxiety, worse life condition and lower quality of life of patients. It has been reported that the level of self-assessment concerning health-related quality of life in some moderate or well-controlled epilepsy patients, is lower than that in the control group, especially when considered in the social aspect [6]. Therefore, effective prediction of the risk of having recurrent epilepsy after stroke is of great importance for the prognosis of patients, the timely initiation of antiepileptic therapy and the reduction of epileptic seizures and their harms. The aim of the present review is to provide a comprehensive discussion on the advantages, disadvantages and the feasibility of the clinically used tools for predicting recurrent seizures after stroke and poststroke epilepsy (PSE), including SeLECT score, Post-Stroke Epilepsy Risk Scale (PoSERS), CAVE score, electroencephalogram (EEG) prediction model and Scandinavian Stroke Scale score model (SSS), in order to provide a basis for the selection of suitable methods for predicting seizures, thus ensuring timely and effective prevention and drug intervention.

Definition

Currently, PSE has different clinical definitions. In 2014, the definition of epilepsy was revised by the International League Against Epilepsy (ILAE). According to that definition, epilepsy is a disease of the brain defined by at least two unprovoked (or reflex) seizures occurring more than 24 h apart, one unprovoked (or reflex) seizure with an at least 60% probability of future seizures, which is similar to the probability after two unprovoked seizures [7]. Seizures after stroke can be divided into early seizures and late seizures according to the time interval between the onset and cerebrovascular events. The dividing line in China is usually set at 2 weeks [8], but some scholars suggest a cutoff of 1 week [9, 10] or 4 weeks [11]. The ILAE prefers to distinguish the seizures within 7 days after the onset of the cerebrovascular disease (≤ 7 days) as early seizures, and those occurring after 7 days (> 7d) as late seizures [12]. The early seizures are considered to be due to the destruction of the blood-brain barrier caused by acute cerebral ischemia, the dysfunction of ion channels, the transient depolarization induced by hemosiderin deposition and other factors. The late seizures are non-induced, associated with both neurons and the formation of focal epilepsy [13, 14]. Some studies showed that an unprovoked poststroke seizure is indicative of structural epilepsy, as the risk of developing a subsequent unprovoked seizure is about 71.5%, so it can be diagnosed as PSE [15].

Risk factors of PSE

There are many risk factors of PSE. The age at onset of PSE was found to be an independent risk factor in the London south prospective stroke registry from 1995 to 2006, with a PSE incidence of 10.7% in patients younger than 65 years and 1.6% in patients older than 85 years ($P < 0.001$). Strokes involving the cortex, or some cortical related initial neurological symptoms, such as language dysfunction, dysarthria, visual neglect and loss of the visual field, are also associated with PSE. In addition, the incidence of epilepsy after anterior circulation infarction is higher than that after posterior circulation infarction [16]. Epileptiform discharge in EEG recording following stroke is a risk factor for PSE and may lead to poorer prognosis [17]. The incidence of PSE is correlated with the lesion diameter, and CT findings showed that with every 10 mm increase in lesion diameter, the incidence of epilepsy will increase by 16% in 7 years [18]. PSE is also associated with specific infarcts, such as those in the parietal temporal cortex and superior temporal gyrus [19]. Cardiogenic cerebral infarction in the parietal lobe might play a critical role in the epileptogenesis of PSE [20]. Cerebral hemorrhage and venous embolism infarction are more common in patients with PSE than in the control group [21]. A positron emission tomography study showed that patients with late-onset epilepsy and leukoencephalopathy had fewer blood flow and lower oxygen consumption than those without epilepsy [22], suggesting that lacunar infarction and leukoencephalopathy are also correlated with PSE. A study in China has suggested that the epileptic occurrence after stroke is related to hypertension, homocysteine, serum lipid level and other indicators [23]. Besides, PSE may also be related to genetic factors [24].

Current methods for predicting PSE or recurrent seizures

Scandinavian stroke scale score

SSS score was used to evaluate PSE in a long-term prospective controlled study on the occurrence and prediction of epilepsy after stroke in 2005. The score was initially used to grade the severity of stroke, and statistical results showed that the score was correlated with the occurrence of epilepsy after stroke. Multivariate logistic regression analysis suggested that an SSS score < 30 was a significant predictor of epilepsy after stroke [25]. However, this score evaluates the severity of stroke, including the patients' consciousness, language, orientation, and muscle strength of the affected limb; in this sense, it is similar to the widely used NIH Stroke Scale score in clinical practice in China. The correlation of

this score with the occurrence of PSE remains statistically significant after excluding the influence of other possible related factors. No specific prediction model and relevant confirmatory tests have been established to confirm the sensitivity and specificity of this score for the prediction of PSE. Moreover, the predictive effect of SSS score on the PSE risk is independent of other known risk factors such as age and imaging, which may be one-sided (Table 1).

Post-stroke epilepsy risk scale

PoSERS [26] is a model that predicts epilepsy caused by ischemic and hemorrhagic cerebrovascular diseases simultaneously. In a prospective study published in 2010, PoSERS was used to assess the risk of seizure after stroke in a 1-year follow-up in 264 stroke patients, comprising 7 items scored in the final prediction model. The scores of the items are shown in Table 2. In this study, 148 patients with epileptic seizures also underwent

Table 1 Scandinavian Stroke Scale score

Item	Manifestations	Score
1. Consciousness	Fully conscious	6
	Somnolent, can be awaked to full consciousness	4
	Reacts to verbal command, but is not fully conscious	2
2. Eye movement	No gaze palsy	4
	Gaze palsy present	2
	Conjugate eye deviation	0
3. Arm, motor power (motor power is assessed only on the affected side)	Raises arm with normal strength	6
	Raises arm with reduced strength	5
	Raises arm with flexion in elbow	4
	Can move, but not against gravity	2
	Paralysis	0
4. Hand, motor power (motor power is assessed only on the affected side)	Normal strength	6
	Reduced strength in full range	4
	Some movement, fingertips do not reach palm	2
	Paralysis	0
5. Leg, motor power (motor power is assessed only on the affected side)	Normal strength	6
	Raises straight leg with reduced strength	5
	Raises leg with flexion of knee	4
	Can move, but not against gravity	2
	Paralysis	0
6. Orientation	Correct for time, place and person	6
	Two of these	4
	One of these	2
	Completely disorientated	0
7. Speech	No aphasia	10
	Limited vocabulary or incoherent speech	6
	More than yes/no, but no longer sentences	3
	Only yes/no or less	0
8. Facial palsy	None/dubious	2
	Present	0
9. Gait	Walks 5 m without aids	12
	Walks with aids	9
	Walks with help of another person	6
	Sits without support	3
	Bedridden/wheelchair	0
Maximal score		58

Table 2 Post-Stroke Epilepsy Risk Scale (PoSERS) [26]

Item	Score
Supratentorial stroke	2
ICH involving cortical areas	2
Ischemia involving cortical or cortical-subcortical areas	1
Ischemia with ongoing neurological deficit	1
Stroke-caused neurological deficit with mRS ≥ 3	1
Seizure occurrence up to 14 days after stroke	1
Seizure occurrence 15 days or later after stroke	2
Maximal score	10

ICH intracerebral hemorrhage

Table 3 CAVE score [28]

Item	Score
Cortical involvement in ICH	1
Age < 65 years	1
Bleeding volume > 10 ml	1
Early seizure within 7 days of ICH	1
Maximal score	4

ICH intracerebral hemorrhage

standard EEG recording, and results showed that EEG did not have good performance in predicting PSE, with a sensitivity of 50% and a positive predictive rate of only 29.4%. However, this study has the following limitations: (1) current studies suggest that the epilepsy caused by hemorrhage has a different mechanism from that caused by ischemic stroke, and predicting the two types of epilepsy with different causes at the same time may be inappropriate [27]; (2) no multivariate analysis was performed during the establishment of the model, and no validation test was conducted for the prediction mode; (3) from the perspective of clinical practice, this model requires more evaluation items, detailed neurological examination, standardized evaluation of stroke classification and accurate localization of the lesions; so, it requires more involvement from clinicians and more complicated operation compared with other models; and (4) the dividing line between early and late seizures was 14 days, which required longer evaluation times and longer hospital stay of patients and a follow up after they are discharged. It was difficult to collect all the above-mentioned data clinically. On the other hand, however, this model can be applied for cerebral hemorrhage and ischemia at the same time, which means that the clinicians do not need to determine the cause.

CAVE score

Given the different mechanisms underlying epilepsy, the CAVE score [28] was demonstrated to be a single predictor for late epileptic seizures after hemorrhagic stroke in a retrospective analysis of 993 intracerebral hemorrhage (ICH) patients in the Helsinki Intracerebral Hemorrhage Study between 2005 and 2010. According to previous studies, hemorrhagic stroke has a greater structural impact on the brain, and epilepsy is more likely to occur after ICH [29]. The CAVE score is mainly based on whether the bleeding involves the cortex, age, previous seizures (within 7 days) and the amount of bleeding (Table 3).

This score has some weakness: (1) this study was a retrospective study of nearly 1 000 patients, but only 70 of them had late-onset epileptic seizures, which indicated a relatively small number; and (2) the epilepsy and epileptic seizures recorded in the medical records may be under-diagnosed, over-diagnosed or over-modeled. However, one advantage of this model is the aspect of clinical practice. The CAVE score contains only four items that are easy to remember and calculate, all of which are feasible based on variables that are soon available after the cerebral hemorrhage. After statistical analysis, all variables in the model were shown to be related to the increased risk of stroke, and after correction, each variable was clearly correlated with the occurrence of seizures after stroke. This model has been validated in an independent prospective intracranial hemorrhage cohort.

Epileptic seizure prediction using machine learning methods

Published in 2017, the EEG monitoring combined with machine learning method [30] is a widely applied prediction method that is not specific to the patients' disease conditions, including cerebrovascular disease, and can be applied to the prediction of stroke related epileptic seizures. This method is based on 4 different stages of an epileptic seizure: the preictal state, the ictal state, the postictal state and the interictal state, which have different EEG morphologies. The epileptic seizures can be monitored and the characteristic pattern of brain waves in the early stages can be analyzed through EEG monitoring, while the machine learning model performs EEG signal acquisition and preprocessing, and feature extraction and classification, which are required for prediction of epileptic seizures, including EEG signal acquisition and preprocessing, and the feature extraction and classification. Since it is currently not common for epilepsy patients to receive long-term EEG monitoring at neurology clinics in China, and that this method can generally produce predictive results about 20 min before the onset of epilepsy, it is then more suitable for patients with continuous EEG monitoring in the neurological intensive care unit (NICU).

Nowadays, this model is facing some problems. On the one hand, it is difficult to perform real-time EEG monitoring for patients with mild and moderate stroke during follow-up outside the hospitals, while standard

EEG has low specificity and sensitivity, especially for the elderly and stroke patients who may have some non-specific focal or widespread slow waves [31, 32]. On the other hand, real-time EEG monitoring in patients without epileptic seizures may not be easily accepted and it may lack convenience and accuracy. The processing and interpretation of the EEG signal have higher requirements for the equipment level and technical support. A large prospective study is currently under the way to predict PSE by an acute EEG measurement using a dry-cap electrode EEG (dEEG) system performed within 7 days of symptom onset. Unlike conventional wet-cap EEG, the dEEG uses little or no electrolyte gel. Through active amplification of the voltage of the electrode using a built-in gain amplifier, reliable EEG recording is possible, even with high impedances. The pilot phase of this study has shown the feasibility of this approach [33]. Continuous improvement of comfort as well as the function and the anti-interference ability of EEG recording tools, and shortening of the recording time are needed to make EEG more applicable in clinical usage.

SeLECT score

The SeLECT score [34] is mainly used for the prediction of ischemic stroke-related epilepsy. In a study published in 2018 that included 1 200 patients with initial ischemic stroke, the SeLECT score was used to predict late seizures in the patients, accompanied by an average of 28 months of telephone follow-up during which epileptic seizures were recorded for the diagnosis of PSE. The prognostic model includes 5 risk factors (shown in Table 4). This method has the following advantages: (1) the study was based on a clinical trial of 1 200 people, including multiple regional trials that involved a wide range of ischemic stroke patients; (2) this method has a high feasibility, since the entire predictive assessment of apoplexy-related epilepsy can be performed at the bedside, and all risk factors are well defined and easy to assess; (3) this model only predicted epilepsy that is related to ischemic stroke and did not include the assessment of primary cerebral hemorrhage, because some previous studies suggested that there are varied mechanisms of epilepsy caused by primary hemorrhage [27], so this design was more targeting. The SeLECT score is widely used in clinical studies, such as for setting biological criteria for recruitment in studies related to drug treatment of epilepsy after stroke, and the stroke patients in the study can be graded according to the risk of epileptic seizure. In addition, the prediction model can, to a certain extent, identify epileptic seizures and PSE in high-risk individuals, which can provide a basis for prophylactic use of antiepileptic drugs in high-risk patients with epilepsy after ischemic stroke in the future.

Table 4 SeLECT score [34]

Item	Score
1. Severity of stroke	
NIHSS 0–3	0
NIHSS 4–10	1
NIHSS ≥11	2
2. Large-artery atherosclerosis	
No	0
Yes	1
3. Early seizure (≤7 days)	
No	0
Yes	3
4. Cortical involvement	
No	0
Yes	2
5. Territory of MCA	
No	0
Yes	1
Maximal score	9

NIHSS National Institute of Health stroke scale, *MCA* middle cerebral artery

Discussion

The risk of PSE or recurrent seizures has significant implications and their prediction is of great importance. First, recurrent seizures after stroke can hinder recovery from cerebrovascular diseases, and hyper-early seizures (within 48 h) are an independent risk factor for hospitalization death and poor prognosis [35]. Second, several studies have suggested that early treatment after stroke and the drug response are key factors affecting long-term outcomes [36]. In the case of seizures that may be difficult to control, there is supposed to be a need for a multi-drug combination therapy and an epilepsy-related education for the patients and their families, to reduce the psychological burden of patients and teach their families how to correctly cope with the seizures once they occur.

Some research is under the way on the prediction of epilepsy after stroke in China and abroad, but there is still no practical experience in the clinical practice. Different prediction methods can be selected for different types of stroke; a comparison of prediction performance of the various prediction methods is shown in Table 5. According to the clinical classification of cerebrovascular events, the above-mentioned prediction models are selected and compared horizontally. The SeLECT score prognostic model is a better choice for ischemic stroke. It has high specificity and high negative prediction rate, so it is more suitable for the exclusive prediction of mild PSE, while having insufficient positive prediction efficacy for epilepsy after stroke. Moreover, this model mainly involves the prediction of early seizures, and it is easier

Table 5 The sensitivity, specificity, positive predictive rate and negative predictive rate of various predictive methods

Comparisons	PoSERS ≥7	CAVE ≥2	EEG analysis	SeLECT ≥6
Sensitivity (%)	70	81	**92.23**	18.2
Specificity (%)	**99.6**	89	93.38	96.7
PPR (%)	**87.5**	18	/	27.2
NPR (%)	**98.8**	97	/	94.6

NPR Negative predictive rate, *PPR* Positive predicitive rate

to obtain complete score items. The CAVE score is a great option for ICH patients. It is simple and provides a high correlation between the risk factors and epilepsy. The PoSERS is used for simultaneous prediction of ischemic and hemorrhagic strokes; it is complex and difficult, but has higher specificity as well as positive and negative prediction rates than other methods despite slightly lower sensitivity, according to the existing literature. The SSS score, which only measures stroke severity, is not strictly considered as a mature predictor, but may be a pilot for the rest prediction. It can be used as a first step screening tool, and then start the whole predictive process. Epileptic seizure prediction using a machine learning method is difficult to perform for clinicians. However, this prediction is more direct and objective. It is more accurate to predict the onset through the characteristic changes of EEG, and the sensitivity and specificity of this method have also been verified. Besides, the emergence of new EEG tools such as the dEEG system will further enhance the application potentials of EEG method in this field, expanding its use beyond the context of neurological intensive care with specialized technicians. The results of PoSERS indicate that the sensitivity of the standard EEG after stroke is relatively lower, which does not contradict the former conclusion, because it may be associated with the short duration of standard EEG. However, more cautions should be paid by clinicians if a cyclical partial epilepsy has a lateral discharge in patients with stroke (periodic lateralized epileptiform discharges), shows associations with a previous stroke site, and is characterized by repetitive spikes or sharp waves, spike and wave discharges or low activities [37]. Moreover, clinicians can also consider predicting PSE using two or more methods. If a patient has a high score after multiple-method prediction, then the possibility of epilepsy and epileptic seizure after stroke is high. During hospitalization, video EEG can be combined to predict and prevent seizures, which can improve the prediction accuracy to some extent.

The prediction methods should be carried out with a follow-up of seizure onset in patients during hospitalization or outside the hospital, so there are some common limitations: (1) during the follow-up, there could be some data loss, especially in some cases with a large stroke area. The medical record may be interrupted due to the death of the patient, which may introduce some bias; (2) the use of different evaluation methods (MRI and CT) may introduce instability into the evaluation of lesions; (3) the method of telephone follow-up is not the golden standard for epilepsy follow-up. Patients and their families with insufficient understanding of epileptic seizures may mislead the seizure records; (4) some patients may take antiepileptic drugs after stroke to treat comorbidities such as neuralgia and mental disorders. These factors will affect the accuracy of the prediction model to some extent; and (5) since no close EEG monitoring has been performed in patients, there may be a possibility of a non-convulsive seizure.

There is still a debate concerning whether and when the preventive antiepileptic therapy should be given to patients. Because of the different mechanisms of early and late seizures, the American Stroke Association (ASA) and the European Stroke Organization do not recommend primary prophylaxis for patients with stroke who do not have seizures [38, 39].

However, the poor prophylactic effect may be related to the older generation of antiepileptic drugs used in most studies. A recent study shows that levetiracetam can inhibit inflammatory response and reduce reactive gliosis in the hippocampus and piriform cortex in epileptic rat models, suggesting that it may be an important promising drug to prevent epileptic occurrences [40]. As a result, patients should be treated with new antiepileptic drugs if they meet the diagnostic criteria for PSE.

It is very difficult to predict recurrent post-stroke seizures and PSE, and there are also barriers and controversies to observe seizures after stroke. Since clinical patients, especially the elderly patients, may have atypical episodes, simply making judgements by “yes” or “no” is not practical in most circumstances. For some episodes, it is also important to correctly identify if they are post-stroke seizures or result from other causes, especially in the elderly, in whom the epileptiform seizures may occur due to abnormalities in glucose and electrolytes, or syncope due to the decreased heart function [41]. This makes studies of post-stroke epilepsy more sophisticated. As a manifestation of abnormal brain function, epileptic seizures may indicate that the patient is experiencing cerebral ischemia (such as TIA attack), cerebral infarction or post-stroke epilepsy. Therefore, epilepsy, as a marker of cerebrovascular disease, plays a great role in the treatment of patients [3].

Conclusion

In conclusion, although there are accumulating studies on the prediction of post-stroke epilepsy, they are still in the clinical trial stage, and it is difficult tailor each

prediction method to each patient. Therefore, more studies are needed both for exploratory research and clinical practice. The development of new cerebrovascular disease diagnosis technologies will help clarify the stroke subtype, its etiology and the classification of confounding factors, improve the accuracy and specificity of the method, and the accuracy of data collection and analysis. Combined stroke and epilepsy research will lead to new discoveries, but this will be a great challenge. Next steps will include clinical practice, the correction of prediction models, EEG equipment improvement, selection of an optimal prediction method and combining a variety of methods to increase the prediction efficiency. Basic research is required to establish animal models, and to fundamentally obtain the detailed information of the antiepileptic drug molecular targets to determine the risk factors for seizures, working towards establishing enhanced prediction methods with clinical feasibility, in order to realize timely protection of PSE patients and avoid unnecessary early treatment or delayed treatment.

Abbreviations

ASA: American Stroke Association; EEG: Electroencephalogram; ICH: Intracerebral hemorrhage; ILAE: International League Against Epilepsy; NICU: Neurological intensive care unit; PLEDs: Periodic lateralized epileptiform discharges; PoSERS: Post-Stroke Epilepsy Risk Scale; PSE: Poststroke epilepsy; SSS: Scandinavian Stroke Scale score; STRE: Stroke related epilepsy; ERICH: Ethnic/Racial Variations of Intracerebral Hemorrhage; dEEG: Dry cap electrode EEG; NPR: Negative predictive rate; PPR: Positive predicitive rate

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Authors' contributions

YC provided the ideas and the revision on the article. SZ searched and read the articles related to seizures and epilepsy after stroke, summarized the views and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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