Preoperative Serum Lactate Dehydrogenase Level Predicts Progression and Prognosis in Patients with Glioma

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Abstract

Background: To evaluate the value of serum Lactate Dehydrogenase (LDH) level in predicting recurrence and the overall survival (OS) of glioma patients.

Methods: A total number of 216 patients with glioma in our institution were retrospectively recruited to analyze the relationship between preoperative serum LDH level and prognosis.

Results: Overall, the average age of patients was 43.58 ± 17.22 years old; 53.7% (116 of 216) of the enrolled patients were male. Multivariate analysis revealed that serum LDH level (odds ratio [OR]=0.97, 95% confidence interval [CI]=0.96-0.98, $P < 0.001$) and World Health Organization (WHO) grade (grade II: OR=19.64, 95%CI=5.56-69.35, $P < 0.001$; grade III: OR=19.50, 95%CI=7.08-53.73, $P < 0.001$; grade IV: OR=15.23, 95%CI=4.94-46.97, $P < 0.001$) were significant and independent of 1-year Progression-free survival (PFS) after adjusting for confounders. The predictive performance of serum LDH level was represented with area under curve (AUC) = 0.741, 95%CI=0.677-0.798. Multivariate Cox analysis revealed that LDH level (hazard ratio [HR]=2.56, 95%CI=1.59-4.15, $P < 0.001$) and WHO grade (grade II: HR=4.58, 95%CI=0.56-37.23, $P = 0.155$; grade III: HR=16.35, 95%CI=2.16-123.80, $P = 0.007$; grade IV: HR=42.13, 95%CI=5.83-304.47, $P < 0.001$) remained associated with survival at 2-year follow-up. At 3-year follow-up, lymphocyte count (HR=0.68, 95%CI=0.51-0.91, $P = 0.008$), LDH level (HR=2.21, 95%CI=1.40-3.49, $P = 0.001$), and WHO grade (grade II: HR=1.44, 95%CI=0.44-4.68, $P = 0.543$; grade III: HR=4.99, 95%CI=1.68-14.87, $P = 0.004$; grade IV: HR=16.96, 95%CI=6.13-46.93, $P < 0.001$) remained associated with survival in multivariate Cox analysis.

Conclusion: Our study demonstrated that preoperative serum LDH level could serve as a reliable indicator for predicting prognosis of glioma patients. Further multicenter studies are still required to verify our findings.

Introduction

Glioma is a common type of intracranial malignant tumor, accounting for 15.1% of central nervous system tumor. There are approximately 30 thousand people die from glioma worldwide every year¹. The clinical behaviors of glioma are highly variable and complex, including hemiplegia, epilepsy, and vomiting. The maximum safe surgical resection combining with radiation therapy and chemotherapy is the current standard therapy which improved the prognosis of those patients. Nonetheless, survival duration remains short, and the median survival time of glioblastoma patients is only 15 months²⁻⁴. High-grade glioma is characterized by high mortality rates and rapid progression. Moreover, it is difficult to ensure the quality of life in patients with glioma due to high rate of operative complications. Predicting prognosis in patients with glioma is both a difficult and important task for clinicians.

Glioma cells are in a microenvironment which is characterized by chronic inflammation and mediates tumor progression. The progression and development of glioma are closely related to the inflammatory state and immune reaction of the body. Therefore, the inflammatory biomarkers which reflect host

inflammation status may also indicate the prognosis of glioma. In recent studies, inflammatory markers in peripheral blood including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte–monocyte ratio (LMR) have been confirmed closely related to the prognosis of patients with glioma^{5–10}. Lactate Dehydrogenase (LDH) is serum inflammatory marker which has been applied to the prediction of pneumonia^{11–13}. However, it remains unknown whether LDH could be used as a prognostic predictor in patients with glioma.

Virtually almost all patients with glioma will undergo routine blood tests including serum LDH level before surgery. Those tests could evaluate the clinical state of patients and may serve as surrogate biomarkers for some specific changes caused by pathological characteristics of the tumor. Due to their standardization, readily availability, and cheapness, it is extremely attractive that the routine blood tests could function as proxy biomarkers for glioma and prognosticators for patients. In our study, we aimed to evaluate the value of serum LDH level in predicting recurrence and the overall survival (OS) of glioma patients.

Results

Patient Characteristics

The demographics and baseline characteristics of the 216 patients were presented in Table 1. In this study, all patients were divided into a recurrence group ($n = 77$, 35.60%) and a non-recurrence group ($n = 139$, 64.40%). Overall, the average age of patients was 43.58 ± 17.22 years old; 53.7% (116 of 216) of the enrolled patients were male and 46.30% of them were female. Age, leukocyte count, neutrophil count, lymphocyte count, NLR, LMR, serum sodium level, serum potassium level, serum LDH level, World Health Organization (WHO) grade were significantly different between the two groups. The difference of Karnofsky Performance Status (KPS) for the two groups was not significant, $P = 0.057$.

Table 1
Comparison of Demographic and Clinical Variables in Patients with PFS < 1 and PFS ≥ 1

Parameter	Total	Recurrence group(n = 77)	Non-recurrence group(n = 139)	P value
Age	43.58 ± 17.22	47.88 ± 19.12	41.20 ± 15.65	0.006
KPS score	80(70–90)	80(70–90)	80(70–90)	0.057
Sex				0.299
Male	116(53.7%)	45(58.4%)	71(51.1%)	
Female	100(46.3%)	32(41.6%)	68(48.9%)	
Hypertension				0.587
No	194(89.8%)	68(88.3%)	126(90.6%)	
Yes	22(10.2%)	9(11.7%)	13(9.4%)	
Diabetes mellitus				0.693
No	209(96.8%)	74(96.1%)	135(97.1%)	
Yes	7(3.2%)	3(3.9%)	4(2.9%)	
WBC count 10 ⁹ /L	7.51 ± 2.96	8.35 ± 3.42	7.06 ± 2.57	0.005
RBC count 10 ¹² /L	4.65 ± 0.48	4.64 ± 0.46	4.65 ± 0.50	0.896
NEU count 10 ⁹ /L	5.02 ± 2.92	6.06 ± 3.53	4.45 ± 2.34	0.001
MON count 10 ⁹ /L	0.41 ± 0.19	0.43 ± 0.18	0.40 ± 0.19	0.366
LYM count 10 ⁹ /L	1.81 ± 0.70	1.62 ± 0.74	1.91 ± 0.65	0.003
PLT count 10 ⁹ /L	234.29 ± 62.70	239.35 ± 63.25	231.49 ± 62.45	0.379
NLR	3.94 ± 5.92	5.34 ± 6.01	3.16 ± 5.75	0.011
PLR	159.98 ± 145.63	180.97 ± 105.08	148.35 ± 163.02	0.115
LMR	4.98 ± 2.29	4.22 ± 2.03	5.40 ± 2.33	< 0.001

Values are reported as number, number(%), mean ± standard deviation, and median (25%–75%).

PFS, progression-free survival; KPS, karnofsky performance status; WBC, white blood cell; RBC, red blood cell; NEU, neutrophil; MON, monocyte; LYM, lymphocyte; PLT, platelet; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte–monocyte ratio; HGB, hemoglobin; LDH, Lactate dehydrogenase; CCRT, concurrent chemoradiotherapy; GTR, gross total resection; STR, subtotal resection; WHO, World Health Organization.

Parameter	Total	Recurrence group(n = 77)	Non-recurrence group(n = 139)	P value
HGB g/L	138.26 ± 16.42	139.43 ± 14.13	137.61 ± 17.58	0.437
Serum glucose mmol/L	5.25 ± 1.57	5.48 ± 1.99	5.13 ± 1.28	0.158
Serum sodium mmol/L	140.95 ± 2.94	140.28 ± 3.35	141.33 ± 2.62	0.011
Serum potassium mmol/L	4.18 ± 0.42	4.09 ± 0.43	4.23 ± 0.41	0.018
Serum calcium mmol/L	2.28 ± 0.15	2.29 ± 0.18	2.28 ± 0.12	0.462
Preoperative LDH U/L	181.07 ± 59.08	215.23 ± 81.40	162.15 ± 27.90	< 0.001
Postoperative LDH U/L	223.41 ± 90.66	255.24 ± 81.85	205.77 ± 90.99	0.005
ΔLDH U/L	43.28 ± 87.93	31.56 ± 81.85	49.77 ± 88.21	0.289
Tumor volume cm ³	39.76 ± 38.94	44.36 ± 39.86	37.22 ± 38.33	0.198
Peritumor edema cm	2.10 ± 1.23	2.27 ± 1.10	2.01 ± 1.30	0.149
CCRT				0.355
No	70(32.4%)	28(36.4%)	42(30.2%)	
Yes	146(67.6%)	49(63.6%)	97(69.8%)	
Surgical therapy				0.972
GTR	155(71.8%)	56(72.7%)	99(71.2%)	
STR	58(26.9%)	20(26.0%)	38(27.3%)	
biopsy	3(1.4%)	1(1.3%)	2(1.4%)	
WHO grade				< 0.001
I	32(14.8%)	3(3.9%)	29(20.9%)	
Values are reported as number, number(%), mean ± standard deviation, and median (25%–75%).				
PFS, progression-free survival; KPS, karnofsky performance status; WBC, white blood cell; RBC, red blood cell; NEU, neutrophil; MON, monocyte; LYM, lymphocyte; PLT, platelet; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte–monocyte ratio; HGB, hemoglobin; LDH, Lactate dehydrogenase; CCRT, concurrent chemoradiotherapy; GTR, gross total resection; STR, subtotal resection; WHO, World Health Organization.				

Parameter	Total	Recurrence group(n = 77)	Non-recurrence group(n = 139)	<i>P</i> value
II	53(24.5%)	5(6.5%)	48(34.5%)	
III	34(15.7%)	4(5.2%)	30(21.6%)	
IV	97(44.9%)	65(84.4%)	32(23.0%)	
Values are reported as number, number(%), mean $\pm$ standard deviation, and median (25%–75%).				
PFS, progression-free survival; KPS, karnofsky performance status; WBC, white blood cell; RBC, red blood cell; NEU, neutrophil; MON, monocyte; LYM, lymphocyte; PLT, platelet; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte–monocyte ratio; HGB, hemoglobin; LDH, Lactate dehydrogenase; CCRT, concurrent chemoradiotherapy; GTR, gross total resection; STR, subtotal resection; WHO, World Health Organization.				

There were 115 patients underwent postoperative reexamination for the serum LDH level. The postoperative serum LDH level was significantly higher than preoperative serum LDH level, 223.41 ± 90.66 vs 181.07 ± 59.08 , $P < 0.001$. The postoperative serum LDH level in recurrence group was significantly higher than that in non-recurrence group, $P = 0.005$. There was no significant difference in Δ LDH between the two groups, $P = 0.289$.

Association between LDH and Tumor Recurrence within 1 Year after Surgery in Glioma Patients

Factors with significant univariate association ($P < 0.10$) for 1-year PFS were all shown in Table 2, including age, KPS score, white blood cell count, neutrophil count, lymphocyte count, NLR, LMR, serum sodium level, serum potassium level, serum LDH level, WHO grade. After multivariate analysis, only serum LDH level (odds ratio [OR] = 0.97, 95% confidence interval [CI] = 0.96–0.98, $P < 0.001$) and WHO grade (grade II: OR = 19.64, 95%CI = 5.56–69.35, $P < 0.001$; grade III: OR = 19.50, 95%CI = 7.08–53.73, $P < 0.001$; grade IV: OR = 15.23, 95%CI = 4.94–46.97, $P < 0.001$) were still significant and independent of 1-year PFS after adjusting for confounders.

Table 2
Univariate and Multivariate Analysis of 1-year PFS with Possible Predictive Factors

Parameter	Univariate analysis			Multivariate analysis		
	OR	95% CI	Pvalue	OR	95% CI	Pvalue
Age	0.98	0.96–0.99	0.007			
KPS score	1.03	1.00-1.06	0.067			
WBC count 10 ⁹ /L	0.86	0.78–0.95	0.004			
NEU count 10 ⁹ /L	0.82	0.74–0.91	< 0.001			
LYM count 10 ⁹ /L	1.90	1.23–2.95	0.004			
NLR	0.92	0.85–0.99	0.029			
LMR	1.31	1.12–1.53	< 0.001			
Serum sodium mmol/L	1.13	1.03–1.25	0.014			
Serum potassium mmol/L	2.30	1.14–4.63	0.020			
LDH U/L	0.97	0.96–0.98	< 0.001	0.97	0.96–0.98	< 0.001
WHO grade			< 0.001			< 0.001
I	1.00	Reference		1.00	Reference	
II	19.64	5.56–69.35	< 0.001	24.22	5.95–98.58	< 0.001
III	19.50	7.08–53.73	< 0.001	39.81	10.62-149.25	< 0.001
IV	15.23	4.94–46.97	< 0.001	28.82	6.22-133.61	< 0.001
PFS, progression-free survival; OR: odds ratio; CI: confidence interval; WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte–monocyte ratio; LDH, Lactate dehydrogenase; WHO, World Health Organization.						

Utilizing ROC analysis, the prognostic value of preoperative LDH level and WHO grade were presented in Fig. 1. The best cut-off value of preoperative LDH level for predicting 1-year PFS was 179 U/L. The predictive performance was represented with AUC = 0.741 (95%CI = 0.677–0.798), sensitivity = 74.8%, specificity = 63.6%, and *Youden* index = 0.385. Based on the best cut-off value of grade III, the predictive performance of WHO grade (AUC = 0.810, 95%CI = 0.751–0.860, sensitivity = 84.4%, specificity = 77.0%, and *Youden* index = 0.614) was also calculated by ROC analysis (Fig. 1). DeLong's test indicated that the AUC of preoperative LDH level was comparable with that of WHO grade ($Z = 1.363$, $P = 0.170$).

In the WHO grade I-II group, the best cut-off value of preoperative LDH level for predicting 1-year PFS was 183.50 U/L. The predictive performance was represented by AUC = 0.934 (95%CI = 0.866-1.000), sensitivity = 100.0%, specificity = 74.0%, and *Youden* index = 0.740 (Figure 2A). In the WHO grade III-IV

group (Figure 2B), the cut-off value was 177.50 U/L for preoperative LDH level (AUC = 0.733, 95%CI = 0.648–0.818, sensitivity = 60.9%, specificity = 80.6%, and *Youden* index = 0.415).

Univariate and Multivariate Survival Analysis in Patients with and without Elevated Preoperative LDH at 2-year Follow-up

Based on the normal threshold of LDH level, patients were divided into normal LDH group (<250U/L) and elevated LDH group (>250U/L). In the Kaplan-Meier curves analysis, the 2-year survival rate was statistically correlated with the LDH level ($P < 0.001$, Fig. 3). In normal LDH group and elevated LDH group, the 2-year survival rates were 61.3% (117/191) and 8.0% (2/25), respectively; the mean 2-year OS were 19.13 (95%CI = 18.10–20.16) and 10.44 (95%CI = 7.36–13.52), respectively. In the subgroup analysis based on WHO grade (low-grade group: grade I-II; high-grade group: grade III-IV), LDH level was still associated with 2-year survival rate. For patients in the low-grade group (Figure 4A), the 2-year survival rates in normal LDH group and elevated LDH group were 96.3% (77/80) and 0% (0/5), respectively ($P < 0.001$). For the other patients in the high-grade group (Figure 4B), the 2-year survival rates in normal LDH group and elevated LDH group were 36.0% (40/111) and 10.0% (2/20), respectively ($P = 0.001$).

In the univariate Cox hazard regression analysis (Table 3), age (hazard ratio [HR] = 1.03, 95%CI = 1.01–1.04, $P < 0.001$), white blood cell count (HR = 1.08, 95%CI = 1.03–1.14, $P = 0.002$), neutrophil count (HR = 1.12, 95%CI = 1.06–1.17, $P < 0.001$), lymphocyte count (HR = 0.57, 95%CI = 0.42–0.78, $P < 0.001$), NLR (HR = 1.02, 95%CI = 1.00–1.04, $P = 0.016$), LMR (HR = 0.84, 95%CI = 0.76–0.93, $P = 0.001$), serum glucose (HR = 1.16, 95%CI = 1.05–1.28, $P = 0.003$), serum sodium (HR = 0.93, 95%CI = 0.87–0.99, $P = 0.027$), serum potassium (HR = 0.65, 95%CI = 0.40–1.07, $P = 0.089$), LDH level (HR = 4.38, 95%CI = 2.73–7.04, $P < 0.001$), and WHO grade ($P < 0.001$) were all significantly associated with survival at 2-year follow-up. Furthermore, multivariate Cox analysis revealed that LDH level (HR = 2.56, 95%CI = 1.59–4.15, $P < 0.001$) and WHO grade (grade II: HR = 4.58, 95%CI = 0.56–37.23, $P = 0.155$; grade III: HR = 16.35, 95%CI = 2.16–123.80, $P = 0.007$; grade IV: HR = 42.13, 95%CI = 5.83–304.47, $P < 0.001$) remained associated with survival at 2-year follow-up (Table 3).

Table 3

Univariate and Multivariate Cox Hazard Regression Analysis of 2-year OS with Possible Predictive Factors

Parameter	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age	1.03	1.01–1.04	< 0.001			
WBC count 10 ⁹ /L	1.08	1.03–1.14	0.002			
NEU count 10 ⁹ /L	1.12	1.06–1.17	< 0.001			
LYM count 10 ⁹ /L	0.57	0.42–0.78	< 0.001			
NLR	1.02	1.00–1.04	0.016			
LMR	0.84	0.76–0.93	0.001			
Serum glucose mmol/L	1.16	1.05–1.28	0.003			
Serum sodium mmol/L	0.93	0.87–0.99	0.027			
Serum potassium mmol/L	0.65	0.40–1.07	0.089			
LDH level(normal or abnormally elevated)	4.38	2.73–7.04	< 0.001	2.56	1.59–4.15	< 0.001
WHO grade			< 0.001			< 0.001
I	1.00	Reference		1.00	Reference	
II	4.55	0.56–36.95	0.157	4.58	0.56–37.23	0.155
III	16.41	2.17–124.24	0.007	16.35	2.16–123.80	0.007
IV	48.01	6.66–346.13	< 0.001	42.13	5.83–304.47	< 0.001
OS: overall survival; HR: hazard ratio; CI: confidence interval; WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte–monocyte ratio; LDH, Lactate dehydrogenase; WHO, World Health Organization.						

Univariate and Multivariate Survival Analysis in Patients with and without Elevated Preoperative LDH at 3-year Follow-up

In the Kaplan-Meier curves analysis, the 3-year survival rate was statistically associated with the LDH level ($P < 0.001$, Fig. 5). In normal LDH group and elevated LDH group, the 3-year survival rates were 49.2% (94/191) and 0% (0/25), respectively; the mean 3-year OS were 25.45 (95%CI = 23.72–27.18) and 10.82 (95%CI = 7.38–14.26), respectively. In the subgroup analysis based on WHO grade, LDH level was still associated with 3-year survival rate. For patients in the low-grade group (Figure 6A), the 3-year survival rates in normal LDH group and elevated LDH group were 90.0% (72/80) and 0% (0/5), respectively ($P < 0.001$). For the other patients in the high-grade group (Figure 6B), the 3-year survival rates in normal LDH group and elevated LDH group were 19.8% (22/111) and 0% (0/20), respectively ($P = 0.001$).

In the univariate Cox hazard regression analysis (Table 4), age (HR = 1.03, 95%CI = 1.02–1.05, $P < 0.001$), white blood cell count (HR = 1.10, 95%CI = 1.05–1.15, $P < 0.001$), neutrophil count (HR = 1.14, 95%CI = 1.09–1.19, $P < 0.001$), lymphocyte count (HR = 0.51, 95%CI = 0.39–0.68, $P < 0.001$), NLR (HR = 1.03, 95%CI = 1.02–1.05, $P < 0.001$), LMR (HR = 0.87, 95%CI = 0.79–0.95, $P = 0.002$), serum glucose (HR = 1.20, 95%CI = 1.10–1.30, $P < 0.001$), serum sodium (HR = 0.93, 95%CI = 0.88–1.00, $P = 0.029$), LDH level (HR = 4.55, 95%CI = 2.89–7.16, $P < 0.001$), and WHO grade ($P < 0.001$) were all significantly correlated with survival at 3-year follow-up. Multivariate Cox analysis revealed that lymphocyte count (HR = 0.68, 95%CI = 0.51–0.91, $P = 0.008$), LDH level (HR = 2.21, 95%CI = 1.40–3.49, $P = 0.001$), and WHO grade (grade II: HR = 1.44, 95%CI = 0.44–4.68, $P = 0.543$; grade III: HR = 4.99, 95%CI = 1.68–14.87, $P = 0.004$; grade IV: HR = 16.96, 95%CI = 6.13–46.93, $P < 0.001$) remained associated with survival at 3-year follow-up (Table 4).

Table 4

Univariate and Multivariate Cox Hazard Regression Analysis of 3-year OS with Possible Predictive Factors

Parameter	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age	1.03	1.02–1.05	< 0.001			
WBC count 10 ⁹ /L	1.10	1.05–1.15	< 0.001			
NEU count 10 ⁹ /L	1.14	1.09–1.19	< 0.001			
LYM count 10 ⁹ /L	0.51	0.39–0.68	< 0.001	0.68	0.51–0.91	0.008
NLR	1.03	1.02–1.05	< 0.001			
LMR	0.87	0.79–0.95	0.002			
Serum glucose mmol/L	1.20	1.10–1.30	< 0.001			
Serum sodium mmol/L	0.93	0.88–1.00	0.029			
LDH level(normal or abnormally elevated)	4.55	2.89–7.16	< 0.001	2.21	1.40–3.49	0.001
WHO grade			< 0.001			< 0.001
I	1.00	Reference		1.00	Reference	
II	1.46	0.45–4.75	0.528	1.44	0.44–4.68	0.543
III	5.28	1.78–15.71	0.003	4.99	1.68–14.87	0.004
IV	20.61	7.51–56.58	< 0.001	16.96	6.13–46.93	< 0.001
OS: overall survival; HR: hazard ratio; CI: confidence interval; WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; NLR, neutrophil-lymphocyte ratio; LMR, lymphocyte–monocyte ratio; LDH, Lactate dehydrogenase; WHO, World Health Organization.						

Discussion

In adults, glioma is the most common primary intracranial tumor. It is characteristic of high invasion, high recurrence risk and short survival especially in glioblastomas. Once tumor relapse occurs, many patients

could not live independently which causes a considerable burden to the patient and society. Finding effective measures to delay the disease progression and improve the survival time has been the focus of intense research. Understanding the crucial markers that play a role in glioma malignant behaviors may assist clinicians in educating patients about prognosis and monitoring therapeutic efficacy. Because of this, a reliable prognostic predictor in glioma has long been appreciated. In recent years, histopathological, immunohistochemical, and molecular features has attracted growing attention for its tremendous potential on suggesting the treatment sensitivity and predicting the prognosis¹⁴. However, molecular detections are complex, expensive, and time-consuming, a convenient, cheap, and routine available serum biomarker is more popular in clinical uses.

LDH is known to be a crucial glycolytic enzyme that exists widely in multiple organs. Moreover, it is also a nonspecific inflammation marker and could have an increased concentration in inflammatory process¹⁵. When tissues are injured, the degree of injury can be sensitively reflected by the serum LDH level¹⁶. Elevated LDH could indicate an active status of inflammation. Indeed, as a well-known marker of inflammation, LDH has been widely recognized for their predictive performance in pneumonia^{11–13}. In patients with melanoma, non small cell lung carcinoma, metastatic breast cancer, and metastatic pancreatic cancer, elevated LDH has been demonstrated to be correlated with poor prognosis^{17–20}. However, the prognostic value of LDH in glioma patients has not received the attention it deserves.

In our study, we evaluated the prognosis of glioma patients by utilizing 1-year PFS, 2-year OS, and 3-year OS. We found that the preoperative serum LDH level of recurrence group was significantly higher than that of non-recurrence group. The same result was achieved in the postoperative serum LDH level between the two groups. In addition, the postoperative serum LDH level was significantly higher than preoperative serum LDH level, but with similar Δ LDH ($P = 0.289$). These results suggested that the surgical effect was near-equal to the recurrence group and non-recurrence group. Meanwhile, they also confirmed that the basic level of serum LDH was determined by their own inflammatory status which further affected their prognosis. In the univariate logistic regression analysis, age, KPS score, white blood cell count, neutrophil count, lymphocyte count, NLR, LMR, serum sodium level, serum potassium level, serum LDH level, and WHO grade were all significantly associated with 1-year PFS. However, in the multivariate analysis, only serum LDH level (OR = 0.97, 95%CI = 0.96–0.98, $P < 0.001$) and WHO grade (grade II: OR = 19.64, 95%CI = 5.56–69.35, $P < 0.001$; grade III: OR = 19.50, 95%CI = 7.08–53.73, $P < 0.001$; grade IV: OR = 15.23, 95%CI = 4.94–46.97, $P < 0.001$) were significant and independent of 1-year PFS. By utilizing ROC analysis, our study found a moderate predictive value of serum LDH level (AUC = 0.741, 95%CI = 0.677–0.798, sensitivity = 74.8%, specificity = 63.6%, and *Youden* index = 0.385) in glioma relapsing at 1 year after surgery. The predictive performance of WHO grade was presented as AUC = 0.810 (95%CI = 0.751–0.860), sensitivity = 84.4%, specificity = 77.0%, and *Youden* index = 0.614. DeLong's test indicated that the predictive performance of serum LDH level was comparable to glioma WHO grade ($Z = 1.363$, $P = 0.170$). In addition, the serum LDH level showed an excellent predictive performance in patients with low-grade glioma (AUC = 0.934, 95%CI = 0.866–1.000, sensitivity = 100.0%, specificity = 74.0%, and *Youden* index = 0.740). The Kaplan-Meier curves analysis suggested that the higher 2-year survival rate

and 3-year survival rate were statistically correlated with the abnormally elevated LDH level ($P < 0.001$). Subgroup analysis based on WHO grade got equally meaningful results. Not only that, multivariate Cox analysis revealed that both serum LDH level and WHO grade were independent prognostic indicator of 2-year survival rate and 3-year survival rate in glioma patients. Patients with abnormally elevated LDH level had 2.56-fold risk of death than those with normal LDH level at 2-year follow-up. The risk was 2.21 times higher than patients with normal LDH level when the length of follow-up was extended to 3 years after surgery. In addition, the risk of death in patients with high-grade glioma was quite high at 2-year follow-up (grade III: HR = 16.35, 95%CI = 2.16–123.80; grade IV: HR = 42.13, 95%CI = 5.83–304.47) and 3-year follow-up (grade III: HR = 4.99, 95%CI = 1.68–14.87; grade IV: HR = 16.96, 95%CI = 6.13–46.93). Due to the truth that WHO grade is a crucial indicator for glioma malignancy and prognosis²¹, the present study strengthened the reliability of serum LDH level as a prognostic indicator.

Malignant tumor could evoke both local and systemic inflammatory responses, which has been recognized as cancer-related inflammation²². Moreover, immune response and inflammation response are closely correlated with the occurrence and development of malignant tumor. The interaction between glioma cells and their microenvironment has received growing attention over the past years. Inflammatory mediators and inflammatory cytokines in the tumor microenvironment could influence glioma progression by participating the metabolism and apoptosis in glioma cells²³. The inflammation status has already been proven to affect proliferation rate in vivo and in vitro²⁴. Also, it has been shown that alteration of the tumor microenvironment could induce the malignancy progression of low-grade glioma under the regulation of inflammatory cytokines²⁵. Therefore, peripheral blood inflammatory biomarkers may provide novel predictors for disease progression and prognosis.

It has been constantly reported that peripheral blood inflammatory biomarkers have predictive value for prognosis of glioma patients. Weng *et al*/proposed that NLR combining with contrast enhancement were clearly associated with the proliferation potency of glioma⁷. He *et al*/reported that pretreatment NLR and albumin-to-gamma-glutamyl transferase ratio aid in predicting diagnosis of grade III oligodendroglial gliomas⁸. Wang *et al*/confirmed the prognostic value of preoperative inflammation markers including NLR and PLR in glioblastomas⁵. However, the reliability of peripheral blood inflammation biomarkers for predicting prognosis of glioma is still in dispute. In a previous study, recently reported by Mass *et al*/, routine blood test including various types of inflammation biomarkers could not independently predict survival in patients with glioblastoma²⁶.

LDH was not valued equally with those mentioned inflammatory markers by clinicians. But in fact, the basic scientific research has clarified the intimate relationship between LDH and glioma. In glioma cells, overexpression of LDH gene could promote their proliferation, invasion, and glycolysis^{27,28}. These experimental findings suggested that glioma patients with abnormally elevated LDH level were more likely to suffer from a dismal prognosis due to their robust state of inflammation, stronger ability for proliferation, and more aggressive behavior. They were consistent with our study and also provided an objective experimental basis for the further exploration of LDH in glioma. In our study, serum LDH level

was confirmed as an independent prognostic predictor in patients with glioma for the first time. It showed good performance both in predicting 2-year survival rate and 3-year survival rate which provided a reliable means to assess the risk of death in glioma patients. Also, it confirmed the crucial role of LDH gene playing in glioma cells in turn and provided new insight into individualized precision therapy for patients.

There were also several inherent limitations apply to our study as well. First, as a single-center, retrospective, and observational study, insufficient sample size could cause selection bias and some interference to the study. Second, as a nonspecific biomarker of inflammation, other unidentified physiological and pathophysiological alterations in the organism may lead to abnormal elevation of serum LDH level. Third, the measurement of LDH level was only performed once before surgery, which may increase the potential bias. Therefore, the predictive value of serum LDH level for the prognosis of glioma patients still needs to be further validated.

In conclusion, our study demonstrated that preoperative serum LDH level could serve as a reliable indicator for predicting prognosis of glioma patients. Abnormally elevated LDH level may suggest rapid proliferation and progression in glioma cells. The generalizability and convenience of this serum biomarker make it clinically feasible to play a role in almost all hospitals. It also has practical clinical implications for the preoperative management and individualized treatment of glioma patients. Further multicenter studies with large sample size and long-term follow-up are still required to verify our findings.

Methods

Study Population

Between January 2016 and January 2019, 216 patients who met the inclusion criteria and exclusion criteria with glioma at the First Affiliated Hospital of Fujian Medical University were retrospectively recruited. It was approved by local ethics committee of the First Affiliated Hospital of Fujian Medical University which waived the requirement of informed consent due to the retrospective design and conformed to the ethical guidelines of the Declaration of Helsinki. The inclusion criteria are as follows: (1) age >18 years old; (2) a diagnosis of glioma based on preoperative imaging; (3) received surgical treatment and confirmed by pathological diagnosis; (4) patients did not receive surgery or chemotherapy, or radiotherapy before admission; (5) preoperative routine blood test including LDH level was obtained. Exclusion criteria were: (1) incomplete medical information or patients lost to follow up; (2) history of infection or surgery within the past 6 month; (3) combined other other systemic diseases or neurological diseases; (4) previous history of using steroids, immunosuppressants, antiplatelet or anticoagulant drugs.

Clinical and Laboratory Variables

Patient data including general demographics, past medical history, surgical schemes (gross-total resection, subtotal resection, or biopsy), treatment regimens (concurrent chemoradiotherapy, CCRT), and other related data were collected. All patients underwent general preoperative blood tests by extracting fasting venous blood in the morning. The routine blood examinations were underwent by standard

laboratory test procedures within one week before surgery. The interval of postoperative reexamination was from 1 week to 1 month after surgery. The normal values of LDH are from 120 to 250 U/L. Δ LDH was calculated by subtracting preoperative LDH from postoperative LDH.

Radiological Examination and Follow-up Evaluation

Two neuroradiologists blinded to the patient information independently analyzed the preoperative and postoperative magnetic resonance imaging (MRI) or computed tomography (CT) images. For each case, preoperative MRI or CT scan was performed to evaluate the diameter of tumor and peritumor edema. After surgery, a follow-up contrast-enhanced CT scan or MR imaging was performed at the first month. The subsequent intervals of follow-up were 3 months at the first year, 6 months at the second year, and 12 months at the next year. Progression-free survival (PFS) in this study was defined as the interval from surgery to relapse confirmed on the imaging. The recurrence group contained patients with growing residual tumor or new lesions detected during the first year follow-up period. The other patients without those lesions were included into the non-recurrence group. Overall survival was defined as the interval from surgery to death or last follow-up. At the end point, the 2-year survival rate and 3-year survival rate of patients were estimated.

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 statistical software (SPSS, Inc., Chicago, Illinois, USA). *P* value less than 0.05 was considered as statistically significant. Continuous variables, presented as mean $\pm$ standard deviation, were analyzed by 2-sample *t* test. They were expressed as median (inter-quartile range) and analyzed by non-parametric test if they did not meet normal distribution. Categorical variables, described as frequency (percentage), were compared by Pearson χ^2 test or Fisher exact test. Univariate logistic regression analysis was used for analyzing the risk factors of 2-year PFS and 3-year PFS. Variables with *P* < 0.10 in univariate analysis were included for further multivariate analysis. Backward stepwise multivariate regression analysis incorporating all those variables with univariate association was performed to create the final model. The predictive value of factors was evaluated by the receiver operating characteristic (ROC) curve analysis. The predictive performance of predictor was presented with its sensitivity, specificity, and *Youden* index. DeLong's test was used to compare the predictive performance in different predictors by area under the curve (AUC). Kaplan-Meier curve analysis was performed to assess 2-year survival rate and 3-year survival rate after surgery. The log-rank test was used to calculate *P* value for comparing survival curves. The univariate and multivariate Cox proportional regression models were utilized to evaluate the prognostic significance of variables.

Declarations

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Author contributions

X.Y.C., J.Y.C. and L.M.C. were major contributors in concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review of the manuscript. J.F.C. and Z.Y.W. analyzed and interpreted the patient data. L.S.D., D.Z.K and C.Y.D. take responsibility for the integrity of the work as a whole from inception to published article.

Declaration of conflict of interest

None.

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Authorship Statements

All authors were involved in the research design, data analysis, drafting and critical review of the paper, and approval of the submitted version. All authors conducted the study and participated in data collection. All authors approved the final manuscript.

References

1. Dolecek, T. A., Propp, J. M., Stroup, N. E. & Kruchko, C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. *Neuro Oncol.* **14 Suppl 5**, v1-v49 (2012).
2. Stupp, R. *et al.* Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* **10**, 459-466 (2009).
3. Brennan, C. W. *et al.* The somatic genomic landscape of glioblastoma. *Cell* **155**, 462-477 (2013).
4. Parsons, D. W. *et al.* An integrated genomic analysis of human glioblastoma multiforme. *Science* **321**, 1807-1812 (2008).
5. Wang, P.-F. *et al.* Preoperative inflammation markers and IDH mutation status predict glioblastoma patient survival. *Oncotarget* **8**, 50117-50123 (2017).
6. Wang, P. F. *et al.* Preoperative Changes in Hematological Markers and Predictors of Glioma Grade and Survival. *Front. Pharmacol.* **9**, 886 (2018).
7. Weng, Y. *et al.* Do Selected Blood Inflammatory Markers Combined with Radiological Features Predict Proliferation Index in Glioma Patients? *World Neurosurg.* **118**, e137-e146 (2018).

8. He, Z.-Q. *et al.* Pretreatment neutrophil-to-lymphocyte ratio plus albumin-to-gamma-glutamyl transferase ratio predict the diagnosis of grade III glioma. *Ann Transl Med* **7**, 623-623 (2019).
9. McNamara, M. G. *et al.* Factors impacting survival following second surgery in patients with glioblastoma in the temozolomide treatment era, incorporating neutrophil/lymphocyte ratio and time to first progression. *J. Neurooncol.* **117**, 147-152 (2014).
10. Han, S. *et al.* Pre-treatment neutrophil-to-lymphocyte ratio is associated with neutrophil and T-cell infiltration and predicts clinical outcome in patients with glioblastoma. *BMC Cancer* **15**, 617 (2015).
11. Breuer, O. *et al.* Predictors of Prolonged Hospitalizations in Pediatric Complicated Pneumonia. *Chest* **153**, 172-180 (2018).
12. Saraya, T. *et al.* Correlation between clinical features, high-resolution computed tomography findings, and a visual scoring system in patients with pneumonia due to *Mycoplasma pneumoniae*. *Respir Investig* **56**, 320-325 (2018).
13. Tao, R.-J. *et al.* Viral infection in community acquired pneumonia patients with fever: a prospective observational study. *J. Thorac. Dis.* **10**, 4387-4395 (2018).
14. Gorlia, T. *et al.* Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. *Lancet Oncol.* **9**, 29-38 (2008).
15. Lu, A., Wang, C., Zhang, X., Wang, L. & Qian, L. Lactate Dehydrogenase as a Biomarker for Prediction of Refractory *Mycoplasma pneumoniae* Pneumonia in Children. *Respir. Care* **60**, 1469-1475 (2015).
16. Mura, M. *et al.* Intestinal ischemia-reperfusion-induced acute lung injury and oncotic cell death in multiple organs. *Shock (Augusta, Ga.)* **28**, 227-238 (2007).
17. Tas, F. *et al.* Serum levels of LDH, CEA, and CA19-9 have prognostic roles on survival in patients with metastatic pancreatic cancer receiving gemcitabine-based chemotherapy. *Cancer Chemother. Pharmacol.* **73**, 1163-1171 (2014).
18. Li, B. *et al.* Predictive value of LDH kinetics in bevacizumab treatment and survival of patients with advanced NSCLC. *Onco Targets Ther.* **11**, 6287-6294 (2018).
19. Wagner, N. B., Forscher, A., Leiter, U., Garbe, C. & Eigentler, T. K. S100B and LDH as early prognostic markers for response and overall survival in melanoma patients treated with anti-PD-1 or combined anti-PD-1 plus anti-CTLA-4 antibodies. *Br. J. Cancer* **119**, 339-346 (2018).
20. Pelizzari, G. A.-O. *et al.* Lactate Dehydrogenase (LDH) Response to First-Line Treatment Predicts Survival in Metastatic Breast Cancer: First Clues for A Cost-Effective and Dynamic Biomarker. LID - 10.3390/cancers11091243 [doi] LID - 1243. *Cancers (Basel)* **11**, 1243 (2019).
21. Server, A. *et al.* Measurements of diagnostic examination performance using quantitative apparent diffusion coefficient and proton MR spectroscopic imaging in the preoperative evaluation of tumor grade in cerebral gliomas. *Eur. J. Radiol.* **80**, 462-470 (2011).
22. Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: the next generation. *Cell* **144**, 646-674 (2011).

23. Jin, X. *et al.* Interferon regulatory factor 7 regulates glioma stem cells via interleukin-6 and Notch signalling. *Brain* **135**, 1055-1069 (2012).
24. Merzak, A. *et al.* Synergism between growth-factors in the control of glioma cell-proliferation, migration and invasion in-vitro. *Int. J. Oncol.* **6**, 1079-1085 (1995).
25. Michelson, N., Rincon-Torroella, J., Quiñones-Hinojosa, A. & Greenfield, J. P. Exploring the role of inflammation in the malignant transformation of low-grade gliomas. *J. Neuroimmunol.* **297**, 132-140 (2016).
26. Maas, S. L. N. *et al.* Routine Blood Tests Do Not Predict Survival in Patients with Glioblastoma-Multivariable Analysis of 497 Patients. *World Neurosurg.* **126**, e1081-e1091 (2019).
27. Hu, S. *et al.* miR-200b is a key regulator of tumor progression and metabolism targeting lactate dehydrogenase A in human malignant glioma. *Oncotarget* **7**, 48423-48431 (2016).
28. Wu, D., Zhao, B., Cao, X. & Wan, J. Long non-coding RNA LINK-A promotes glioma cell growth and invasion via lactate dehydrogenase A. *Oncol. Rep.* **38**, 1525-1532 (2017).

Figures

Figure 1

Receiver operating characteristic curve analyses comparing serum lactate dehydrogenase level and World Health Organization grade for predicting patients reaching 1-year progression-free survival.

Figure 2

Receiver operating characteristic curve analyses of lactate dehydrogenase level for predicting patients reaching 1-year progression-free survival in (A) low-grade group and (B) high-grade group.

Figure 3

Kaplan-Meier curve of the 2-year overall survival rate in patients with normal lactate dehydrogenase level and elevated lactate dehydrogenase level.

Figure 4

Subgroup analysis of Kaplan-Meier curve of the 2-year overall survival rate in patients with normal lactate dehydrogenase level and elevated lactate dehydrogenase level. (A) Patients with low-grade glioma. (B) Patients with high-grade glioma.

Figure 5

Kaplan-Meier curve of the 3-year overall survival rate in patients with normal lactate dehydrogenase level and elevated lactate dehydrogenase level

Figure 6

Subgroup analysis of Kaplan-Meier curve of the 3-year overall survival rate in patients with normal lactate dehydrogenase level and elevated lactate dehydrogenase level. (A) Patients with low-grade glioma. (B) Patients with high-grade glioma.