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ORIGINAL RESEARCH

An Integrative Nomogram for Identifying Cognitive Impairment Using Seizure Type and Cerebral Small Vessel Disease Neuroimaging Markers in Patients with Late-Onset Epilepsy of Unknown Origin

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ABSTRACT

Introduction: Cognitive impairment (CI) is a common comorbidity in patients with late-onset epilepsy of unknown origin (LOEU). However, limited data are available on effective screening methods for CI at an early stage. We aimed to develop and internally validate a nomogram for identifying patients with LOEU at risk of CI and investigate the potential moderating effect of education on the relationship between periventricular white matter hyperintensities (PVHs) and cognitive function.
Methods: We retrospectively reviewed the clinical data of 61 patients aged ≥ 55 years diagnosed with LOEU. The main outcome was CI, reflected as an adjusted Montreal Cognition Assessment score of < 26 points. A nomogram based on a multivariable logistic regression model was constructed. Its discriminative ability, calibration, and clinical applicability were tested using calibration plots, the area under the curve (AUC), and decision curves. Internal model validation was conducted using the bootstrap method. The moderating effect of education on the relationship between PVH and cognitive function was examined using hierarchical linear regression.
Results: Forty-four of 61 (72.1%) patients had CI. A nomogram incorporating seizure type, total cerebral small vessel disease burden score, and PVH score was built to identify the risk factors for CI. The AUC of the model was 0.881 (95% confidence interval: 0.771–0.994) and 0.78 (95% confidence interval: 0.75–0.8) after internal validation. Higher educational levels

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blunted the negative impact of PVH on cognitive function.
Conclusion: Our nomogram provides a convenient tool for identifying patients with LOEU who are at risk of CI. Moreover, our findings demonstrate the importance of education for these patients.

Keywords: Cerebral small vessel disease; Cognitive function; Epilepsy; Nomogram

Key Summary Points

Why carry out this study?

Cognitive impairment (CI) is more prevalent among people who develop late-onset epilepsy of unknown etiology (LOEU) and under-evaluated by patients and neurologists because of the misinterpretation of the questionnaire responses from patients and family members or the large demand for outpatient services and short treatment times

To address this, we aimed to develop a nomogram to identify CI in patients with LOEU based on routine clinical evaluation data, which would enhance clinical decision making and address the limitations of cognitive scales

What has been learned from the study?

We developed a nomogram combining cerebral small vessel disease burden and seizure type for patients with LOEU to identify CI

Higher levels of education may mitigate the negative impact of periventricular white matter hyperintensities on cognitive function by increasing the cognitive reserve or as a result of greater pre-existing intelligence

Our findings demonstrate the importance of education for these patients

INTRODUCTION

New-onset epilepsy, referred to as late-onset epilepsy (LOE), markedly develops after 50 years of age [1, 2]. There are no established definitions of LOE. The current age thresholds range from 50 to 70 years among different studies [3]. Approximately 20% of LOE cases lack an identifiable cause and are diagnosed as LOE of unknown etiology (LOEU) [4]. Epilepsy is characterized by unpredictable seizures that can disrupt the normal organization of networks related to cognition, which can limit the participation of affected individuals in social activities [5]. Dementia is more prevalent among people who develop LOE [6, 7].

Epilepsy is characterized by unpredictable seizures, which can limit the participation of affected individuals in social activities. Cognitive impairment (CI), including decreased executive function, memory, and lack of attention, can make communication and establishing interpersonal relationships difficult for patients with epilepsy [8]. CI is more likely to occur in older patients with epilepsy than in younger individuals [9]; moreover, it often remains undetected by family members and is less likely to be given the required attention.

Epilepsy and its comorbidities (e.g., CI) impose an increasing burden on the healthcare system and are exacerbated by the aging of the population [3]. Early recognition of cognitive complications and risk factors would allow timely interventions before negative social and psychological consequences emerge. Despite this perspective gaining increasing recognition, limited data are available on effective screening methods for CI at an early stage or the effect of interventions on prognosis. Cognitive symptoms in patients with LOEU are under-evaluated and under-managed by patients and neurologists because of the misinterpretation of the questionnaire responses from patients and family members or the large demand for outpatient services and short treatment times. In the clinical evaluation of LOEU, cranioencephalic magnetic resonance imaging (MRI) scans and clinical history play important roles in diagnosis and differential diagnosis [3].

Thus, using a practical and objective tool to identify CI in patients with LOEU based on routine clinical evaluation data would enhance clinical decision making and address the limitations of currently available cognitive scales.

Cerebral small vessel disease (CSVD), which manifests with white matter hyperintensities (WMH), enlarged perivascular spaces (EPVSs), lacunar infarcts, cerebral microbleeds (CMBs), and brain atrophy on MRI, is one of the most common degenerative vessel disorders of aging brains [10]. The estimated incidence of CSVD in patients with LOEU is 39.8–49.5% [11, 12], which is higher than that in age- and sex-matched controls [11]. CSVD is a complex whole-brain disorder and an important cause of CI among older individuals [13, 14].

Few studies have reported a connection between vascular pathology and the cognitive functions of patients with epilepsy. Vascular risk factors influence cognitive functions in patients with LOEU with CSVD [15]. LOEU and CSVD can be comorbid, sharing common pathophysiological mechanisms such as blood–brain barrier disruption, neuroinflammation, and brain network dysfunction [13, 14, 16–18]. Therefore, considering the overlapping mechanism or the additive effect of the symptoms, CSVD may worsen cognitive outcomes in patients with LOEU.

This retrospective study was conducted based on the hypothesis that CSVD would exacerbate cognitive decline in patients with LOEU. We aimed to create logistic regression models based on CSVD burden and epilepsy-related factors to screen the occurrence of CI in patients with LOEU, which would provide a valuable tool for the early identification of CI among these patients in clinical settings. Furthermore, we aimed to explore controllable factors that may affect cognitive outcomes.

METHODS

Study Design and Participants

This double-center retrospective cohort study included a consecutive series of 1308 patients aged > 55 years who were diagnosed with LOEU at the inpatient unit of the Department of Neurology of the Beijing Tiantan Hospital affiliated with Capital Medical University and at the First Affiliated Hospital affiliated with Xiamen University between 2019 and 2021. Patient demographics, blood chemistry results, cognitive assessment results, and other medical data were retrieved from the electronic clinical medical record system. The study inclusion criteria were: (1) a LOEU diagnosis according to the criteria for an epilepsy diagnosis based on the definition of the International League Against Epilepsy [19], age at onset > 55 years [4, 20], and no currently known clear etiology (including structural, genetic, metabolic, immune, and infectious etiology); (2) complete MRI examination (including T1-weighted, T2-weighted, susceptibility-weighted, and T2 fluid-attenuated inversion recovery [FLAIR] imaging) results for evaluating CSVD markers were available; (3) Montreal Cognitive Assessment (MoCA) results were available. The exclusion criteria were: (1) a previous history of other major neurological disorders such as Parkinson's disease, multiple sclerosis, or intracranial tumors; (2) a previous history of major psychiatric disorders such as major depressive disorder, schizophrenia, or bipolar disorder; (3) poor MRI quality. The flowchart of the study procedure is provided in Fig. S1.

This study was performed according to the principles of the Declaration of Helsinki and was approved by the medical ethics committees of Beijing Tiantan Hospital (No. KYSQ2023-239-01) and the First Affiliated Hospital affiliated with Xiamen University (no. KY2022-035). Informed consent was obtained from the patients upon admission to the hospital for using their anonymized clinical data for scientific investigations and publication. The visual rating scales (Fazekas scale, total CSVD burden score, and GCA grade) used in this study have been developed and widely used in the past [21–28]. These scales are allowed to be publicly available, and the original authors have provided researchers with permission to use the scales.

Clinical Data Evaluation and Definitions

All data were retrospectively collected from the electronic medical record system. Demographic data included sex, age, and years of education. Epilepsy-related characteristics included onset age, seizure types, electroencephalography (EEG), interictal discharge (IED) frequency, seizure frequency, presence of status epilepticus, and use of anti-seizure medications (ASMs). Medical history included a history of febrile seizures, cranial trauma, family history of epilepsy, stroke, hypertension, diabetes, coronary artery disease, lipid metabolism disorder, hyperhomocysteinemia, smoking, and drinking. Seizure types were categorized as focal without impaired consciousness, focal with impaired consciousness, focal to bilateral tonic–clonic seizures (FBTCSs), or mixed seizures (any two of the three above seizure types occurring in one patient), based on medical history and EEG recordings according to the operational classification of seizure types proposed by the International League Against Epilepsy 2017 [19]. Generalized and unknown onset seizures were not observed in our cohort. The original EEG data of all the patients were reanalyzed by two trained epileptologists (HJW and CC) who were blinded to the clinical data, and discrepancies were resolved by a senior epileptologist (XQS). The frequency of IEDs was classified into two groups based on the index of IEDs [29] on EEG: 0–10% or > 10% groups (See Appendix S1 for details). IEDs were classified based on location into frontal lobe, temporal lobe, parietal lobe, occipital lobe, multiple lobe, unknown onset, and no IEDs. IEDs in the parietal lobe were not observed in our cohort. Seizure frequency was categorized as daily, weekly, monthly, yearly, or seizure-free. Cognitive functions were evaluated using the MoCA at admission, with the evaluation scheduled to be conducted at least 1 day after a seizure involving impaired consciousness. The MoCA scores were adjusted for years of education. The outcome measure was CI, defined as a baseline-adjusted MoCA score < 26 [30].

MRI Acquisition

MRI data were acquired using the 3-T Siemens MAGNETOM Prisma system from the Beijing Tiantan Hospital and First Affiliated Hospital Affiliated with Xiamen University. Details of the MRI acquisition parameters are shown in Appendix S2.

Neuroimaging Markers of CSVD

Two well-trained readers (HJW and QL) who were blinded to all clinical data performed a visual evaluation of CSVD imaging markers following the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) instructions [10]. Additionally, a senior neurologist, Xiaoqiu Shao, resolved any discrepancies that arose. The scoring of basal ganglia (BG) perivascular spaces (PVSs) was done using a semi-quantitative scale developed at the University of Edinburgh [31]. The total number of microbleeds and lacunar infarcts were also counted by visual inspection. Deep WMH (DWMH) and periventricular WMH (PVH) were rated using the Fazekas scale [21]. The total CSVD burden score was calculated with 1 point allocated to each of the following items [24]: severe WMH (Fazekas score = 3 in PVH or 2–3 in DWMH), ≥ 1 microbleeds, ≥ 1 lacune, and moderate-to-severe BG-PVSs (grade 2–4), with total scores ranging from 0 to 4 points. Brain atrophy was evaluated using a 4-point rating scale for assessment according to global cortical atrophy (GCA) [25]. The GCA grade was dichotomized into none to mild (grade 0–1) or moderate to severe (grade 2–3). The inter-rater agreement was tested using the weighted kappa measure. The weighted kappa coefficient values for CSVD burden score (kappa index = 0.939, $P < 0.001$), DWMH Fazekas score (kappa index = 0.951, $P < 0.001$), PVH Fazekas score (kappa index = 0.979, $P < 0.001$), and total WMH Fazekas score (kappa index = 0.959, $P < 0.001$) were excellent.

Furthermore, the unidentified bright object (UBO) detector was used to automatically extract and quantify WMH volume [32]. Briefly, the processing steps entailed linear registration

of the T1 image with the FLAIR image. First, the aligned T1-weighted images were segmented and normalized to standard space using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algorithm. Subsequently, FLAIR images were registered to the standard space using the same deformation fields. Segmentation of tissues with different contrasts was performed on the FLAIR image after normalization with the FMRIB's Automated Segmentation Tool. Voxel classification on the FLAIR image with different tissue contrasts was performed to obtain WMH probability maps by implementing the pre-trained k-nearest neighbor using the UBO detector. A probability threshold value of 0.8 was considered the judgment standard for WMH based on the literature and our experience [32]. WMHs in standard space were registered to the FLAIR space through the inverse deformation field. For additional quality assurance, extracted WMH data for each individual were visually checked and manually edited by a trained image analyst (HJW) using ITK-SNAP (www.itksnap.org) to correct any erroneous WMH classifications (e.g., incorrectly segmented WMH because of inaccurate mapping of T1 scans to DARTEL space and incorrectly segmented WMH caused by cranial trauma or previous stroke). WMH maps were segmented into PVH and non-PVH regions by constructing the ventricle distance brain map using the FMRIB Software Library distance map command. The distance threshold of segmentation between PVH and DWMH is reportedly 10 mm [33]. However, a WMH was manually delineated and labeled as periventricular if a confluent lesion extended from the periventricular space to $>$ 10 mm into the deep white matter. Finally, consistent with STRIVE, PVH volume and DWMH volume were output, and the total WMH was calculated (total WMH volume = PVH volume + DWMH volume).

Statistical Analyses

Statistical analysis was performed using R v. 4.1.2 and SPSS for Windows v. 22.0 (IBM Corp., Armonk, NY, USA). Patients were divided into two groups based on the presence or absence of CI. The normality of the variables was tested using the Shapiro-Wilk normality test, and no variables were normally distributed. Non-normal continuous variables are expressed as the median (interquartile range, IQR) and were evaluated using the Mann-Whitney U test. Categorical variables are expressed as numbers and percentages and were compared using the chi-square or Fisher's exact test. Then, the univariate logistic regression analysis was conducted. Clinical factors with P values < 0.1 in the univariate logistic regression analysis were included in the multivariate logistic regression model to identify risk factors for CI. Odds ratios (ORs) are reported with 95% confidence intervals.

The optimal model selection was performed using a backward step-down selection process by the Akaike information criterion (AIC) value [34]. A nomogram was constructed based on statistically significant variables from the final selected multivariable logistic regression model, and coefficients of the predictors were calculated.

The Fazekas scale was selected during model building, rather than the quantitative measurement of WMH volume, because the visual assessment of WMH may be easier to use clinically. Nomogram accuracy was evaluated with a receiver operating characteristic curve. A calibration curve was generated to evaluate the calibration performance (agreement between model predictions and actual outcomes). The net benefit at different threshold probabilities of the model was evaluated using decision curve analysis (DCA). We did not divide it into training and validation sets because of the small sample size. Internal validation of the final model, regarding calibration, discrimination, and DCA, was determined using bootstrap methods to mitigate possible issues of over-fitting or under-fitting problems (number of replicates = 1000; size of bootstrap samples = size of whole original sample; number of bootstrap samples = 61).

To investigate the potential influence of years of education on the relationship between the PVH (PVH volume) and cognitive function (MoCA scores), quantitative indicators were used to calculate moderator analysis using the

SPSS PROCESS macro. Before model building, centering was performed as preprocessing of the continuous variables. Hierarchal linear regression was conducted with the MoCA score as the dependent variable, years of education as the moderator variable, and PVH volume as an independent variable. Model 1 of the regression analysis included PVH volume and education. Model 2 included the variables from model 1 plus CSVD burden, brain atrophy, and CMBs as covariates. We included the interaction terms (PVH volume × education) in model 3 to test moderating effects of education. Simple slope analyses were used to aid interaction plot interpretation with different levels of the moderator variable.

RESULTS

Comparison of Demographic and Clinical Characteristics Between the CI and Non-CI Group

Of the 1308 patients enrolled in this study, 61 patients with LOEU, comprising 44 (72.1%) men and 17 (27.9%) women, met the inclusion criteria; their median age was 64 (IQR 58–68.5) years. The median onset age was 61 (IQR 56.5–67.3) years. Forty-four patients (72.1%) had CI. The median education duration was 11 years (8, 14.5), and 42 patients (68.9%) had CSVD with a CSVD burden score ≥ 1. Patients with CI were significantly more likely to have higher score of total CSVD burden; higher score and volume of PVH, and total WMH; more often present with CMB and moderate-to-severe brain atrophy ($P < 0.05$). These variables were included in subsequent models to adjust for baseline differences. More information on the patients' characteristics is shown in Table 1.

Risk Factors for CI Based on Univariate and Multivariate Analyses

The results of the univariate logistic regression analysis are presented in Table 2. Seizure types (focal with impaired consciousness), PVH Fazekas score, presence of CMBs, moderate-to-severe brain atrophy, and total CSVD burden score were significantly associated with CI ($P < 0.05$). Seizure types (FBTCSs) and total WMH Fazekas scores showed nonsignificant trends ($P < 0.1$).

Variables with $P < 0.1$ in univariate analyses were included in the next multivariate logistic regression analysis. The final model, selected based on the lowest AIC value, included seizure types: FBTCSs (OR: 38.81, 95% confidence interval: 2.5–603.51, $P = 0.009$); focal seizures with impaired consciousness (OR: 7.96, 95% confidence interval: 0.91–69.99, $P = 0.061$); mixed seizures (OR: 14.54, 95% confidence interval: 1.14–185.89, $P = 0.040$); total CSVD burden score (OR: 3.53, 95% confidence interval: 1.21–10.33, $P = 0.021$), and PVH Fazekas score (OR: 5.93, 95% confidence interval: 1.30–27.04, $P = 0.021$) (Table 2).

Development and Validation of a Nomogram Model for Identifying CI

A nomogram model was further constructed to identify the risk probability of CI in each patient from this cohort according to the final logistic regression analysis (Fig. 1). The nomogram was obtained by summing the points identified on the points scale for each factor. The added score projected on the bottom scale indicated the probability of CI. For example, a PVH Fazekas score of 0 was associated with 0 points, a CSVD burden score of 3 was associated with 70 points, and the mixed seizure type was associated with 50 points. Thus, the cumulative points for this patient with a PVH Fazekas score of 3, CSVD burden of 3, and mixed seizure type was 120. Accordingly, the likelihood of cognitive impairment was approximately 82%.

The nomogram showed excellent accuracy with an AUC value of 0.881 (95% confidence interval: 0.771–0.994, Fig. 2A). After bootstrap internal validation with 1000 repetitions, the remaining nomogram model had an acceptable bias-corrected AUC value of 0.78 (95% confidence interval: 0.75–0.8, Fig. 2B), demonstrating a good discrimination ability of our risk factor identification model.

The calibration curve and internal validation by bootstrap analysis with 1000 repetitions were

Table 1 Baseline clinical characteristics of LOEU patients with and without CI

Characteristics	*N* = 61	Non-CI group (*N* = 17)	CI group (*N* = 44)	*P* value
Sex (male), *n* (%)	44 (72.1%)	11 (64.7%)	33 (75%)	0.527
Age, median (IQR), years	64 (58–68.5)	65 (59–70.8)	59 (57.5–68)	0.140
Age at onset, median (IQR), years	61 (56.5–67.3)	58 (56–67)	61.6 (56.8–69)	0.200
Seizure type, *n* (%)				0.166
Focal without impaired consciousness	8 (13.1%)	5 (29.4%)	3 (6.8%)	
Focal with impaired consciousness	23 (37.7%)	5 (29.4%)	18 (40.9%)	
Focal to bilateral tonic-clonic seizures	15 (24.6%)	3 (17.6%)	12 (27.3%)	
Mixed seizures	15 (24.6%)	4 (23.5%)	11 (25%)	
IED frequency, *n* (%)[a]				0.776
0–10%	38 (62.3%)	10 (58.8%)	27 (61.4%)	
> 10%	22 (36.1%)	7 (41.2%)	16 (36.4%)	
IED localization, *n* (%)[a]				0.447
None	9 (14.8%)	2 (11.8%)	7 (15.9%)	
Frontal lobe	7 (11.5%)	2 (11.8%)	5 (11.4%)	
Temporal lobe	21 (34.4%)	5 (29.4%)	16 (36.4%)	
Occipital lobe	1 (1.6%)	1 (5.9%)	0 (0%)	
Multiple brain	18 (29.5%)	7 (41.2%)	11 (25%)	
Unknown	4 (6.6%)	0 (0%)	4 (9.1%)	
Seizure frequency, *n* (%)				0.865
Daily	13 (21.3%)	3 (17.6%)	10 (22.7%)	
Weekly	3 (4.9%)	1 (5.9%)	2 (4.5%)	
Monthly/yearly	45 (73.8%)	13 (76.5%)	32 (72.7%)	
Status epilepticus, *n* (%)	3 (4.9%)	0 (0%)	3 (6.8%)	0.553
Medical history, *n* (%)				
Febrile seizures	4 (6.6%)	1 (5.9%)	3 (6.8%)	0.894
Cranial trauma	5 (8.2%)	1 (5.9%)	4 (9.1%)	0.673
Family history of epilepsy	3 (4.9%)	0 (0%)	3 (6.8%)	0.553
Stroke	2 (3.3%)	0 (0%)	2 (4.5%)	1
Hypertension	25 (41%)	5 (29.4%)	20 (45.5%)	0.253
Diabetes	14 (23%)	3 (17.6%)	11 (25%)	0.738
Coronary artery disease	11 (18%)	4 (23.5%)	7 (15.9%)	0.481
Lipid metabolism disorder	21 (34.4%)	6 (35.3%)	15 (34.1%)	0.929

Table 1 continued

Characteristics	*N* = 61	Non-CI group (*N* = 17)	CI group (*N* = 44)	*P* value
Alzheimer's disease	3 (4.9%)	0 (0%)	3 (6.8%)	0.553
Hyperhomocysteinemia	26 (42.6%)	7 (41.2%)	19 (43.2%)	0.887
Current or previous smoking	23 (37.7%)			
Current or previous drinking	26 (42.6%)	8 (47.1%)	18 (40.9%)	0.663
Anti-seizure medications, *n* (%)				0.158
Unmedicated	10 (16.4%)	1 (5.9%)	9 (20.5%)	
Monotherapy	41 (67.2%)	11 (64.7%)	30 (68.2%)	
Polytherapy	10 (16.4%)	5 (29.4%)	5 (11.4%)	
Education, median (IQR), years	11 (8–14.5)	12 (9–15)	11 (7.3–13.8)	0.390
CSVD imaging characteristics				
DWMH Fazekas score, median (IQR)	1 (1–1)	1 (1–1)	1 (1–2)	0.202
PVH Fazekas score, median (IQR)	2 (1–2)	1 (1–2)	2 (1–2)	0.029
Total WMH Fazekas score, median (IQR)	3 (2–3.5)	2 (2–3)	3 (2–4)	0.034
DWMH volume, median (IQR), cm^3	1235.3 (708.8–2856.9)	1016.8 (646.8–1230.1)	1496.4 (803.3–2902.5)	0.051
PVH volume, median (IQR), cm^3	3233.3 (1539.9–5810.1)	2325.4 (1093.5–3614.6)	3699 (1555.9–7788.7)	0.021
Total WMH volume, median (IQR), cm^3	4431.4 (2359.1–9124.3)	3628.1 (1491.8–4431.4)	6218.4 (2877.2–10,703.0)	0.015
BG-PVS, median (IQR), points	1 (1–1)	1 (1–1)	1 (1–1)	0.164
Presence of lacune, *n* (%)	25 (41.0)	5 (29.4)	20 (45.5)	0.253
Presence of CMB, *n* (%)	17 (27.9)	1 (5.9)	16 (36.4)	0.024
Moderate-to-severe brain atrophy, *n* (%)	31 (50.8)	5 (29.4)	26 (59.4)	0.038
Total CSVD burden score, median (IQR), points	1 (0–2)	0 (0–1)	1 (1–2)	0.001
Total CSVD burden score, *n* (%)				0.028
0	19 (31.1)	10 (58.8)	9 (20.5)	
1	25 (41)	6 (35.5)	19 (43.2)	
2	11 (18)	1 (5.9)	10 (22.7)	
3	4 (6.6)	0 (0%)	4 (9.1)	

Table 1 continued

Characteristics	*N* = 61	Non-CI group (*N* = 17)	CI group (*N* = 44)	*P* value
4	2 (3.3)	0 (0%)	4 (4.5)	

LOEU late-onset epilepsy of unknown etiology, *CI* cognitive impairment, *IEDs* interictal discharges, *CSVD* cerebral small vessel disease, *DWMH* deep white matter hyperintensity, *PVH* periventricular white matter hyperintensity, *BG-PVS* basal ganglia perivascular space, *CMB* cerebral microbleed, *IQR* interquartile range, *SD* standard deviation
[a]Indicates that there are missing data for the variable

established to confirm model validity using R software (Fig. S2). All figures showed an acceptable calibration (all Brier scores = 0.122).

DCA revealed a good high net benefit. When the threshold probability of CI is 0.38–0.9 in the modeling dataset or 0.36–0.9 in the internal validation set (bootstrap validation algorithm with 1000 repetitions), using the nomogram for timely diagnosis of patients with CI confers more benefit than diagnosing either all or no patients (Fig. S3).

Moderating Role of Education Between PVH and Cognitive Function

The PVH volume ($B = -0.240$, 95% confidence interval: -0.438 to -0.042, $P = 0.018$) was significantly negatively associated with MoCA scores in model 1. When control variables were included in model 2, the PVH volume ($B = -0.228$, 95% confidence interval: -0.444 to -0.012, $P = 0.039$) was still significantly negatively associated with the MoCA scores. Education was significantly positively associated with the MoCA scores in models 1, 2, and 3. Model 3 included the interaction term (PVH volume × education) to explore whether education moderated the PVH volume and MoCA score (Table 3). The significant interaction term ($B = 0.181$, 95% confidence interval: 0.003–0.360, $P = 0.047$) showed that education blunted the effect of PVH on cognitive function. Furthermore, the higher the education level, the less the degree that PVH influenced cognitive function (Table 3 and Fig. 3).

DISCUSSION

To the best of our knowledge, this is the first study to integrate CSVD burden and epilepsy-related factors into a visual, convenient nomogram for early identification of CI in patients with LOEU and to explore the moderating role of education between CSVD and cognitive function. We found that seizure types, PVH Fazekas score, and the total CSVD burden score are important independent risk factors for CI in patients with LOEU. Internal validation of the nomogram demonstrated good clinical practicability, discrimination, and calibration. Education, as a modifiable moderating factor, was found to blunt the effect of PVH on cognitive function.

CI is common in patients with LOEU, with a prevalence rate of 72.1% in our dataset, similar to previous findings [15]. The identification of CI among patients and family members was frequently inadequate. Moreover, for various reasons (e.g. misinterpretation of questionnaires or fatigue), patients and family members were unwilling to cooperate with the cognitive scale assessment. Therefore, complementary measures reflecting the severity of CI in patients with LOEU are needed. The nomogram comprises a practical tool for quick, individualized identification of CI in patients with LOEU using readily available routine examinations and clinical history. This prompts patients and physicians to pay more attention to cognitive function and actively engage in longitudinal neuropsychological testing (e.g., MoCA) during the disease course. Moreover, the sample size of our study was small with only 17 cases of

Table 2 Univariate and multivariate analyses of CI in patients with LOEU

Variable	Univariate analysis		Multivariate analysis	
	OR (95% confidence interval)	*P* value	OR (95% confidence interval)	*P* value
Sex (male)	0.61 (0.18–2.04)	0.424		
Age (years)		0.537		
55–65	1 [Reference]			
≥ 65	0.70 (0.24–2.17)			
Age at onset		0.126		
55–65	1 [Reference]			
≥ 65	3.50 (0.70–17.44)			
Seizure type				
Focal without impaired consciousness	1 [Reference]		1 [Reference]	
Focal with impaired consciousness	6.00 (1.05–34.21)	**0.044**	7.96 (0.91–69.99)	**0.061**
Focal to bilateral tonic-clonic seizures	6.67 (0.99–45.03)	**0.052**	38.81 (2.5–603.51)	**0.009**
Mixed seizures	4.58 (0.73–28.65)	0.103	14.54 (1.14–185.89)	**0.040**
IED frequency		0.864		
0–10%	1 [Reference]			
> 10%	0.91 (0.31–2.65)			
IED localization				
None	1 [Reference]			
Frontal lobe	0.71 (0.07–6.92)	0.772		
Temporal lobe	0.91 (0.14–5.9)	0.925		
Occipital lobe[a]	–			
Multi lobe	0.45 (0.07–2.81)	0.392		
Unknown origin[a]	–			
Seizure frequency				
Daily	1 [Reference]			
Weekly	1.35 (0.32–5.73)	0.680		
Monthly/yearly	0.81 (0.07–9.76)	0.870		
Status epilepticus[a]	–	–		
Medical history				
Febrile seizures	1.17 (0.11–12.11)	0.895		

Table 2 continued

Variable	Univariate analysis		Multivariate analysis	
	OR (95% confidence interval)	*P* value	OR (95% confidence interval)	*P* value
Cranial trauma	1.6 (0.17–15.45)	0.684		
Family history of epilepsy[a]	–	–		
Stroke[a]	–	–		
Hypertension	2.0 (0.60–6.64)	0.258		
Diabetes	1.56 (0.38–6.44)	0.542		
Coronary artery disease	0.61 (0.15–2.45)	0.490		
Lipid metabolism disorder	0.95 (0.29–3.07)	0.929		
Alzheimer's disease[a]	–	–		
Hyperhomocysteinemia	1.09 (0.35–3.38)	0.887		
Current or previous smoking	0.71 (0.20–2.49)	0.588		
Current or previous drinking	0.78 (0.25–2.4)	0.664		
Anti-seizure medications				
Unmedicated	1 [Reference]			
Monotherapy	1.56 (0.24–9.91)	0.640		
Polytherapy	2.07 (0.48–8.83)	0.327		
Education				
Primary school	1 [Reference]			
Secondary school	2.67 (0.21–33.49)	0.447		
College	1.89 (0.45–7.86)	0.382		
CSVD imaging characteristics				
Presence of CMB	9.14 (1.11–75.48)	**0.040**		
Presence of lacune	2 (0.6–6.64)	0.258		
BG-PVS	2.72 (0.65–11.34)	0.171		
Moderate-to-severe brain atrophy	3.47 (1.04–11.55)	**0.043**		
Total CSVD burden score	3.64 (1.46–9.03)	**0.005**	3.53 (1.21–10.33)	**0.021**
PVH Fazekas score	2.44 (1.05–5.69)	**0.039**	5.93 (1.3–27.04)	**0.021**
DWMH Fazekas score	1.89 (0.74–4.81)	0.180		

Table 2 continued

Variable	Univariate analysis		Multivariate analysis	
	OR (95% confidence interval)	*P* value	OR (95% confidence interval)	*P* value
Total WMH Fazekas score	1.72 (1–2.95)	**0.050**		

LOEU late-onset epilepsy of unknown etiology, *CI* cognitive impairment, *OR* odds ratio, *IEDs* interictal discharges, *CSVD* cerebral small vessel disease, *DWMH* deep white matter hyperintensity, *PVH* periventricular white matter hyperintensity, *BG-PVS* basal ganglia perivascular space, *CMB* cerebral microbleed

[a]The odds ratio and *P* value cannot be calculated because the value in one of the cells was zero. *P* values < 0.1 are highlighted in bold

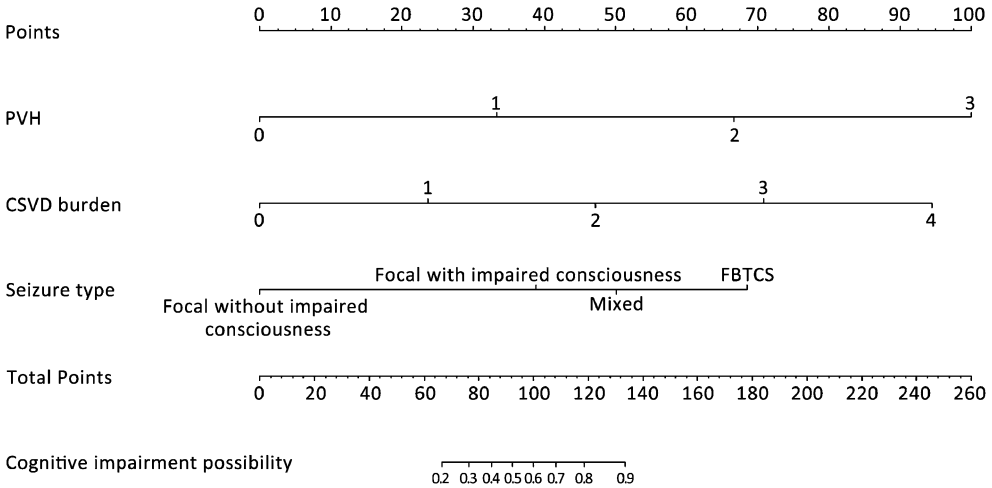

Fig. 1 Nomogram for identifying the risk of CI in patients with LOEU. The application is as follows: The top axis shows the prognostic points. First, connect the position on each variable axis to the top axis to determine the number of points corresponding to the appropriate variable position. Subsequently, the total points are the sum of three variables. Based on the total points, another line is drawn from the axis of the total points. It connects it to the relevant position on the "cognitive function possibility" [bottom] axis to determine the patient's individual risk of cognitive impairment. Abbreviations: *CI* cognitive impairment, *LOEU* late-onset epilepsy of unknown etiology, *PVH* periventricular hyperintensity, *CSVD* cerebral small vessel disease, *FBTCS* focal to bilateral tonic-clonic seizure

epilepsy without comorbid CI. Although we explored the internal validation of this modelling approach using 1000 bootstrapped resamplings to obtain relatively unbiased estimates, the construction of the nomogram was based on retrospective clinical data, which may be insufficient to obtain accurate predictions. Accordingly, these results provided us with new insights into the association between CSVD and CI in patients with LOEU; however, they must be interpreted with caution. Studies with larger sample sizes and more robust prospective study designs will be needed in the future study to verify our conclusions.

Epilepsy-related factors, such as etiology and onset age, seizure frequency, ASMs, seizure type, and IED frequency, affect the cognitive functions of patients with epilepsy [8]. We selected patients with LOEU to minimize the effect of different epilepsy etiologies on the cognitive results. However, the effects of seizure frequency, IED frequency, and number of ASMs on

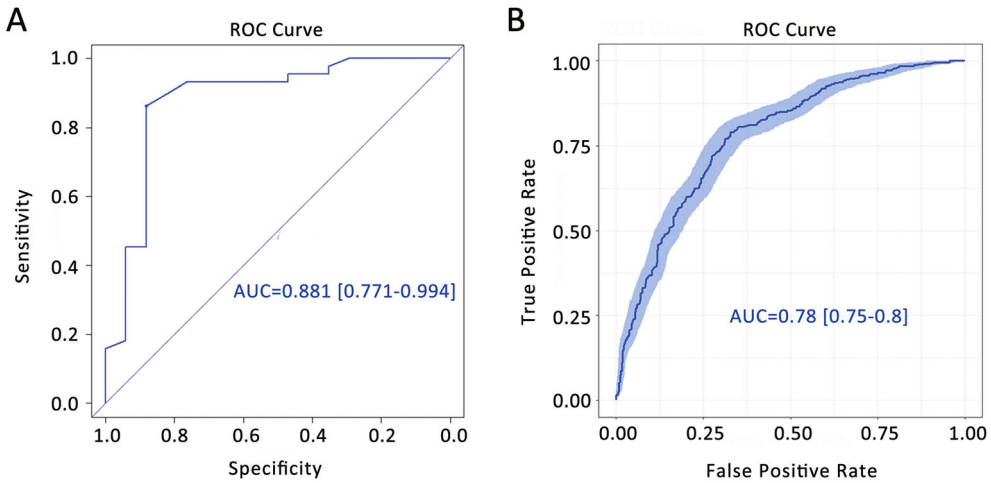

Fig. 2 ROC curve for the discrimination of the nomogram. **A** ROC curves showed that the AUC of the nomogram was 0.881 (95% confidence interval, 0.771–0.994); **B** after internal validation using the bootstrap method after 1000 replicates, the AUC of this nomogram was 0.78 (95% confidence interval: 0.75–0.8). *AUC* area under the curve, *ROC* receiver-operating characteristic

cognitive function were not observed in our study. This may be owing to the relatively low seizure and IED frequencies among our patients. Due to the small sample size, we considered only the number of ASMs used and not details on specific ASMs. However, our results are supported by several new notions. Clinical and epidemiological studies have shown that CI can occur not only during the onset of epilepsy but also before it [35]. These studies demonstrated a bidirectional relationship between epilepsy and CI [36, 37]. Notably, this bidirectional relationship does not imply a causal relationship between them, such as CI being a direct effect of seizures or ASMs. Instead, it shows that both epilepsy and CI possibly share underlying pathogenic mechanisms, which, in turn, may explain their substantial comorbidity [35–37].

We found that the total CSVD burden score and severity of PVH were risk factors for CI in patients with LOEU, consistent with the current understanding. In a study on the interaction of CSVD and epilepsy [38], the increased WMH burden was speculated to be due to epilepsy, whether as the underlying etiology or as a consequence of recurrent seizures. Our findings of the effects of CSVD on cognitive function and the high frequency of CSVD in our LOEU cohort show that CSVD may be involved in the common pathophysiological mechanisms between LOEU and CI. Traditional risk factors for cerebrovascular disease, aging, oxidative stress, neuroinflammation, and hereditary factors cause changes in the wall structure of small vessels, disrupting the blood-brain barrier and reducing the number and reactivity of small vessels, thereby causing CSVD. The abovementioned pathological process develops gradually and destroys normal brain network connections, leading to abnormal brain function, such as CI [13, 14]. The total CSVD load score excellently reflects the overall CSVD load of the whole brain [24]. Thus, explaining why the total CSVD burden score is a good indicator for CI in our model is not difficult. A synergistic effect between CSVD burden and seizures may exist in patients with LOEU, leading to progressive cognitive deterioration and further deviation from normal cognitive aging. However, future multi-center, larger prospective longitudinal studies should corroborate this speculation.

Our results were similar to previous findings indicating PVH rather than DWMH is associated with cognition in different study populations [39–41]—several possible explanations exist. WMHs are widely recognized as an indicator of poor brain health [42] and are associated with

Table 3 Moderated effect of education between PVH volume and MoCA score

Variables	Model 1[a]		Model 2[b]		Model 3[c]	
	B (95% confidence interval)	*P* value	*B* (95% confidence interval)	*P* value	*B* (95% confidence interval)	*P* value
Constant	− 1.374 (− 1.877 to − 0.872)	< 0.001	− 1.199 (− 1.867 to − 0.531)	0.001	− 1.112 (− 1.768 to − 0.457)	0.001
PVH volume	− 0.240 (− 0.438 to − 0.042)	**0.018**	− 0.228 (− 0.444 to − 0.012)	**0.039**	− 0.228 (− 0.438 to − 0.018)	**0.034**
Education	0.133 (0.088–0.178)	**< 0.001**	0.119 (0.068–0.170)	**< 0.001**	0.113 (0.063–0.163)	**< 0.001**
Total CSVD burden score			− 0.213 (− 0.766 to 0.340)	0.443	− 0.137 (− 0.680 to 0.406)	0.615
Moderate-to-severe brain atrophy			0.057 (− 0.374 to 0.488)	0.792	0.054 (− 0.366 to 0.473)	0.799
Number of CMBs			− 0.078 (− 0.301 to 0.144)	0.482	− 0.041 (− 0.260 to 0.178)	0.708
PVH volume × education					0.181 (0.003–0.360)	**0.047**
R-square	0.470		0.487		0.523	
R-square change	0.470		0.016		0.037	

P values < 0.05 are highlighted in bold

B unstandardized coefficient, *CSVD* cerebral small vessel disease, *PVH* periventricular white matter hyperintensity, *CMB* cerebral microbleed, *MoCA* Montreal Cognitive Assessment

[a]Unadjusted model

[b]Adjusted for CSVD burden, brain atrophy, and CMB

[c]Adjusted for model 2 criteria and the interaction between PVH volume and education

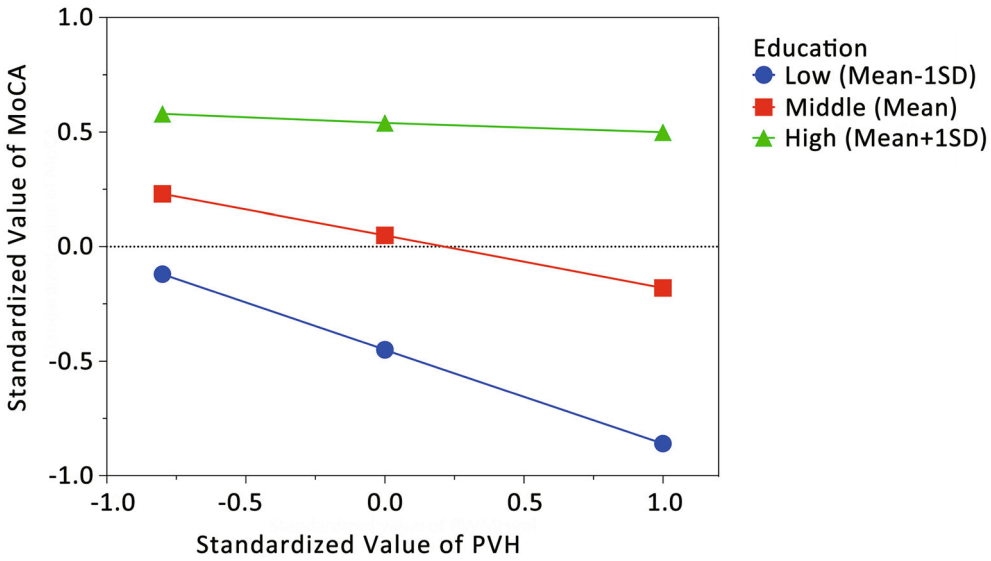

Fig. 3 Moderating effect of education on the relationship of the PVH with cognitive function. The simple slope analysis shows that the line for higher education is steeper, showing that a higher level of education significantly moderated the influence of PVH on cognitive function. *PVH* periventricular white matter hyperintensity

an increased risk of dementia [43]. Different pathological processes may underlie WMH in different regions [44]. The periventricular region has a high density of long associating fibers and projection fiber tracts, while the deep region has a high density of short associating fibers [44]. The vascular architecture of the periventricular area could be more vulnerable to white matter damage, which influences cognition [45]. Alternatively, periventricular WMH may damage periventricular corticospinal cholinergic nerve fibers arising from the BG of Meynert, which are important in cognitive processes [46]. Our results demonstrate the need for additional attention to be paid to cognitive function in patients with LOEU with PVH.

We also found that different seizure types are risk factors for CI in patients with LOEU. Patients who presented with FBTCSs were more likely to develop CI than those with focal seizures without impaired consciousness, which is consistent with previous results [47]. The effect of FBTCSs on the cognitive function of patients with epilepsy can be attributed to functional connectivity alterations in brain networks, such as the dynamic restructuring of large-scale brain networks [48]. Excessive and frequent information exchange among cognition-related networks, especially in the default mode network (DMN), may play a role in CI in patients with epilepsy [48]. Patients who presented with focal impaired awareness and mixed seizures were more likely (although non-significantly) to develop CI than those with focal seizures without impaired consciousness. There is an argument that the onset of seizures induces loss of consciousness caused by abnormal activity in cortical and subcortical areas, including the DMN [49], which may explain the present result.

We also explored the potential moderating effect of education on the relationship between PVH and cognitive function. We used automated segmentation and a visual inspection of PVH volume to assess WMH severity more robustly in the moderating role analysis [50]. No direct relationship between education and cognitive function was found; however, education blunted the effect of PVH on cognitive function. The higher the educational level in patients with LOEU, the less negative the impact of PVH on cognitive function. The theory of cognitive reserve may provide a plausible interpretation for the moderating role of

education. Cognitive reserve refers to differences in the cognitive processes of socio-cultural and environmental factors, which explain different coping abilities in the presence of pathological injury [51]. Higher educational levels may entail increased intellectual reserves [52]. The brain, through reserves (including the cognitive reserve) and compensatory mechanisms, delays the progression of CSVD [52] to slow cognitive decline. Additionally, patients with higher education are usually more knowledgeable about the disease and follow the treatment protocol more strictly, enhancing the treatment effect and slowing functional decline [53]. However, the relationship should be interpreted cautiously, given our small sample size. The data in our study cannot rule out the possibility that patients with a higher level of education may have initially had a higher level of pre-existing intelligence, and their cognitive decline occurred at a slower rate due to this higher baseline level. Regardless, these results highlight the need to raise awareness of LOEU, avoid stigmatization, and increase educational opportunities for patients with LOEU.

We found an interesting phenomenon. Although females have a longer life expectancy, our study had a higher proportion of males (72.1%). In other related literature, the proportion of males with LOEU was 32–66.7% [54, 55]. We believe there are two reasons that may explain this phenomenon. First, the selection of a younger threshold (55 years) narrowed the discrepancy in incidence between females and males. Second, males may be more affected by the social and self-stigma of epilepsy [3], which may prompt them to actively seek medical attention.

This study has some limitations. First, data were retrospectively collected from electronic medical records of hospitalized patients at a comprehensive epilepsy center. However, many patients with LOEU are treated only in outpatient clinics. Second, we did not fully assess the type and dosage of ASMs, genetic predisposition, and concurrent medications, each of which might have affected the cognitive outcomes. Future studies will need to expand upon this work by including larger sample sizes and applying detailed neuropsychological assessments for different cognitive domains to provide more methods for identifying CI in patients with LOEU and to explore the causes of CI in greater depth. Third, the model may still be affected by over-fitting risk because of the lack of external validation. Finally, this study employed a retrospective design, which, in turn, restricts the ability to draw inferences on causality. Similarly, seizures were characterized based on retrospective data, and incorporating these data into a nomogram model has inherent limitations that may result in insufficiently robust predictions.

CONCLUSION

Our nomogram model combining CSVD burden and seizure type provides a convenient tool for quickly identifying cognitive outcomes in patients with LOEU. Additionally, higher educational levels blunted the negative impact of PVH on cognitive function, illustrating the importance of education in patients with LOEU. A well-designed prospective clinical trial is warranted to confirm whether more aggressive management of vascular risk factors or more educational opportunities would protect cognitive function in patients with LOEU. Although we performed rigorous validation of the nomogram using 1000 bootstrapped resamplings, future studies must externally validate the proposed nomogram independently.

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Data Availability. All data used for this study are provided in the manuscript. Additional details are available from the corresponding author on request.

Declarations

Conflict of Interest. None of the authors has any conflict of interest to disclose.

Ethical Approval. This study was performed according to the principles of the Declaration of Helsinki and was approved by the medical ethics committees of Beijing Tiantan Hospital (no. KYSQ2023-239-01) and the First Affiliated Hospital affiliated with Xiamen University (no. KY2022-035). Informed consent was obtained from the patients upon admission to the hospital for using their anonymized clinical data for scientific investigations and publication. The visual rating scales (the Fazekas scale, total CSVD burden score, and GCA grade) used in this study have been developed and widely used in the past [21–28]. These scales are allowed to be publicly available, and the original authors have provided researchers with permission to use the scales.

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