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ORIGINAL RESEARCH

Association Between IL-6 and Seizure Recurrence in Patients with the First Post-Ischemic Stroke Seizure

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Purpose: To study the association between IL-6 level and seizure recurrence in patients with the first post-ischemic stroke seizure and assess its predictive value for seizure recurrence.

Patients and Methods: A total of 2976 consecutive ischemic stroke patients were retrospectively enrolled. Among them, 209 (7.02%) patients with the first post-ischemic stroke seizure were included in this analysis. The IL-6 mRNA expression level was evaluated through quantitative real-time PCR (qRT-PCR) and the $2^{-\Delta\Delta Ct}$ method. Demographic data and clinical characteristics were collected. Univariate analysis was performed with independent-samples *t*-test, Mann–Whitney *U*-test, or chi-square test. Multivariate analysis was conducted using a backward stepwise logistic regression model for variables with $P<0.10$ in univariate analysis. The predictive value was assessed using a receiver operating characteristic (ROC) curve.

Results: Among the patients included, 105 (50.24%) had recurrence of seizures, and 104 (49.76%) had no recurrence. Multivariate analysis demonstrated that the IL-6 mRNA expression level was independently correlated with seizure recurrence in patients with the first post-ischemic stroke seizure after adjusting for age, NIHSS scores, time of seizure, seizure type, lesion size, location of the offending lesion to different hemispheric lobes, cortical involvement, gender, electroencephalography (EEG) findings, and hemorrhagic transformation. When the IL-6 mRNA expression level was used to predict seizure recurrence, the area under the ROC curve (AUC) was 0.763 (SE=0.033, 95% CI=0.698–0.829). The diagnostic power was moderate.

Conclusion: IL-6 was independently correlated with seizure recurrence in patients with the first post-ischemic stroke seizure and might be a potential biomarker for prediction of seizure recurrence.

Keywords: post-ischemic stroke seizure, seizure recurrence, IL-6, predictive value

Introduction

Epilepsy is a complex, multifactorial neurological disease, which is mainly characterized by a predisposition to seizure recurrence.[1] About 70 million people are affected by epilepsy all over the world, and one third of them are never free of seizures even when they receive a therapy employing anti-epileptic drugs.[2] Ischemic stroke is an important cause of epilepsy, especially in elderly people.[3] In the last decades, the incidence of post-stroke epilepsy has increased due to important advances in the therapeutic management of stroke that have reduced its mortality rate in the acute phase.[4,5] A recent investigation reported that the

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incidence of post-stroke seizures could reach 15.3%.[6] After stroke, epilepsy can threaten patients not only through potential physical injuries, but also through deleterious effects on the brain with stroke lesion and degenerative changes.[7] In addition, recurrent peri-infarct depolarization may harm already vulnerable tissues through further neuronal injuries caused by the additional metabolic stress.[8,9] Epilepsy after stroke has been demonstrated to be associated with decreased survival at 30-day and 1-year time points as well as increased length of hospital stay and resource utilization.[10,12] The importance of post-stroke epilepsy also contemplates cognitive functioning, a lower disease-specific quality-of-life, and more disability and neurological impairment.[13] Therefore, prediction and management of seizure recurrence is critical for stroke care. However, other studies did not observe any association between post-stroke seizures and long-term disability/mortality.[14,15]

Inflammation induced by the ischemic cerebrovascular process participates in the initiation and continuation of seizures.[16,18] Interleukin-6 (IL-6) is a pro-inflammatory cytokine and associated with cardiovascular diseases,[19,22] suggesting its critical role in the inflammatory response to cerebral ischemia.[23] In addition, studies show that IL-6 is associated with development of seizures.[24,26] Elevated IL-6 levels are confirmed in several different epilepsy etiologies and media.[27] However, no previous studies investigated the association between IL-6 levels and seizure recurrence in patients with the first post-ischemic stroke seizure and its value in predicting seizure recurrence. In this study, we performed the above investigation with the aim of providing a basis for clinicians to predict seizure recurrence.

Patients and Methods

Included Patients

Between March 2013 and March 2018, 2976 consecutive ischemic stroke patients were retrospectively enrolled in the Third People's Hospital of Xinjiang Uygur Autonomous Region. Among them, 209 (7.02%) patients were diagnosed with post-stroke seizure and included in this study. Data were obtained through reviewing medical records of their routine care for ischemic stroke and seizure at outpatient department visits and admission. Seizure recurrence was followed up by neurologists in all participants until March 2019. This study was conducted in accordance with the Declaration of Helsinki and received the approval of the ethics committee of the Third People's Hospital of Xinjiang Uygur Autonomous Region (20130241018), and each participant provided written informed consent.

Inclusion and Exclusion Criteria of Included Patients

Inclusion criteria included 1) patients with first-ever ischemic stroke which was definitely diagnosed through signs and symptoms, magnetic resonance imaging (MRI), or computed tomography (CT) findings, and medical histories; 2) patients with the first post-ischemic stroke seizure which was determined based on the definition described by Fisher et al;[28] 3) complete medical records; and 4) informed consent. Exclusion criteria included 1) patients with potential epileptogenic lesions, such as cerebral vascular malformation, cerebral hemorrhage, brain tumor, traumatic brain injury, and cortical dysplasia; 2) patients with a family history of epilepsy or patients previously diagnosed with epilepsy; and 3) patients with transient ischemic attack (TIA).

Key Definitions

Early onset was defined as the first post-ischemic stroke seizure occurring within 1 week after stroke insult and late onset as occurring outside 1 week. Seizure recurrence referred to the second unprovoked and separated seizure from the first one by >24 hours. Standard EEG of 20–30 minutes duration was conducted in all 209 patients within 24–72 hours of the first post-ischemic stroke seizure onset. Abnormal EEG findings included epileptiform discharge, generalized slow, and regional slow. Partial seizures were defined as originating within networks limited to one hemisphere, and generalized seizures were defined as originating at some point within, and quickly involving, bilaterally distributed networks.

Detection of the IL-6 mRNA Expression Level

The blood samples were collected after acute ischemic stroke (AIS) in all 209 patients. Total RNA was extracted from blood samples through the miRCURY^{TM} RNA Isolation kit for Biofluids (Exiqon, Vedbaek, Denmark). cDNA was then synthesized with the miRCURY LNA Universal cDNA Synthesis Kit II (Exiqon, Vedbaek, Denmark). Quantitative Real-Time PCR (qRT-PCR) was performed with the Rotor-Gene® Q Real-Time Fluorescence Quantitative PCR Analyzer (Qiagen, Germany). The $2^{-\Delta\Delta Ct}$ method was employed to assess the IL-6 mRNA expression level using

GADPH as a reference gene. The primer sequences of IL-6 were 5′-ATCAGGAGACCTGCTTGATG-3′ (sense) and 5′-TGGTGGCTTTGTCTGGATTC-3′ (anti-sense), and the primer sequences of GADPH were 5′-AGCCTCAAGATCA GCAATG-3′ (sense) and 5′-CACGATACCAAAGTTGTC ATGGAT-3′ (anti-sense).

Statistical Analysis

All data were statistically analyzed through the SPSS version 19.0 for Windows (SPSS Inc., USA), and significance was set at $P<0.05$. Continuous data were validated for normality with Kolmogorov–Smirnov test. Normal data were demonstrated as mean±standard deviation (SD), and independent-samples *t*-test was used to perform univariate analysis; and non-normal data were demonstrated as median and interquartile range, and Mann–Whitney *U*-test was used to perform univariate analysis. Categorical data were demonstrated as ratios or percentages (%), and chi-square test was used to perform univariate analysis. Multivariate analysis was then conducted using a backward stepwise logistic regression model for variables with $P<0.10$ in univariate analysis. Among the variables included in multivariate analysis, age was a continuous variable, grades of the IL-6 mRNA expression level, NIHSS scores, and lesion size were multicategorical variables, and time of seizure, seizure type, cortical involvement, gender, EEG findings, and hemorrhagic transformation were binary variables. The predictive value was assessed using a receiver operating characteristic (ROC) curve.

Results

Demographic Data and Clinical Characteristics

All 209 patients with the first post-ischemic stroke seizure included 117 (55.98%) males and 92 (44.02%) females. Their average age was 62.93±8.82 years, ranging from 37–82 years. Among them, 105 (50.24%) patients had recurrence of seizures (case group) and 104 (49.76%) patients had no recurrence (control group). The detailed demographic data and clinical characteristics are shown in Table 1. According to univariate analysis (Table 1), age, NIHSS scores, time of seizure, seizure type, lesion size, location of the offending lesion to different hemispheric lobes, and cortical involvement were statistically different between case group and control group ($P<0.05$), and the remaining variables were not statistically different ($P>0.05$).

IL-6 mRNA Expression Level

The average expression level of IL-6 mRNA was 4.87 ±1.91 for all 209 patients with the first post-ischemic stroke seizure, and the expression level was higher in the case group than in the control group (6.32±2.18 vs 3.41 ±1.64, $t=10.912$, $P<0.001$). The expression level were then classified into four grades according to the quartiles (Q1, Q2, and Q3) of the control group. Chi-square test also demonstrated that the expression level was higher in case group than in control group (Table 2).

Multivariate Analysis

Grades of the IL-6 mRNA expression level, age, NIHSS scores, time of seizure, seizure type, lesion size, location of the offending lesion to different hemispheric lobes, cortical involvement, gender, EEG findings, and hemorrhagic transformation were included in multivariate analysis. Multivariate analysis demonstrated that the IL-6 mRNA expression level was independently correlated with seizure recurrence in patients with the first post-ischemic stroke seizure after adjusting for age, NIHSS scores, time of seizure, seizure type, lesion size, location of the offending lesion to different hemispheric lobes, cortical involvement, gender, EEG findings, and hemorrhagic transformation (Table 3).

ROC Analysis

As shown in Figure 1, when grades of the IL-6 mRNA expression level was used to predict seizure recurrence in patients with the first post-ischemic stroke seizure, the area under the ROC curve (AUC) was 0.763 (SE=0.033, 95% CI=0.698–0.829), and the AUC adding IL-6 to the other independent variables associated with seizure recurrence was 0.820 (SE=0.029, 95% CI=0.762–0.877). When the IL-6 mRNA expression level >Q3 (5.27) was used as the diagnosis criterion, the diagnosis results are shown in Table 4. The AUC was 0.718 (SE=0.036, 95% CI=0.647–0.788). The sensitivity, specificity, accuracy, false positive rate, false negative rate, positive predictive value, and negative predictive value were 68.57%, 75.00%, 71.77%, 26.53%, 29.73%, 73.47%, and 70.27%, respectively. Therefore, its diagnostic power was moderate.

Discussion

Inflammation after ischemic stroke is an unavoidable pathological process associated with post-ischemic injury in the brain.[29,30] Peripheral and central inflammation can

Table 1 Demographic Data and Clinical Characteristics of Case Group and Control Group

		Case Group (n=105)	Control Group (n=104)	χ^2/Z/t	P
Male (n, %)		65 (61.90%)	52 (50.00%)	3.005	0.083
Age (years)		60.92±7.91	64.96±9.74	3.29	0.002
Nationalities (n, %)	Han Uygur Other	53 (50.48%) 39 (37.14%) 13 (12.38%)	48 (46.15%) 42 (40.38%) 14 (13.46%)	0.391	0.822
Educational level (n, %)	Primary school and below Junior high school Senior high school and above	26 (24.76%) 45 (42.86%) 34 (32.38%)	29 (27.88%) 44 (42.31%) 31 (29.81%)	0.309	0.857
Annual family income (RMB) (n, %)	<10,000 10,000–20,000 >20,000	24 (22.86%) 41 (39.05%) 45 (42.86%)	21 (20.19%) 45 (43.27%) 48 (46.15%)	0.412	0.814
Occupation (n, %)	Farmer Worker Civil servant/teacher/doctor	36 (34.29%) 39 (37.14%) 30 (28.57%)	40 (38.46%) 35 (33.65%) 29 (27.88%)	0.439	0.803
Smoking (n, %) Drinking (n, %) Diabetes mellitus (n, %) Hypertension (n, %) Coronary heart disease (n, %) Atrial fibrillation (n, %)		33 (31.43%) 22 (20.95%) 18 (17.14%) 69 (65.71%) 38 (36.19%) 16 (15.24%)	30 (28.85%) 25 (24.04%) 14 (13.46%) 60 (57.69%) 43 (41.35%) 11 (10.58%)	0.165 0.285 0.546 1.423 0.585 1.009	0.684 0.593 0.46 0.233 0.444 0.315
TOAST classification (n, %)	Large artery atherosclerosis Cardioembolism Small vessel occlusion Other determined Undetermined	49 (46.67%) 24 (22.86%) 12 (11.43%) 2 (1.90%) 18 (17.14%)	52 (50.00%) 19 (18.27%) 15 (14.42%) 2 (1.92%) 16 (15.38%)		0.897*
NIHSS scores (n, %)	Mild (≤8) Moderate (9–15) Severe (≥16)	34 (32.38%) 42 (40.00%) 29 (27.62%)	51 (49.04%) 39 (37.50%) 14 (13.46%)	8.739	0.013
Total cholesterol (mmol/L) Triacylglycerol (mmol/L) Low density lipoprotein cholesterol (mmol/L) High density lipoprotein cholesterol (mmol/L) Status epilepticus (n, %)		4.81±1.05 1.41±0.75 3.12±0.96 0.97±0.42 10 (9.52%)	4.62±0.89 1.33±0.60 2.94±0.58 1.06±0.57 7 (6.73%)	1.412 0.852 1.642 1.298 0.545	0.158 0.406 0.132 0.174 0.614
Time of seizure (n, %)	Early onset Late onset	41 (39.05%) 64 (60.95%)	58 (55.77%) 46 (44.23%)	5.86	0.019
Seizure type (n, %)	Generalized Partial	46 (43.81%) 59 (56.19%)	61 (58.65%) 43 (41.35%)	4.608	0.032
EEG findings (n, %)	Normal Abnormal	47 (44.76%) 58 (55.24%)	60 (57.69%) 44 (42.31%)	3.496	0.062
Lesion size (n, %)	Small Moderate Large	12 (11.43%) 31 (29.52%) 62 (59.05%)	28 (26.92%) 30 (28.85%) 46 (44.23%)	8.782	0.012

(*Continued*)

Table 1 (Continued).

		Case Group (n=105)	Control Group (n=104)	χ^2/Z/t	P
Lesion location (n, %)	Anterior infarct	83 (79.05%)	76 (73.08%)	1.023	0.313
	Posterior infarct	22 (20.95%)	28 (26.92%)		
Location of the offending lesion to different hemispheric lobes (n, %)	Temporal lobes	43 (40.95%)	26 (25.00%)	6.012	0.014
	Frontal lobes	41 (39.05%)	24 (23.08%)	6.219	0.013
	Parietal lobes	37 (35.24%)	26 (25.00%)	2.601	0.109
	Occipital lobes	34 (32.38%)	27 (25.96%)	1.042	0.307
	Basal ganglia	28 (26.67%)	24 (23.08%)	0.360	0.548
	Thalamus	20 (19.05%)	18 (17.31%)	0.106	0.744
Reperfusion therapy (n, %)		35 (33.33%)	25 (24.04%)	2.206	0.138
Antiepileptic drugs (n, %)		97 (92.38%)	101 (97.12%)	2.349	0.125
Hemorrhagic transformation (n, %)		30 (28.57%)	19 (18.27%)	3.09	0.079
Cortical involvement (n, %)		46 (43.81%)	29 (27.88%)	5.759	0.016

Notes: Lesion size: large (>50×50 mm and >5 slices), moderate (≤15×15 mm and >5 slices or >50×50 mm and ≤5 slices) and small (≤15×15 mm and ≤5 slices). * Fisher's Exact Test.
Abbreviations: TOAST, trial of org 10172 in acute stroke treatment; EEG, electroencephalography.

contribute to damage of the blood–brain barrier through upregulating inflammatory mediators. On the other hand, persistent inflammation can affect neuronal plasticity with network reorganization through several transcriptionally modulated mechanisms, which is potentially associated with aberrant and epileptogenic circuits.[31,35] Seizures are well-acknowledged complications following ischemic stroke.[36,37] Although their exact mechanism remains unknown, neurologic inflammation and damage to the blood–brain barrier are demonstrated indispensable components of epileptogenesis after brain injury.[38] Several inflammatory cytokines, such as IL-6, IL-1β, etc., have been detected in human epileptogenic tissue and cerebrospinal fluid, and, meanwhile, they have also been shown as involvements in the initiation and continuation of seizures through experimental models.

IL-6 is a pro-inflammatory cytokine and its levels are low in the central nervous system under normal conditions.

Table 2 Number of Patients in Four Grades of the IL-6 mRNA Expression Level

	Case Group (n=105)	Control Group (n=104)	χ^2	P
Grade 1 [≤Q1 (1.82)]	3	26	49.692	<0.001
Grade 2 [>Q1 and ≤Q2 (3.53)]	8	26		
Grade 3 [>Q2 and ≤Q3 (5.27)]	22	26		
Grade 4 (>Q3)	72	26		

However, its levels elevate significantly in many diseases, for example, stroke, epilepsy, brain damage, and so on.[39,40] During brain inflammation, IL-6 is primarily secreted by glial cells.[41] Stimulation of microglia and astrocytes may result in increased secretion of IL-6.[42] In addition, elevated levels of other inflammatory cytokines, such as IL-1β, IL-17, TNF-α, etc., can also upregulate the expression of IL-6.[43] Fang et al[44] demonstrated that IL-6 could inhibit neuronal necrosis and apoptosis through decreasing cytosolic Ca^{2+} overload induced by N-methyl D-aspartate, implying a neuroprotection of IL-6. However, Wang et al[45] found that a chronic infusion of IL-6 could attenuate miniature excitatory postsynaptic currents regulated by N-methyl D-aspartate receptor in the hippocampal neurons of rats treated with anti-N-methyl D-aspartate receptor, which exacerbated memory impairment of rats. Therefore, IL-6 may bidirectionally impose influence on memory and synaptic plasticity.

Upregulated IL-6 levels can not only decrease hippocampal neurogenesis and long-term potentiation (LTP) but also increase gliosis and create conditions that may contribute to the onset of epilepsy.[43,46] IL-6 can increase the blood–brain barrier permeability and has been shown as an association with development of seizures.[24,26,47] Ho et al[50] indicate that peripheral inflammation caused by lipopolysaccharide can increase seizure susceptibility through upregulating expression of IL-6, IL-1β, and TNF-α in the hippocampus. Erta et al[43] found that transgenic IL-6 expression is pro-convulsive in mice. Samuelsson et al[51]

Table 3 Results of Multivariate Analysis

	Regression Coefficient	Standard Error	Wald χ^2	Hazard Ratio	95% Confidence Interval	*P*
IL-6 mRNA expression level			13.487			<0.001
Grade 2	0.469	0.146	1.047	1.859	0.579–4.018	0.249
Grade 3	0.743	0.271	5.118	4.513	1.414–9.122	0.021
Grade 4	1.262	0.489	25.309	13.893	5.071–29.948	<0.001
Age	−0.506	0.212	5.285	0.627	0.413–0.914	0.019
NIHSS scores			5.442			0.015
Moderate	0.632	0.252	3.925	1.689	1.159–3.376	0.041
Severe	1.013	0.494	7.184	2.249	1.275–4.683	0.009
Late onset	0.784	0.321	5.172	1.761	1.183–3.549	0.021
Partial seizure	0.640	0.283	5.035	1.686	1.174–3.493	0.023
Lesion size			5.821			0.013
Moderate	0.645	0.246	4.141	1.703	1.168–3.621	0.037
Large	1.029	0.448	7.283	2.312	1.328–3.587	0.008
Location of the offending lesion to different hemispheric lobes			4.735			0.028
Temporal lobes	0.912	0.457	8.743	2.454	1.423–4.974	0.004
Frontal lobes	0.877	0.416	8.669	2.398	1.391–4.858	0.005
Parietal lobes	0.572	0.249	2.954	1.506	0.841–2.983	0.114
Occipital lobes	0.349	0.143	2.506	1.397	0.792–2.889	0.158
Basal ganglia	0.351	0.152	0.875	1.159	0.583–2.468	0.313
Cortical involvement	1.104	0.467	6.028	1.903	1.211–4.195	0.011
Male	0.389	0.151	1.919	1.398	0.628–2.716	0.196
Hemorrhagic transformation	0.467	0.213	2.575	1.457	0.830–2.782	0.156
Abnormal EEG findings	0.496	0.231	3.089	1.504	0.863–3.145	0.123

showed that prenatal exposure to IL-6 may lead to a higher risk of neurodegeneration of the hippocampus, inducing changes in both hippocampal morphology and structure. Pineda et al[52] report that polyinosinic-polycytidylic acid can increase IL-6 in the offspring hippocampus through inducing maternal immune activation in experimental pregnancy, eventually resulting in faster progression of epileptogenesis and hippocampal hyperexcitability in the offspring.

In summary, IL-6 levels elevate significantly after stroke, and upregulation of IL-6 may contribute to the onset of epilepsy. In this study, the incidence of post-stroke seizures was 7.02%, which was basically consistent with the result of Fu et al[53,54] (8.1%) and higher than Kim et al (3.3%). Multivariate analysis demonstrated that the IL-6 level was independently correlated with seizure recurrence in patients with the first post-ischemic stroke seizure after adjusting for NIHSS scores and lesion size. Therefore, IL-6 does not simply mediate the association between larger/more severe AIS and recurrent seizures. In addition to IL-6, the factors associated with seizure recurrence also included age, lesion size, cortical involvement, hemorrhagic transformation, and so forth. Higher age is a protective factor, which may be correlated with smaller cerebral cortex and decreased excitability induced by degenerative changes in elderly people.[55] Cortical involvement is a recognized independent risk factor, especially the temporal and frontal lobe, which may be associated with dense cortical nerve cells with a lower threshold for seizures in this region.[56] The extravasation and stimulation of blood metabolites may have epileptogenic effects in the acute phase of stroke,[57] and so hemorrhagic transformation is a risk factor. Large lesions usually involve the temporal and frontal lobe.[56] Therefore, large lesions are also associated with seizure recurrence.

We further assessed the value of IL-6 level in predicting seizure recurrence. The results showed that the diagnostic power was moderate with sensitivity of 68.57% and specificity of 75.00%. Therefore, IL-6

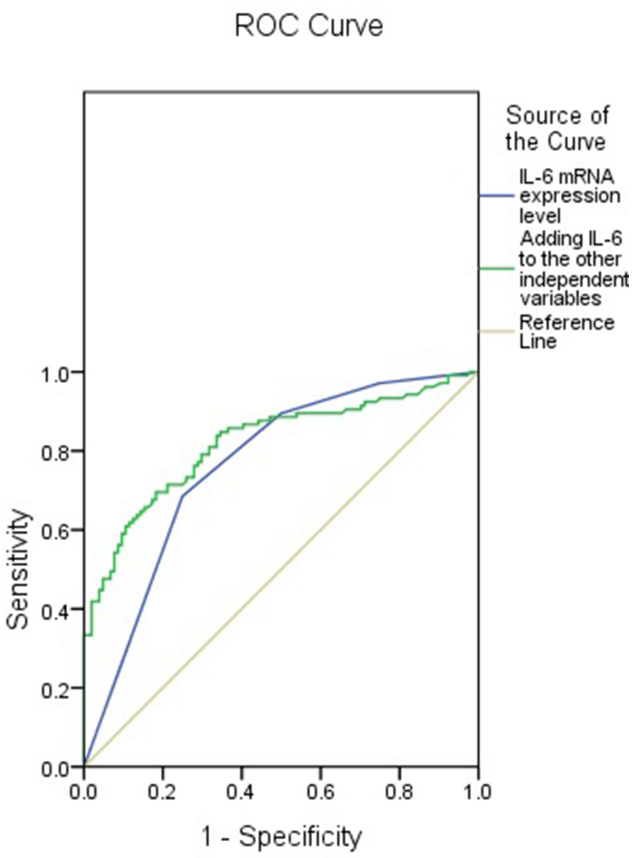

Figure 1 ROC curves of grades of the IL-6 mRNA expression level and adding IL-6 to the other independent variables in predicting seizure recurrence.

might be a potential biomarker for prediction of seizure recurrence. Kim et al[54] developed a seizure recurrence risk score in the early post-stroke seizure after ischemic stroke patients. This score was based on atrial fibrillation, gender, functional disability, partial seizure type, and cortical lesion with sensitivity of 70.6% and specificity of 71.0%.

The main limitations of this study included 1) it was a retrospective analysis; 2) there was an unequivocal distribution of the follow-up period; and 3) other unknown variables, able to potentially influence the association between IL-6 and seizure recurrence, might have not been included in the analyses.

Table 4 Distribution Results of the IL-6 mRNA Expression Level >Q3 in the Case Group and Control Group

	Case Group	Control Group	Total
>Q3 (5.27)	72	26	98
≤Q3 (5.27)	33	78	111
Total	105	104	209

Conclusion

IL-6 level was independently associated with seizure recurrence in patients with the first post-ischemic stroke seizure. Therefore, IL-6 might be a potential biomarker for prediction of seizure recurrence.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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