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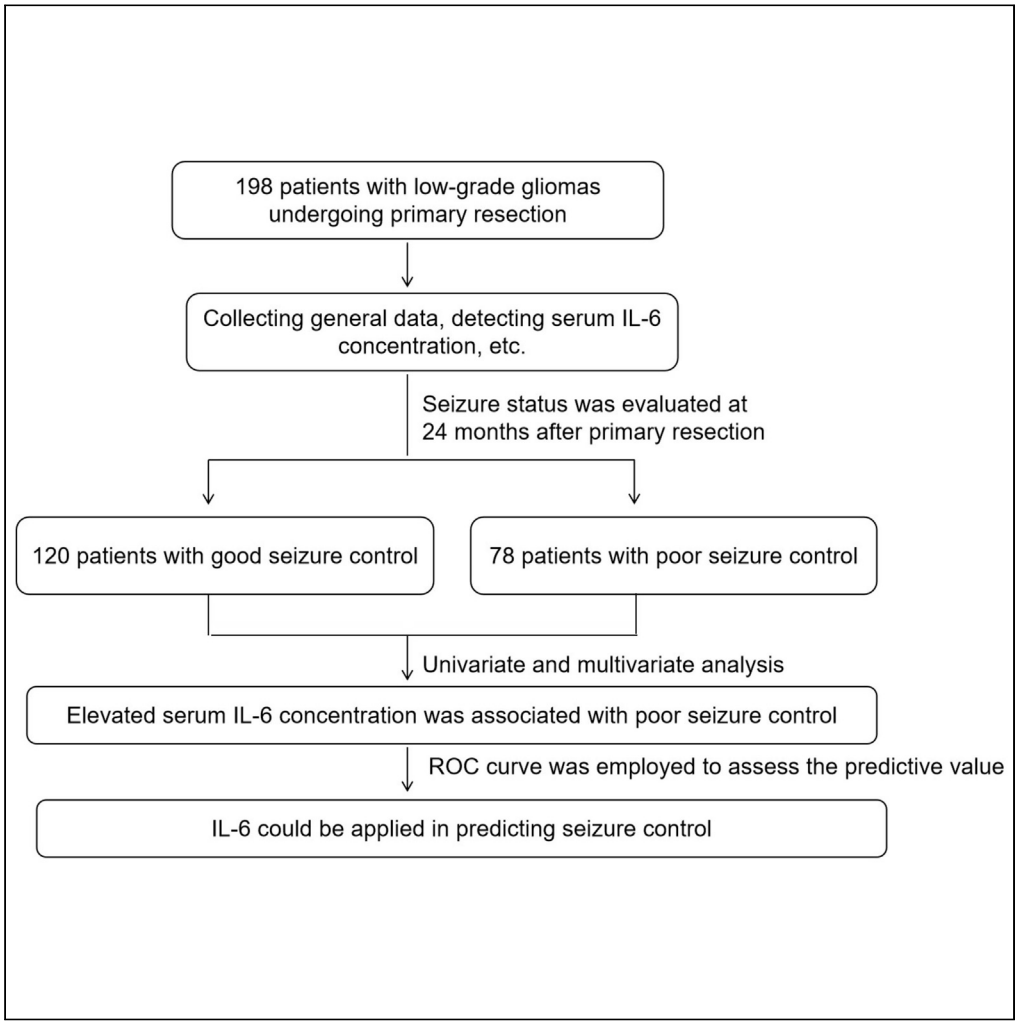

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Highlights

IL-6 was associated with poor seizure control in LLG patients

IL-6 could be applied in predicting seizure control in LLG patients

The predictive value could be elevated through adding other serum indices to IL-6

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IL-6 is associated with poor seizure control in low-grade glioma patients undergoing primary resection

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SUMMARY

In this study, 198 patients with low-grade gliomas (LGGs) undergoing primary resection were evaluated for seizure status at 24 months after primary resection with the Engel classification of seizures, and 120 patients had good seizure control (class I) while 78 patients had poor seizure control (class II–IV). Multivariate analysis showed that cortex involvement, subtotal resection, serum IL-6 concentration, and neutrophil to lymphocyte ratio (NLR) were associated with poor seizure control. The area under curve (AUC) of serum IL-6 concentration, NLR and their combination applied in predicting poor seizure control was 0.756, 0.714, and 0.857, respectively. The AUC of combination prediction was significantly higher than those of individual prediction. Therefore, elevated serum IL-6 concentration was associated with poor seizure control in LLG patients undergoing primary resection and could be applied in predicting seizure control, and the predictive value could be elevated through adding other serum indices to IL-6.

INTRODUCTION

Gliomas are the most frequent primary brain tumors, accounting for about 70% of primary brain tumors.[1,2] Seizure is a common symptom in patients with primary brain tumors, especially in patients with low-grade gliomas (LGGs). Symptomatic seizure occurs in most of patients with LGGs at disease onset.[3] The majority of patients can acquire good seizure control after primary resection, but some patients still have postoperative seizures despite similar tumor location, surgical treatment, and histology. Seizure is associated with postoperative life quality of patients with LGGs, and approximately 30% of patients with LGGs experience uncontrolled seizures, leading to increased psychological and economic burden on individuals and their families.[4] Therefore, it is useful to identify the predictors of seizure control after primary resection in patients with LGGs in order to improve their prognosis.

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that mediates the inflammatory microenvironment of tumors.[5] The expression of IL-6 is markedly upregulated in glioma and correlated with the grade and prognosis of glioma.[6] *In vitro* studies demonstrate that IL-6 can promote proliferation, invasion, and migration of glioma cells.[6,7] Meanwhile, IL-6 plays an important role in the development of seizures.[8,9] Elevation of IL-6 levels has been proven in multiple different epilepsy media and etiologies.[10] However, the association of IL-6 with poor seizure control in LGG patients undergoing primary resection is still not investigated. In this study, LGG patients undergoing primary resection were evaluated by Engel classification at 12 months after surgery. Multivariate analysis was performed to identify the independent association of serum IL-6 concentration with poor seizure control. Finally, the value of serum IL-6 concentration applied in predicting poor seizure control was evaluated with receiver operating characteristics (ROC) curve.

RESULTS

General data

These patients included 91 oligoastrocytomas (46.0%), 71 astrocytomas (35.9%), and 36 oligodendrogliomas (18.2%). Among these patients, 120 patients (60.6%) had good seizure control (class I), and 78 patients (39.4%) had poor seizure control (class II–IV). The serum IL-6 concentration was 8.62 $\pm$ 2.96 ng/L and 3.74 $\pm$ 1.83 ng/L, respectively, for LGG patients and healthy controls, and the serum IL-6 concentration of LGG patients was significantly higher than that of healthy controls ($t = 12.768$, $p < 0.001$).

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Table 1. Univariate analysis between Class I group (good seizure control) and Class II–IV group (poor seizure control)

	Class II–IV group (n = 78)	Class I group (n = 120)	$\chi^2/Z/t$	p
Male (n, %)	49 (62.82%)	70 (58.33%)	0.664	0.415
Age (years, mean ± *SD*)	36.92 ± 10.54	39.74 ± 12.08	−2.198	0.032
Tumor location (n, %)				
Left-sided	42 (53.85%)	50 (41.67%)	4.453	0.035
Frontal	56 (71.79%)	84 (70.00%)	0.157	0.692
Temporal	32 (41.02%)	45 (37.50%)	0.407	0.523
Parietal	7 (8.97%)	8 (6.67%)	0.402	0.526
Insula	15 (19.23%)	28 (23.33%)	0.61	0.435
MRI characteristics (n, %)				
Mean size [cm, *M*, (*IQR*)]	4.8 (2.9)	4.6 (2.8)	0.748	0.425
Edema	13 (16.67%)	18 (15.00%)	0.234	0.629
Enhancement	30 (38.46%)	41 (34.17%)	0.413	0.52
Cystic change	16 (20.51%)	15 (12.50%)	3.721	0.054
Mass effect	14 (17.95%)	20 (16.67%)	0.119	0.73
Calcification	11 (14.10%)	20 (16.67%)	0.684	0.408
Cortex involvement (n, %)	29 (37.18%)	32 (26.67%)	3.990	0.043
Extent of resection (n, %)				
Gross-total	20 (25.64%)	52 (43.33%)	10.136	0.001
Subtotal	58 (74.36%)	68 (56.67%)		
KPS score ≥80 (n, %)	69 (88.46%)	105 (87.50%)	0.152	0.696
Radiotherapy (n, %)	71 (91.02%)	107 (89.17%)	0.176	0.675
Chemotherapy (n, %)	13 (16.67%)	14 (11.67%)	1.358	0.244
ECoG (n, %)	17 (21.79%)	29 (24.17%)	0.147	0.701
CDES (n, %)	10 (12.82%)	17 (14.17%)	0.134	0.714
Tumor pathology (n, %)				
Oligodendroglioma	15 (19.23%)	21 (17.50%)	1.187	0.552
Oligoastrocytoma	38 (48.72%)	53 (44.17%)		
Astrocytoma	25 (32.05%)	46 (38.33%)		
IL-6 (ng/L, mean ± SD)	10.73 ± 3.24	7.25 ± 2.78	9.891	<0.001
NLR(mean ± SD)	3.62 ± 1.47	2.38 ± 1.19	6.239	<0.001
PLR(mean ± SD)	135.53 ± 52.64	123.48 ± 46.25	1.650	0.117
MLR(mean ± SD)	0.25 ± 0.13	0.23 ± 0.12	1.090	0.293

ECoG: electrocorticogram, CDES: cortical direct electrical stimulation, IL-6: interleukin-6, MRI: magnetic resonance imaging, *SD*: standard deviation, *M*: median, *IQR*: interquartile range, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MLR: monocyte to lymphocyte ratio.

Univariate analysis

The results of univariate analysis (Table 1) demonstrated that age, left-sided tumor location, cortex involvement, extent of resection, serum IL-6 concentration, and neutrophil to lymphocyte ratio (NLR) were associated with seizure control (all $p < 0.05$). The rest variables were not associated with seizure control (all $p > 0.05$), but cystic change had a p value of <0.10.

Multivariate analysis

The following variables were included in a backward stepwise *logistic* regression model to perform multivariate analysis, including age, left-sided tumor location, cortex involvement, extent of resection, serum IL-6 concentration, NLR, and cystic change. The results (Table 2) showed that cortex involvement, subtotal resection, serum IL-6 levels, and NLR were significantly associated with poor seizure control after adjusting for age, left-sided tumor location, and cystic change.

Table 2. Multivariate analysis results for the variables significantly associated with poor seizure control

	β	*SE*	Wald χ^2	*OR*	95% *CI*	*p*
Subtotal resection	1.187	0.471	6.514	1.568	1.213–3.412	0.006
Age	−0.892	0.306	1.854	0.802	0.518–1.194	0.215
Left-sided tumor location	0.549	0.218	1.695	1.204	0.852–1.746	0.223
IL-6	1.125	0.462	6.017	1.193	1.074–2.569	0.011
Cortex involvement	1.096	0.447	5.813	1.289	1.102–2.785	0.014
NLR	1.075	0.394	5.278	1.176	1.084–2.517	0.021
Cystic change	0.478	0.209	1.291	1.396	0.627–2.714	0.258

Predictive value

The AUCs of serum IL-6 concentration and NLR applied in predicting poor seizure control was 0.756 [standard error (*SE*): 0.028, $p < 0.001$, 95% confidence interval (*CI*): 0.702–0.810] and 0.714 (*SE*: 0.029, $p < 0.001$, 95% *CI*: 0.683–0.802), as demonstrated in Figure 1. The optimal cutoff value of serum IL-6 concentration was 8.47 ng/L, and the sensitivity, specificity, accuracy, false positive rate, false negative rate, positive predictive value, and negative predictive value were 75.4%, 68.1%, 71.0%, 31.9%, 24.6%, 60.9%, and 80.7%, respectively. These results indicated a modest predictive value of serum IL-6 concentration for the prediction of poor seizure control among patients with LGGs undergoing primary resection. In order to elevate the predictive value, the combination of serum IL-6 concentration and NLR was applied in predicting poor seizure control, and the area under curve (AUC) was 0.857 (*SE*: 0.024, $p < 0.001$, 95% *CI*: 0.739–0.926) as demonstrated in Figure 1. The AUC of combination prediction was significantly higher than those of serum IL-6 concentration and NLR alone (0.857 vs. 0.756, $Z = 2.739$, $p < 0.05$; 0.857 vs. 0.714, $Z = 3.799$, $p < 0.05$).

DISCUSSION

IL-6 is promptly produced responding to tissue injuries and infections, contributing to host defense via stimulating immune reactions, hematopoiesis, and acute phase responses. It can modulate proliferation, growth, apoptosis, differentiation and invasion of various tumor cells including glioma cells.[6,7,11] Moreover, it is also associated with neuroprotective effects, neurogenesis, and gliogenesis.[12,13] In glioma, the expression of IL-6 is markedly upregulated and correlated with its grade and prognosis.[14,15] Furthermore, IL-6 in the peripheral blood and CSF of glioma patients also increases significantly and demonstrate a positive correlation with glioma grade. This suggests that IL-6 can be released into the CSF and blood through the disrupted blood brain barrier (BBB), thereby affecting the whole body and tumor microenvironment.[6] Therefore, serum IL-6 was selected as a target for seizure control in LGG patients undergoing primary resection.

IL-6 expression and release are mediated by a plenty of factors in tumor cells, mainly including the feedback of Notch, S1PR1, STAT3, and NF-κB phosphorylation.[16,17] Stimulation of IL-6 can activate Ras/mitogen-activated protein kinase (MAPK), Janus kinase 2 (JAK2)/signal transducer, and activator of transcription (STAT3) and phosphoinositide (PI)-3 kinase signaling pathways.[18] For glioma, Cao et al. demonstrated that IL-6 could induce the expression of SDCBP through JAK2/STAT3 signaling pathway, thus promoting the proliferation and invasion of glioma cells.[7] Weissenberger et al. showed that abrogation of IL-6 expression inhibited the formation of astrocytic tumor through a mouse model.[19]

Studies have demonstrated that the elevated IL-6 level not only increases gliosis but also decreases hippocampal neurogenesis and creates conditions that facilities epileptogenesis.[20,21] IL-6 may lead to increased permeability of BBB, which is correlated with occurrence and development of epilepsy.[8,9] Ho et al. demonstrated that peripheral inflammation induced by lipopolysaccharide could increase the susceptibility for seizure via elevating the expression of IL-6 in the hippocampus.[22] Pineda et al. showed that polyinosinic-polycytidylic acid might upregulate the expression of IL-6 in the offspring hippocampus by causing maternal immune activation in experimental pregnancy, finally leading to hippocampal hyper excitability and faster progression of epileptogenesis in the offspring.[23] Jia et al. showed that the elevated IL-6 level was associated with seizure recurrence in patients with the first post-ischemic stroke seizure and might be able to be applied in the prediction of seizure recurrence.[24]

According to previous studies, age, seizure type, and extent of resection were independently correlated with seizure control in LLG patients undergoing primary resection.[4,25] Our study also demonstrated consistent results. In our study, multivariate analysis was performed to identify the independent association of IL-6 with seizure control with adjustment for these confounders, which demonstrated that elevated serum IL-6 concentration was associated with poor seizure control in LLG patients undergoing primary resection. Then, we evaluated the value of serum IL-6 concentration applied in predicting poor seizure control. The results showed that the predictive value was modest with a sensitivity of 75.4% and a specificity of 68.1%. In order to elevate the predictive value, the combination of serum IL-6 concentration and NLR was applied, and the AUC was 0.857, significantly higher than those of serum IL-6 concentration and NLR alone.

In conclusion, elevated serum IL-6 concentration was associated with poor seizure control in LLG patients undergoing primary resection and could be applied in predicting seizure control with a sensitivity of 75.4% and a specificity of 68.1%, and the predictive value could be elevated through adding other serum indices to IL-6.

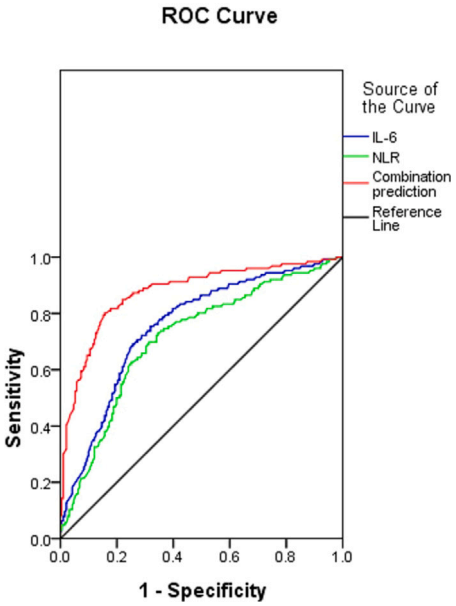

Figure 1. ROC curve of serum IL-6 concentration applied in predicting poor seizure control in LLG patients undergoing primary resection

Limitations of the study

The main limitation of this study was the narrow cytokine panel. In the next, we will expand the cytokine panel to validate these findings through further studies.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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ACKNOWLEDGMENTS

None.

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; agreed on the journal to which the article will be submitted; and agree to be accountable for all aspects of the work.

DECLARATION OF INTERESTS

All the authors do not have any conflict of interest.

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REFERENCES

1. Omuro, A., and Deangelis, L.M. (2013). Glioblastoma and other malignant gliomas: a clinical review. JAMA-J. Am. Med. Assoc. *310*, 1842–1850. https://doi.org/10.1001/jama.2013.280319.
2. Liu, D., Dai, X., Ye, L., Wang, H., Qian, H., Cheng, H., and Wang, X. (2023). Nanotechnology meets glioblastoma multiforme: Emerging therapeutic strategies. Wiley. Interdiscip. Rev. Nanomed. Nanobiotechnol. *15*, e1838. https://doi.org/10.1002/wnan.1838.
3. Lee, J.W., Wen, P.Y., Hurwitz, S., Black, P., Kesari, S., Drappatz, J., Golby, A.J., Wells, W.M., 3rd, Warfield, S.K., Kikinis, R., and Bromfield, E.B. (2010). Morphological characteristics of brain tumors causing seizures. Arch. Neurol. *67*, 336–342. https://doi.org/10.1001/archneurol.2010.2.
4. Shan, X., Fan, X., Liu, X., Zhao, Z., Wang, Y., and Jiang, T. (2018). Clinical characteristics associated with postoperative seizure control in adult low-grade gliomas: a systematic review and meta-analysis. Neuro Oncol. *20*, 324–331. https://doi.org/10.1093/neuonc/nox130.
5. Hong, D.S., Angelo, L.S., and Kurzrock, R. (2007). Interleukin-6 and its receptor in cancer: implications for translational therapeutics. Cancer *110*, 1911–1928. https://doi.org/10.1002/cncr.22999.
6. Shan, Y., He, X., Song, W., Han, D., Niu, J., and Wang, J. (2015). Role of il-6 in the invasiveness and prognosis of glioma. Int. J. Clin. Exp. Med. *8*, 9114–9120.
7. Cao, F., Zhang, Q., Chen, W., Han, C., He, Y., Ran, Q., and Yao, S. (2017). Il-6 increases sdcbp expression, cell proliferation, and cell invasion by activating jak2/stat3 in human glioma cells. Am. J. Transl. Res. *9*, 4617–4626.
8. Alapirtti, T., Lehtimäki, K., Nieminen, R., Mäkinen, R., Raitanen, J., Moilanen, E., Mäkinen, J., and Peltola, J. (2018). The production of il-6 in acute epileptic seizure: a video-eeg study. J. Neuroimmunol. *316*, 50–55. https://doi.org/10.1016/j.jneuroim.2017.12.008.
9. Taalab, Y.M., Mohammed, W.F., Helmy, M.A., Othman, A., Darwish, M., Hassan, I., and Abbas, M. (2019). Cannabis influences the putative cytokines-related pathway of epilepsy among egyptian epileptic patients. Brain Sci. *9*, 332. https://doi.org/10.3390/brainsci9120332.
10. de Vries, E.E., van den Munckhof, B., Braun, K.P.J., van Royen-Kerkhof, A., de Jager, W., and Jansen, F.E. (2016). Inflammatory mediators in human epilepsy: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. *63*, 177–190. https://doi.org/10.1016/j.neubiorev.2016.02.007.
11. Sun, X., Qu, Q., Lao, Y., Zhang, M., Yin, X., Zhu, H., Wang, Y., Yang, J., Yi, J., and Hao, M. (2019). Tumor suppressor hic1 is synergistically compromised by cancer-associated fibroblasts and tumor cells through the il-6/pstat3 axis in breast cancer. BMC Cancer *19*, 1180. https://doi.org/10.1186/s12885-019-6333-6.
12. Kishimoto, T. (2010). Il-6: from its discovery to clinical applications. Int. Immunol. *22*, 347–352. https://doi.org/10.1093/intimm/dxq030.
13. Islam, O., Gong, X., Rose-John, S., and Heese, K. (2009). Interleukin-6 and neural stem cells: more than gliogenesis. Mol. Biol. Cell *20*, 188–199. https://doi.org/10.1091/mbc.e08-05-0463.
14. Li, R., Li, G., Deng, L., Liu, Q., Dai, J., Shen, J., and Zhang, J. (2010). Il-6 augments the invasiveness of u87mg human glioblastoma multiforme cells via up-regulation of mmp-2 and fascin-1. Oncol. Rep. *23*, 1553–1559. https://doi.org/10.3892/or_00000795.
15. Michaud-Levesque, J., Bousquet-Gagnon, N., and Béliveau, R. (2012). Quercetin abrogates il-6/stat3 signaling and inhibits glioblastoma cell line growth and migration. Exp. Cell Res. *318*, 925–935. https://doi.org/10.1016/j.yexcr.2012.02.017.
16. Schafer, Z.T., and Brugge, J.S. (2007). Il-6 involvement in epithelial cancers. J. Clin. Invest. *117*, 3660–3663. https://doi.org/10.1172/JCI34237.
17. Grivennikov, S., Karin, E., Terzic, J., Mucida, D., Yu, G.Y., Vallabhapurapu, S., Scheller, J., Rose-John, S., Cheroutre, H., Eckmann, L., and Karin, M. (2009). Il-6 and stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell *15*, 103–113. https://doi.org/10.1016/j.ccr.2009.01.001.
18. Hirano, T., Nakajima, K., and Hibi, M. (1997). Signaling mechanisms through gp130: a model of the cytokine system. Cytokine Growth Factor Rev. *8*, 241–252. https://doi.org/10.1016/s1359-6101(98)80005-1.
19. Weissenberger, J., Loeffler, S., Kappeler, A., Kopf, M., Lukes, A., Afanasieva, T.A., Aguzzi, A., and Weis, J. (2004). Il-6 is required for glioma development in a mouse model. Oncogene *23*, 3308–3316. https://doi.org/10.1038/sj.onc.1207455.
20. Erta, M., Quintana, A., and Hidalgo, J. (2012). Interleukin-6, a major cytokine in the central nervous system. Int. J. Biol. Sci. *8*, 1254–1266. https://doi.org/10.7150/ijbs.4679.
21. Levin, S.G., and Godukhin, O.V. (2017). Modulating effect of cytokines on mechanisms of synaptic plasticity in the brain. Biochemistry *82*, 264–274. https://doi.org/10.1134/S000629791703004X.
22. Ho, Y.H., Lin, Y.T., Wu, C.W.J., Chao, Y.M., Chang, A.Y.W., and Chan, J.Y.H. (2015). Peripheral inflammation increases seizure susceptibility via the induction of neuroinflammation and oxidative stress in the hippocampus. J. Biomed. Sci. *22*, 46. https://doi.org/10.1186/s12929-015-0157-8.
23. Pineda, E., Shin, D., You, S.J., Auvin, S., Sankar, R., and Mazarati, A. (2013). Maternal immune activation promotes hippocampal kindling epileptogenesis in mice. Ann. Neurol. *74*, 11–19. https://doi.org/10.1002/ana.23898.
24. Jia, Q., Jiang, F., Ma, D., Li, J., Wang, F., and Wang, Z. (2020). Association between il-6 and seizure recurrence in patients with the first post-ischemic stroke seizure. Neuropsychiatr. Dis. Treat. *16*, 1955–1963. https://doi.org/10.2147/NDT.S257870.
25. You, G., Huang, L., Yang, P., Zhang, W., Yan, W., Wang, Y., Bao, Z., Li, S., Li, S., Li, G., and Jiang, T. (2012). Clinical and molecular genetic factors affecting postoperative seizure control of 183 chinese adult patients with low-grade gliomas. Eur. J. Neurol. *19*, 298–306. https://doi.org/10.1111/j.1468-1331.2011.03509.x.
26. Louis, D.N., Perry, A., Wesseling, P., Brat, D.J., Cree, I.A., Figarella-Branger, D., Hawkins, C., Ng, H.K., Pfister, S.M., Reifenberger, G., et al. (2021). The 2021 who classification of tumors of the central nervous system: a summary. Neuro Oncol. *23*, 1231–1251. https://doi.org/10.1093/neuonc/noab106.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE Reagent	SOURCE	IDENTIFIER
Reagent		
Human IL-6 ELISA Kit	Elabscience Biotechnology Co., Ltd	Cat#E-HSEL-H0003
Software		
SPSS	SPSS Inc., USA	Version 22.0
Magnetic Resonance Imaging system	GE Medical Systems, USA	Signa HDxt 1.5T

RESOURCE AVAILABILITY

Lead contact

Information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Shabier Tuerxun (Drtuerxun@163.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- This study analyzed the data of 198 patients with LGGs undergoing primary resection and 46 healthy controls.
- The datasets supporting the current study have not been deposited in a public repository privacy reasons but are available from the lead contact on request.
- Any additional information required to reanalyse the data reported in this paper is available from the lead contact on request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Consecutive patients with LGGs undergoing primary resection were retrospectively enrolled in The First Affiliated Hospital of Xinjiang Medical University between July 2017 and December 2020. The criteria for inclusion of LLG patients included ①LLG definitively diagnosed and graded by two neuropathologists based on the 2021 WHO Classification[26]; ②patients without preoperative seizure status; and ③patients receiving no treatment of antiepileptic drugs. Pathological diagnosis was reviewed and confirmed by the third neuropathologist. Re-review should be performed in patients with discrepancies by the three neuropathologists until an agreement was reached. Clinical and MRI characteristics were collected, serum IL-6 concentrations were detected, and seizure control at 24 months after surgery was followed up. Additionally, the blood samples of 46 healthy controls were collected to compare IL-6 levels between healthy controls and LLG patients. A total of 198 Asian patients with LGGs undergoing primary resection during the aforementioned period were enrolled, including 119 males and 79 females. Their mean age was 38.63 $\pm$ 11.47 years. All 46 healthy controls were Asian with a mean age of 38.72 $\pm$ 12.05 years, including 27 males and 19 females.

This study was permitted by the ethics committee of The First Affiliated Hospital of Xinjiang Medical University (No. 2017026135), and informed consent was provided by all patients.

METHOD DETAILS

MRI characteristics

The collected MRI characteristics included the size and location of the glioma, edema, presence or absence of enhancement, mass effect, calcification and cystic change. The size was defined as mean largest diameter in three directions according to FLAIR or T2 and the location as the lobe in which the glioma resided. All MRI characteristics were independently evaluated by two neuroradiologists. Re-evaluation should be performed in patients with discrepancies by the two neuroradiologists until a consensus was reached.

Surgical procedures

Surgery was performed aiming for gross total removal of the glioma while protecting functional brain tissue as far as possible. Subtotal resection was carried out mainly in the case of tumor involvement in verbal brain areas. Extended lesionectomy was conducted only when the glioma was small enough in the "nonverbal" temporal or frontal lobe.

Evaluation of seizure

Seizure status was evaluated at 24 months after primary resection by the Engel Classification of Seizures which consisted of four classes. Class I was defined as free of disabling seizures, including ①completely free of seizure; ②nondisabling, simple partial seizures only; ③some disabling seizures, but free of disabling seizures for 2 years at least; and ④generalized convulsion using antiepileptic drug (AED) withdrawal only. Class II was defined as rare disabling seizures, including ①initially free of disabling seizures, but rare seizures now; ②rare disabling seizures since primary resection; ③more than rare disabling seizures, but rare seizures for 2 years at least; and ④nocturnal seizures only. Class III was defined as worthwhile improvement, including ①worthwhile seizure reduction; and ②prolonged seizure-free intervals amounting to more than half the follow-up period, but not less than 2 years. Class IV was defined as no worthwhile improvement, including ①no significant seizure reduction; ②no appreciable change; and ③seizures worse. For seizure prognosis analysis after primary resection, all patients with LLGs were divided into Class I (good seizure control) versus Class II–IV (poor seizure control).

Detection of serum IL-6 concentration

The blood samples were collected within 1 d of admission after an overnight fasting. Centrifugation was performed at 3000 g for 10 min to obtain the serums. The serums were then stored at -80°C for detection. The concentration of IL-6 in serum was detected using enzyme-linked immunosorbent assay (ELISA) method. The Human IL-6 ELISA Kit was provided by Elabscience Biotechnology Co., Ltd (Wuhan, China).

QUANTIFICATION AND STATISTICAL ANALYSIS

All statistical analysis was conducted with the SPSS version 22.0 (SPSS Inc., USA). The distribution of quantitative data was assessed using Kolmogorov-Smirnov test. The intergroup differences were compared with the Student's *t* test and Mann-Whitney U test, respectively for data with and without normal distribution. The intergroup differences of qualitative data were compared with Chi-square test. Multivariate analysis was performed for variables with two sided $P<0.10$ in univariate analysis through a backward stepwise *logistic* regression model. ROC curve was employed to assess the predictive value for poor seizure control in patients with LGGs undergoing primary resection, and the area under curve (AUC) was compared using *Z* test. Significance was set at two sided $P<0.05$.