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ARTICLE

Clinical analysis on risk factors and prognosis of early post-traumatic epilepsy

Análise clínica de fatores de risco e prognóstico da epilepsia pós-traumática precoce

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ABSTRACT

Objective: To analyze the risk factors and prognosis related to early post-traumatic epilepsy (EPTE). **Methods:** One hundred and eighty-six patients with traumatic brain injury were enrolled. Their full clinical data were collected. Single factor analysis and logistic regression analysis of risk factors related to EPTE were performed. The prognosis of patients was determined. **Results:** Single factor analysis showed that there were significant differences of age ($p = 0.011$), epilepsy history ($p < 0.001$), injury site ($p = 0.004$), injury type ($p < 0.001$) and injury degree ($p < 0.001$) between the EPTE group (40 patients) and non-EPTE group (146 patients). Logistic regression analysis showed that the injury site, injury type and injury degree were the main risk factors for EPTE. The odds ratio values of injury site, injury type and injury degree were 1.977 (1.473–2.679), 2.096 (1.543–2.842) and 2.376 (1.864–3.609), respectively. The logistic regression equation was P = Exp (-1.473 + 0.698 × injury site + 0.717 × injury type + 0.935 × injury degree). The sensitivity and specificity of injury site, injury type and injury degree for predicting EPTE were 79.2% and 80.5%, 78.9% and 85.7% and 84.2% and 81.0%, respectively. The analysis of prognosis showed that the Glasgow Outcome Scale/Activity of Daily Living Scale scores in the EPTE group were significantly lower than those in non-EPTE group ($p < 0.05$). **Conclusions:** Injury site, injury type and injury degree are the main risk factors for EPTE. The prognosis of patients with traumatic brain injury can be affected by EPTE.

Keywords: Epilepsy, post-traumatic; risk factors; logistic models; prognosis.

RESUMO

Objetivo: Analisar os fatores de risco e prognóstico relacionados à epilepsia pós-traumática precoce (EPTE). **Métodos:** Cento e oitenta e seis pacientes com lesão cerebral traumática foram incluídos. Seus dados clínicos completos foram coletados. A análise fatorial única e a análise de regressão logística dos fatores de risco relacionados à EPTE foram realizadas. O prognóstico dos pacientes foi observado. **Resultados:** A análise fatorial única mostrou que houve diferenças significativas de idade ($p = 0,011$), história de epilepsia ($p < 0,001$), local da lesão ($p = 0,004$), tipo de lesão ($p < 0,001$) e grau de lesão ($p < 0,001$) entre o grupo EPTE (40 casos) e o grupo não-EPTE (146 casos), respectivamente. A análise de regressão logística mostrou que o local da lesão, tipo de lesão e grau de lesão foram os principais fatores de risco para EPTE. Os valores de razões de chance do local da lesão, tipo de lesão e grau de lesão foram 1.977 (1.473-2.679), 2.096 (1.543-2.842) e 2.376 (1.864-3.609), respectivamente. A equação de regressão logística foi P = Exp (-1,473 + 0,698 × local de lesão + 0,717 × tipo de lesão + 0,935 × grau de lesão). A sensibilidade e especificidade do local da lesão, tipo de lesão e grau de lesão para a predição da EPTE foram de 79,2% e 80,5%, 78,9% e 85,7% e 84,2% e 81,0%, respectivamente. A análise do prognóstico mostrou que o escore da Escala de Desfechos de Glasgow / Atividade de Vida Diária no grupo EPTE foi significativamente menor do que no grupo não-EPTE ($P < 0,05$). **Conclusões:** O local da lesão, tipo de lesão e grau de lesão são os principais fatores de risco para EPTE. A EPTE pode afetar o prognóstico de pacientes com lesão cerebral traumática.

Palavras-chave: Epilepsia pós-traumática; fatores de risco; modelos logísticos; prognóstico.

Epilepsy is a common disease of the central nervous system in which the recurrent excitatory discharge of brain neurons causes transient brain dysfunction. Long-term frequent epilepsy attacks can lead to varying degrees of mental or psychological disorders, which bring serious economic and mental burdens to the family and society[1]. The

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brain trauma can significantly increase the risk of epilepsy. Post-traumatic epilepsy refers to the epilepsy seizure secondary to traumatic brain injury, which can occur at any time after brain injury[2]. Post-traumatic epilepsy accounts for about 20% of patients with epilepsy. The total incidence of epilepsy is 5-7% in patients with brain trauma and 11% in patients with severe nonpenetrating craniocerebral trauma[3]. Post-traumatic epilepsy is divided into immediate epileptic seizure (occurring less than 24 hours after injury), early epileptic seizure (occurring less than one week after injury) and late epileptic seizure (occurring more than a week after injury)[4]. Early post-traumatic epilepsy (EPTE) often occurs during hospitalization in patients with brain injury. An EPTE has a great impact on the development of the disease condition in patients, and can increase the risk of late epilepsy seizure[5]. A severe EPTE may cause a cerebral hernia due to increased intracranial pressure, and even respiratory and cardiac arrest and death[6]. Therefore, it is of great significance to evaluate the risk factors and prognosis of EPTE. This study retrospectively analyzed the clinical data of 186 patients with traumatic brain injury, and analyzed the risk factors and prognosis of EPTE. The objective was to provide a reference for preventing and treating EPTE.

METHODS

Participants

One hundred and eighty-six patients with traumatic brain injury who received treatment in the Renmin Hospital of Wuhan University from July 2014 to June 2017 were enrolled in this cross-sectional study. The sample size was not estimated beforehand. The inclusion criteria were as follows: a) the patients had a definite history of trauma; b) brain CT confirmed an intracranial cerebral contusion, subarachnoid hemorrhage, epidural or subdural hematoma that were clearly organic lesions; c) the patients had no history of malignancy, or other nervous system or immune diseases; d) the patients had no clear bacterial or viral infection[7]. The exclusion criteria were as follows: a) liver or kidney dysfunction; b) major organ diseases or systemic metabolic diseases; c) uncontrolled diabetes mellitus; d) impaired lipid metabolism. This study was approved by the Ethics Committee of the Renmin Hospital of Wuhan University. Written informed consent was obtained from all participants.

Diagnostic criteria and measurement methods

Data of the patients' general condition were provided by their families. The site, type and degree of traumatic brain injury were determined by imaging examination. The injury degree was scored according to the revised injury severity classification for traumatic brain injury[8]. The EPTE was diagnosed by at least two physicians in the epilepsy field, and it was determined and specified according to the new classification of epilepsies and epileptic seizures (International League Against Epilepsy, 2017)[9], combined with an evaluation of the disease history, neurological examination, electroencephalography and imaging examination data.

Evaluation of prognosis

A follow-up of the patients, by telephone or in the outpatient clinic was performed. The long-term prognosis of the patients was evaluated using the Glasgow Outcome Scale (GOS)[10]. The quality of life of the patients was evaluated using the Activity of Daily Living Scale (ADL)[11]. The short-term efficacy was evaluated by the post-traumatic four-week GOS score, among which good (5 points) and mild disability (4 points) were classified as a good prognosis, while severe disability (3 points), vegetative state (2 points) and death (1 point) were classified as a poor prognosis. The long-term efficacy was assessed by the post-traumatic six-month ADL classification, and the outcomes of full recovery of daily living (ADL1), partial recovery of daily living (ADL2) and being able to walk with the help of someone and crutches (ADL3) after six months of treatment were classified as a good prognosis, while being severely disabled and bedridden but conscious (ADL4), vegetative state (ADL5) and death (ADL6) were classified as a poor prognosis[12].

Statistical analysis

All statistical analyses were carried out using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Single factor analysis was performed to compare the variables between the non-EPTE group and the EPTE group. The enumeration data were presented as number, and were compared using the Chi-square test with Yates' correction. Logistic regression analysis was conducted for further analyzing the significant variables in single factor analysis. The odds ratio values were calculated, and the receiver operating characteristic curves of significant variables for predicting EPTE were drawn. A p-value < 0.05 was considered as statistically significant.

RESULTS

General information of patients

Of 186 patients with traumatic brain injury, there were 108 males and 78 females, with an average age of 39.97 ± 14.53 years (range, 20–60 years). Forty-two patients had an epilepsy history, and 144 patients had no epilepsy history. One hundred and twenty-two patients had injury to the temporal/parietal lobe, and 64 patients had injury to other areas. Ninety patients had a closed injury, and 96 patients had an open injury. One hundred and forty patients had mild/moderate injury, and 46 patients had severe injury. According to

Table 1. Single factor analysis on variables related to EPTE (n[%]).

Variable	Total	EPTE	Non-EPTE	χ^2	p-value
Sex					
Male	108	22 (20.37)	86 (79.63)	0.197	0.658
Female	78	18 (23.08)	60 (76.92)		
Age					
< 20 years	39	16 (41.03)	23 (58.97)	11.168	0.011
20-39 years	55	9 (16.36)	46 (83.64)		
40-60 years	45	7 (15.56)	38 (84.44)		
> 60 years	47	8 (17.02)	39 (82.98)		
Epilepsy history					
Yes	42	18 (42.86)	24 (57.14)	14.651	< 0.001
No	144	22 (15.28)	122 (84.72)		
Injury site					
Temporal/ parietal	122	34 (27.87)	88 (72.13)	8.505	0.004
Other areas	64	6((9.38)	58 (90.63)		
Injury type					
Open	96	34 (35.42)	62 (64.58)	22.745	< 0.001
Closed	90	6 (6.67)	84 (93.33)		
Injury degree					
Mild/ moderate	140	17 (12.14)	123 (87.86)	29.396	< 0.001
Severe	46	23 (50.00)	23 (50.00)		

EPTE: early post-traumatic epilepsy.

the diagnostic criteria of EPTE, there were 40 EPTE cases and 146 non-EPTE cases. In the EPTE group, there were 12 patients with partial seizure, 10 patients with complex partial seizure and 18 patients with generalized seizure.

Results of single factor analysis on variables related to EPTE

The age of the patients in the non-EPTE group was 40.95 ± 5.97 years, and in the EPTE group was 43.47 ± 6.60 years. There were 86 males and 60 females in the non-EPTE group, and 22 males and 18 females in the EPTE group. In the non-EPTE group, 24 patients had a history of epilepsy, 88 patients had injury in the temporal/parietal lobe, with 58 patients having injury in other areas; 84 patients had a closed injury, and 62 patients had an open injury; and there were 17 patients with a mild/moderate injury, and 22 patients with severe injury. In the EPTE group, 18 patients had a history of epilepsy, 34 patients had injury at the temporal/parietal lobe, with six patients having injury in other areas; six patients had a closed injury, and 34 patients had an open injury; and there were 140 patients with a mild/moderate injury, and 46 patients with severe injury. The single factor analysis on variables related to epilepsy showed that there were significant differences of age ($p = 0.011$), epilepsy history ($p < 0.001$), injury site ($p = 0.004$), injury type ($p < 0.001$) and injury degree ($p < 0.001$) between the two groups. There was no significant difference in sex ($p = 0.658$) between the two groups ($p > 0.05$) (Table 1).

Results of logistic regression analysis

The significant variables in single factor analysis, including age, epilepsy history, injury site, injury type and injury degree were assigned to the data (Table 2), and the logistic regression analysis was performed. The results showed that the injury site, injury type and injury degree were the main risk factors for EPTE. The odds ratio values of the injury site, injury type and injury degree were 1.977 (1.473-2.679), 2.096 (1.543–2.842) and 2.376 (1.864–3.609), respectively (Table 3). The logistic regression equation was as follows: $p = Exp(-1.473 + 0.698 \times \text{injury site} + 0.717 \times \text{injury type} + 0.935 \times \text{injury degree})$. The receiver operating characteristic curves of injury type and injury degree for predicting the epilepsy after craniocerebral injury are shown in the Figure. The sensitivity and specificity of the injury site for predicting the epilepsy after craniocerebral injury were 79.2% and 80.5%, respectively. The sensitivity and specificity of injury type were 78.9% and 85.7%, respectively. The sensitivity and specificity of injury degree were 84.2% and 81.0%, respectively.

Comparison of prognosis between the two groups

All patients received a follow-up by telephone or as an outpatient within one year after discharge. In the EPTE

group, 15 patients had intermittent epilepsy seizures, with no obvious remission. In 12 patients, the seizure frequency was decreased or the symptoms were obviously relieved. In 13 patients, there were no epileptic seizures for more than one year. All the patients received regular therapy with antiepileptic drugs (sodium phenytoin, phenobarbital, carbamazepine, ethosuximide, etc.). In the non-EPTE group, there were no epilepsy seizures in any of the patients after discharge, and no antiepileptic drugs were used. The comparison of prognoses between two groups is shown in Table 4. The GOS and ADL prognoses showed a significance difference between the EPTE group and non-EPTE group ($p < 0.05$).

Table 2. Data assignment of variable for logistic regression analysis.

Variable	Data assignment
Age in years	0, < 20; 1, 20–39; 2, 40–60; 3 > 60
Epilepsy history	0, no; 1, yes
Injury site	0, other parts; 1, temporal/ parietal
Injury type	0, closed; 1, open
Injury degree	0, mild/ moderate; 1, severe

DISCUSSION

The occurrence of EPTE is closely related to the location of the traumatic brain injury. Epilepsy is most likely to occur when the parietal lobes are damaged, as they are near the center anterior/posterior gyrus of the brain cortex[13].

Table 3. Results of logistic regression analysis.

Variable	B	SE	Wald	Sig.	EXP(B)	95%CI for EXP(B)	
						Lower	Upper
Age	0.243	0.106	4.896	0.056	1.283	0.901	1.602
Epilepsy history	-1.567	0.396	18.794	0.067	0.209	0.096	1.409
Injury site	0.698	0.139	27.785	0.000	1.997	1.473	2.679
Injury type	0.717	0.146	29.673	0.000	2.096	1.543	2.842
Injury degree	0.935	0.159	31.577	0.005	2.376	1.846	3.609
Constant	-1.473	0.173	33.105	0.003	0.007		

B: coefficient of regressio; SE.: standard error; Sig: P value; EXP (B): odds ratio.

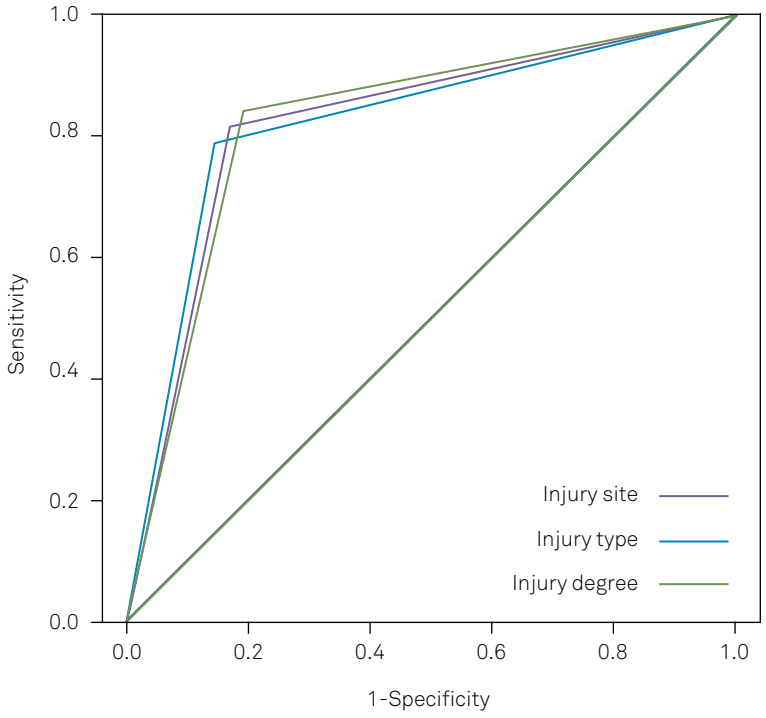

Figure. Receiver operating characteristic curves of injury type and injury degree for predicting the early post-traumatic epilepsy.

Table 4. Comparison of prognosis between the two groups.

Variable	Total	EPTE	Non-EPTE	χ^2	p-value
Glasgow outcome scale					
Good	165	30	135	9.563	0.002
Poor	21	10	11		
Activities of daily living scale					
Good	156	28	128	7.248	0.007
Poor	30	12	18		

EPTE: post-traumatic epilepsy.

Compared with other areas, the electrical activity in the parietal lobes is more frequent, and the seizure threshold is lower. Damage to the temporal lobe of the brain will result in disruption of synaptic function in the hippocampus, leading to the seizures[14,15]. In this study, the single factor analysis and logistic regression analysis showed that there was a significant difference of the craniocerebral injury site between the non-EPTE group and EPTE group ($p < 0.05$). This indicates that the temporal/parietal lobe injury is more likely to cause traumatic epilepsy compared with other areas.

In an open craniocerebral injury, EPTE is likely to be related to a dural tear, heavy pollution, intracranial hemorrhage, and infection[16]. In the early stage of infection, the increased vascular permeability of the cerebral cortex leads to aggregation of excitatory or inhibitory amino acids and levels of riboflavin, which affects the ionic stability of neuronal membranes and induces the seizures[17]. In addition, the cerebral parenchyma damage can cause intracerebral hemorrhage and cerebral edema. An intracranial hematoma pressing on the cerebral parenchyma can also cause brain edema. A depressed fracture can puncture the dura, which damages its integrity, leading to subdural hematoma and cerebral parenchyma injury[18]. These constitute one possible pathological basis for EPTE. In this study, the single factor analysis and logistic regression analysis showed that there was a significant difference in craniocerebral injury type between the non-EPTE group and EPTE group ($p < 0.05$). This indicates that open craniocerebral injury is more likely to cause traumatic epilepsy compared with closed craniocerebral injury.

Severe craniocerebral injury can lead to cerebral contusion, laceration and cerebral parenchyma hemorrhage, leading to increased intracranial pressure, cerebral ischemia and hypoxia. The cerebral parenchyma injury can lead to the formation of lesions with local abnormal discharge. This causes abnormal discharge of a large number of cortical neurons, thus leading to the epilepsy seizure[18]. Temkin[19] found that the incidence of EPTE in severe craniocerebral injury was 19.5%, higher than that in patients with mild or moderate craniocerebral injury. In the present study, there were 17 patients with mild/moderate craniocerebral injury and 23 patients with severe injury in the non-EPTE group, with 123 patients with mild/moderate craniocerebral injury and 23 patients with severe injury in the EPTE group. Single factor analysis showed that there was a significant difference of injury degree between the two groups ($p < 0.05$). Logistic regression analysis showed that the injury degree was one of the main risk factors for epilepsy after craniocerebral injury. This is consistent with the conclusion in Temkin's study.

Epileptic seizure obviously affects the rehabilitation of neurological function after craniocerebral injury. Early post-traumatic epilepsy can cause increased oxygen consumption in brain tissue, excessive release of excitatory neurotransmitters and elevated intracranial pressure[20]. On the basis of the primary injury, the pathological changes and biochemical changes of the brain tissue are further aggravated, thus affecting the prognosis of traumatic brain injury[21]. In the present study, the GOS and ADL prognosis showed a significant difference between the EPTE group and the non-EPTE group, respectively ($p < 0.05$). The reason may be that the recurrent epilepsy seizures and long-term use of antiepileptic drugs decrease the ability and possibility for patients to participate in work and learning. In clinical practice, prophylactic antiepileptic drugs should be administered according to the high-risk factors of EPTE. Attention should be paid to the route and dosage of prophylactic antiepileptic drugs, to avoid side effects. This can effectively improve the prognosis of the patients[22,23].

In conclusion, the injury site, injury type and injury degree are the main risk factors for EPTE. Early post-traumatic epilepsy can affect the prognosis of patients with traumatic brain injury. Therefore, in the course of clinical diagnosis and treatment, for patients with open and severe brain injuries occurring in the temporal or parietal lobes, prophylactic antiepileptic drug treatment should be administered in the early stage. This is beneficial for preventing the occurrence of EPTE, and has positive significance in improving the prognosis of patients. This study has some limitations. Firstly, the sample size was relatively small. A larger sample size would make the results more convincing. In future studies, the sample size should be further increased to obtain more satisfactory outcomes. Secondly, there may be other factors affecting EPTE, which still need to be further investigated.

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