Original Article

Prognostic significance of alterations in fibrinogen level and fibrinogen-to-lymphocyte ratio after radiotherapy on survival outcomes in glioblastoma

Rong Huang, Xiaoxu Lu, Xueming Sun, Hui Wu^

Department of Radiation Oncology, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China

Contributions: (I) Conception and design: H Wu; (II) Administrative support: H Wu; (III) Provision of study materials or patients: R Huang; (IV) Collection and assembly of data: R Huang; (V) Data analysis and interpretation: X Lu, X Sun; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Hui Wu, MD. Department of Radiation Oncology, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, 127 Dongming Road, Zhengzhou 450008, China. Email: zlyywuhui202@zzu.edu.cn.

Background: Fibrinogen (FIB) plays an important role in tumor initiation, progression, and metastasis, but its clinical significance in glioblastoma has not been studied. We intend to explore the prognostic value by retrospectively analyzing the changes in FIB and fibrinogen-to-lymphocyte ratio (FLR) in glioblastoma patients before and after radiotherapy, and study the impact of radiotherapy on them.

Methods: This study retrospectively included 104 patients who were newly diagnosed with glioblastoma between February 2017 and February 2022 and analysed their clinical data from before to after radiotherapy. The cut-off values for FLR and FIB were calculated using a receiver operating characteristic curve. For inter-group comparisons, the Mann-Whitney *U* or *t*-test was applied. The prognostic importance of FIB and FLR was evaluated using the Kaplan-Meier curve and the Cox regression model. Spearman correlation coefficients were calculated to evaluate the association of FIB and FLR with radiotherapy-related dose-volume parameters.

Results: The mean progression-free survival (PFS) and overall survival (OS) of the high FIB and high FLR groups were significantly lower than those of the low FIB and low FLR groups (P<0.05). Larger planning target volume (PTV), mean brain dose, and mean brainstem dose were independent prognostic factors for poor PFS and OS in patients with glioblastoma.

Conclusions: FLR was a unique and very accurate predictor for the prognosis of glioblastoma, and FIB rise after radiation was a predictive sign of poor survival. Both PTV volume and dose volume for involved organs could significantly affect the FIB and FLR values in patients with glioblastoma.

Keywords: Fibrinogen (FIB); fibrinogen-to-lymphocyte ratio (FLR); radiotherapy; prognosis; glioblastoma

Submitted Dec 11, 2023. Accepted for publication Feb 19, 2024. Published online Apr 15, 2024.
doi: 10.21037/tcr-23-2271
View this article at: https://dx.doi.org/10.21037/tcr-23-2271

Introduction

Glioblastoma belongs to the family of intracranial primary tumours with the highest degree of malignancy and an extremely poor prognosis (1). Surgery followed by chemoradiotherapy remains the mainstay of current treatment for glioblastoma (2). Despite novel tumour treating fields (TTFields) therapy and immunotherapy (3,4), the survival of glioblastoma patients has not increased remarkably, and treatment options and drugs for

^ ORCID: 0000-0003-3669-0915.

glioblastoma are limited (5). In recent years, prognosis-related molecular markers have been increasingly investigated (6). Hematologic markers that are frequently employed in prognosis, such as the lymphocyte and neutrophil counts, can be easily and quickly obtained among clinical markers (7). It has been claimed that fibrinogen (FIB) has a significant role in carcinogenesis, development, and metastasis (8,9). In addition to its well-established function in coagulation, FIB has emerged as a key player in various aspects of cancer biology. A large number of studies have shown that FIB contributes to the complex interactions between tumor cells and the tumor microenvironment, affecting tumor progression and treatment response (10). FIB can promote tumor angiogenesis and provide a scaffold for tumor cell migration and invasion (11). Understanding the complex interactions between FIB and cancer is becoming increasingly important to elucidate tumor progression and develop new therapeutic strategies. At present, there is no research on the clinical significance of FIB in glioblastoma.

This study was conducted with an aim to analyze whether changes in FIB levels are associated with poor prognosis in glioblastoma and to explore whether the fibrinogen-to-lymphocyte ratio (FLR) value can serve as a novel hematological biomarker for prognostic assessment. Furthermore, we try to explore the impact of radiotherapy on FIB and FLR. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2271/rc).

Highlight box

Key findings

- The radiation therapy-related dose and volume parameters can influence the changes in fibrinogen (FIB) and fibrinogen-to-lymphocyte ratio (FLR), which may be associated with the prognosis of glioblastoma.

What is known and what is new?

- FIB may be involved in tumor progression. Severe lymphopenia is associated with prognosis in glioblastoma.
- Our study shows that elevated FIB and increased FLR values after radiotherapy are associated with worse prognosis in glioblastoma.

What is the implication, and what should change now?

- We need to monitor the changes in FIB levels and FLR values in patients and employ measures such as optimizing radiation therapy planning to minimize the impact on FIB levels and FLR values.

Methods

Clinical data

General information

From among 669 glioblastoma patients who underwent postoperative radiotherapy from February 2017 and February 2022, this retrospective study included 104 participants with glioblastoma who received postoperative concurrent and adjuvant chemo-radiotherapy. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital ethics committee (No. 2022-541-001) and individual consent for this retrospective analysis was waived.

Inclusion and exclusion criteria

Inclusion criteria: (I) age ≥18 years; (II) Eastern Cooperative Oncology Group (ECOG) score ≤2 points; (III) documented complete pathology report or glioblastoma diagnosis by pathologic consultation in The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital [the histopathological diagnosis of glioblastoma was based on the 2016 World Health Organization (WHO) classification of tumors of the central nervous system (CNS)]; (IV) no previous surgery or postoperative chemotherapy and radiotherapy; (V) blood and biochemical indices that were less than two times the upper limit of normal before radiotherapy; and (VI) no antineoplastic drugs other than temozolomide (TMZ) were used during radiotherapy. Exclusion criteria: (I) occurrence of postoperative infection, or hyperthermia; (II) complications such as coagulative dysfunction, haemorrhagic disorder, autoimmune disease, or other severe comorbidities; and (III) incomplete radiotherapy, or insufficient radiation dose.

Follow-up

All participants were followed up after the completion of radiotherapy via outpatient visit, medical record review, or telephonic interview. Patient overall survival (OS) was the interval from diagnosis to death of any causes or the last follow-up, whereas progression-free survival (PFS) was the period from diagnosis to first radiographic progression or death.

Research methods

Hematologic data collection

The participants' general data were collected from the

electronic medical record system of the hospital. Data of peripheral blood sample analysis conducted within one week before and after radiotherapy were obtained. According to the CTCAE5.0, hypoalbuminemia is defined as albumin (ALB) value less than 35 g/L, the range of grade 1 is: 30 g/L—the lower limit of the normal value; grades 2, 3, and 4 are characterised by ALB levels of 20–30 g/L, <20 g/L, and life-threatening hypoalbuminemia necessitating urgent treatment, respectively. Anaemia was classified as grades 1, 2, 3, and 4 based on haemoglobin (HGB) 100 g/L—the lower limit of normal, 80–100 g/L, <80 g/L, and life-threatening anaemia necessitating emergency treatment, respectively. Grades 1, 2, 3, and 4 FIB elevations were 25% below baseline (g/L), 25–49% above baseline, 50–74% from baseline, and ≥75% from baseline. The FLR was defined as the FIB (g/L) to lymphocyte (10^9/L) ratio.

Radiotherapy

The Eclipse treatment planning system (TPS) (Version 15.6) was used for treatment planning and dose calculation. Computed tomography (CT) was performed after 4-hour fasting. The participants were placed in a position based on their body size, and the head-neck and shoulders were fixed using a thermoplastic mask. After positioning in the Philips 16-detector row CT scanner (Philips, The Netherlands), 100 mL contrast agent was administered as intravenous bolus injections at 3 mL/s using a high-pressure injector. The whole brain was scanned with 3 mm layer thickness and 3 mm layer space. Images were transmitted to the Eclipse TPS and fused with the enhanced magnetic resonance imaging (MRI) image of the head before radiotherapy to outline the target area. Target regions including gross tumour volume (GTV), clinical target volume (CTV), and planning target volume (PTV), involved organs and brainstem were delineated. All participants underwent volumetric modulated arc therapy (VMAT). The prescribed radiation dose was 60 Gy administrated with conventional radiotherapy in 30 fractions within 6 weeks. Radiation dose parameters, including prescribed dose for PTV (Gy), PTV volume [cc (cubic centimeter)], mean dose for whole brain (Gy), whole-brain volume (cc), whole brain V10, V15, V20, V25, V30, V35, and V50 (%), mean dose for brainstem (Gy), brainstem volume (cc), brainstem V10, V15, V20, V25, V30, V35, and V50 (%), were collected from dose-volume histograms (DVH). Monitor units (MUs) were recorded.

Chemotherapy

All participants underwent concurrent TMZ-based chemotherapy during radiotherapy, followed by adjuvant TMZ-based chemotherapy (Stuup scheme) starting 4 weeks after the completion of the radiotherapy.

Statistical analysis

All data were collected and analysed with SPSS 26.0. Measurement data with normal distribution were obtained as mean ± standard deviation and compared using a two independent-sample *t*-test; otherwise, data were expressed by median (interquartile range) and compared with the Mann-Whitney *U* test. Numerical data were presented by frequency (percentage) and compared using the Chi-square test. Uni- and multivariate Cox regression analyses were employed to explore the influencing factors for PFS and OS outcomes. The Kaplan-Meier method was used to generate survival curves of PFS and OS. Spearman's correlation analysis was conducted. P<0.05 was considered statistically significant.

Results

Characteristics of study cohort

In this cohort of 104 participants, including 64 men and 40 women, and the median age at diagnosis was 52 years; 20, 22, and 62 participants completed ≤2, 3–4, and >4 chemotherapy cycles, respectively. The time to follow-up ranged from 5 to 60 months (July 2017–August 2022), with a median duration of 16.6 months.

Optimal cut-off values of FIB and FLR

The best cut-off values of FIB and FLR for predicting PFS and OS were determined using receiver operating characteristic (ROC) curve analysis. For FIB, the best cut-off for predicting PFS was 2.44, with an area under the curve (AUC) value of 0.922 [95% confidence interval (CI): 0.869, 0.974] (P<0.001), specificity of 1.000, sensitivity of 0.851, and the Youden index of 0.851; while the greatest cut-off for predicting OS was 2.44, with an AUC value of 0.997 (95% CI: 0.990, 1.000) (P<0.001), specificity of 1.000, sensitivity of 0.976, and the Youden index of 0.976. For FLR, the best cut-off for predicting PFS was 1.92, with an AUC value of 0.796 (95% CI: 0.630, 0.962) (P=0.002), specificity of 0.800, sensitivity of 0.851, and the Youden index of 0.651; while the best cut-off for predicting OS was 1.92, with an AUC value of 0.849 (95% CI: 0.732, 0.965)

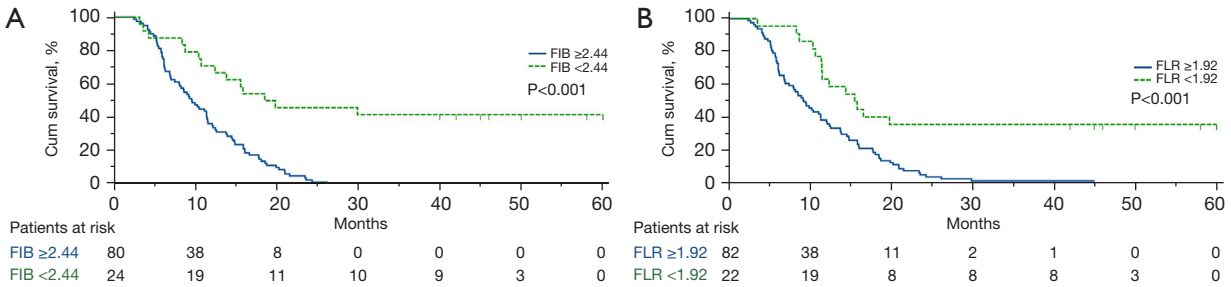

Figure 1 Survival curve for PFS. (A) Survival curve for PFS in high- and low-FIB groups; (B) survival curve for PFS in high- and low-FLR groups. FIB, fibrinogen; FLR, fibrinogen-to-lymphocyte ratio; PFS, progression-free survival.

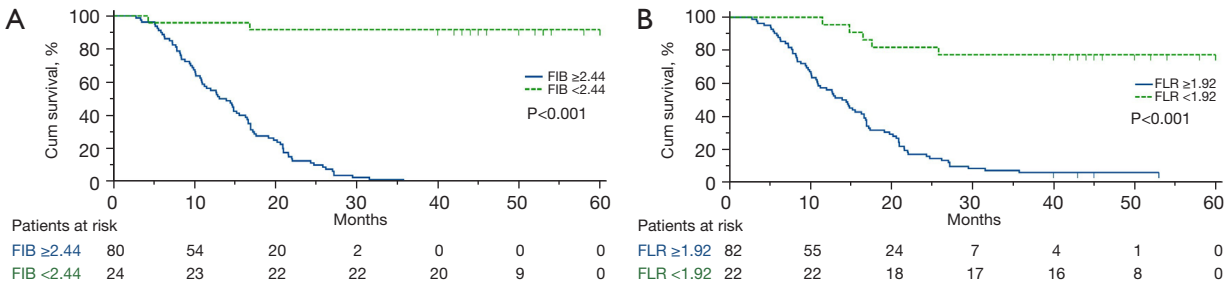

Figure 2 Survival curve for OS. (A) Survival curve for OS in high- and low-FIB groups; (B) survival curve for OS in high- and low-FLR groups. FIB, fibrinogen; FLR, fibrinogen-to-lymphocyte ratio; OS, overall survival.

(P<0.001), specificity of 0.773, sensitivity of 0.939, and the Youden index of 0.712.

Survival significance of FIB and FLR

According to the best cut-off of 2.44 determined by ROC curve, patients were divided into the high FIB (≥2.44) and low FIB (<2.44) groups. In the same way, patients were classified into the high FLR (FLR ≥1.92) and low FLR (FLR <1.92) groups according to the cut off of 1.92. The Kaplan-Meier method and the log rank (Mantel-Cox) test were used for the survival study. It was discovered that the mean PFS and OS of the high FIB and high FLR groups were considerably poorer than those of the corresponding low FIB and low FLR groups (P<0.05; *Figures 1,2*).

Comparison of clinical data between high and low FIB groups

According to the best cut-off of 2.44 determined by ROC curve, patients were divided into the high FIB (≥2.44) and low FIB (<2.44) groups. Following two independent-sample *t*-tests, the Chi-square test, and the Mann-Whitney *U* test, no distinct intergroup difference was found with regard to the dexamethasone dose during radiotherapy, body mass index (BMI) before and after radiotherapy, weight loss >3 kg within 3 months, HGB after radiotherapy, ALB after radiotherapy, proportion of O6-methylguanine-DNA methyl-transferase (MGMT) methylation, isocitrate dehydrogenase (IDH) mutation, tumour site, ECOG score, postoperative tumor volume, PTV dose, brain V10, brainstem V10, brainstem V15, brainstem V20, brainstem V25, brainstem V30, brainstem V35, and brainstem V50 (all P>0.05). The age, male ratio, PTV volume, mean brain dose, brain V15, brain V20, brain V25, brain V30, brain V35, brain V50, brain volume, mean brainstem dose, and brainstem volume in the high FIB group were significantly higher than those in the low FIB group (P<0.05), whereas the total MU was significantly lower (P<0.05, *Table 1*).

Comparison of clinical data between high and low FLR groups

According to the best cut-off of 1.92 determined by ROC curve, patients were divided into the high FLR (FLR ≥1.92) and low FLR (FLR <1.92) groups. Following two

Table 1 Comparison for clinical data between high and low FIB groups

Variables	Low FIB group (n=24)	High FIB group (n=80)	χ^2/t/z value	P value
Age (years)	47.13±13.22	53.36±13.42	–2.004	0.048
Gender			5.205	0.02
Male	10 (41.7)	54 (67.5)		
Female	14 (58.3)	26 (32.5)		
Dose of dexamethasone (mg)	19.38±20.07	20.80±18.79	–0.321	0.74
BMI before radiotherapy (kg/m^2)	22.99±3.28	23.10±2.93	–0.170	0.86
BMI after radiotherapy (kg/m^2)	22.66±3.36	22.45±2.83	0.313	0.75
Weight loss >3 kg within 3 months	5 (20.8)	18 (22.5)	0.030	0.86
HGB after radiotherapy (g/L)			1.288	0.52
≥100	21 (87.5)	74 (92.5)		
80–99	3 (12.5)	5 (6.3)		
<80	0	1 (1.3)		
ALB after radiotherapy (g/L)			–	0.54
≥30	23 (95.8)	78 (97.5)		
20–29	1 (4.2)	2 (2.5)		
MGMT methylation	10.99±12.39	11.19±13.67	–0.065	0.94
IDH mutation	1 (4.2)	6 (7.5)	0.011	0.91
Tumor site			2.704	0.43
Parietal lobe	5 (20.8)	31 (38.8)		
Frontal lobe	7 (29.2)	18 (22.5)		
Temporal lobe	8 (33.3)	22 (27.5)		
Occipital lobe	4 (16.7)	9 (11.3)		
ECOG score	1.21±0.41	1.38±0.49	–1.655	0.10
Postoperative residue	13 (54.2)	55 (68.8)	1.735	0.18
PTV dose (Gy)	58.51±3.15	59.46±2.36	–1.589	0.11
PTV volume (mL)	250.38±206.02	817.96±152.85	–14.662	<0.001
Brain				
Mean dose (Gy)	29.61±8.80	35.92±2.58	–2.667	0.009
V10 (Gy)	73.8 (63.65, 87.98)	83.25 (72.7, 91.2)	–1.659	0.09
V15 (Gy)	59.2 (48.5, 79.58)	78.85 (66.35, 86.75)	–2.616	0.009
V20 (Gy)	48.45 (40.03, 69.23)	71.7 (55.35, 80.93)	–2.758	0.006
V25 (Gy)	39.5 (33.15, 56.7)	61.85 (45.35, 73.83)	–2.832	0.005
V30 (Gy)	31.75 (26, 45.3)	52.55 (36.83, 64.6)	–3.248	0.001
V35 (Gy)	24.95 (16.15, 37.95)	44.3 (32.23, 53.63)	–3.835	<0.001
V50 (Gy)	14.6 (6.03, 24.23)	30.45 (23.15, 35.8)	–4.502	<0.001

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Low FIB group (n=24)	High FIB group (n=80)	χ^2/t/z value	P value
Brain volume (mL)	1303.52±140.97	1489.27±159.63	–5.129	<0.001
Brainstem				
Mean dose (Gy)	24.56±2.21	37.10±2.84	–8.946	<0.001
V10 (Gy)	54.7 (33.73, 89.05)	64 (35.23, 91.6)	–0.880	0.37
V15 (Gy)	50.65 (25.9, 78.4)	59.35 (24.78, 87.75)	–1.019	0.30
V20 (Gy)	47.8 (16.23, 74)	56.25 (15.4, 85.85)	–1.046	0.29
V25 (Gy)	46.30 (9.23, 68.8)	52.65 (9.43, 82.8)	–0.962	0.33
V30 (Gy)	39.35 (3.43, 57.43)	42.4 (5.45, 77.2)	–0.901	0.36
V35 (Gy)	21.35 (0.73, 52.30)	33.45 (4.1, 70.4)	–0.782	0.43
V50 (Gy)	4 (0, 11.65)	3.5 (0.03, 24.68)	–1.326	0.18
Brainstem volume (mL)	32.41±17.74	74.03±43.10	–4.603	<0.001
Total MU	496.33±133.54	427.48±97.90	2.766	0.007

Measurement data with normal distribution were obtained as mean ± standard deviation and compared using a two independent-sample *t*-test; otherwise, data were expressed by median (interquartile range) and compared with the Mann-Whitney U test. Numerical data were presented by frequency (percentage) and compared using the Chi-square test. FIB, fibrinogen; BMI, body mass index; HGB, haemoglobin; ALB, albumin; MGMT, O6-methylguanine-DNA methyl-transferase; IDH, isocitrate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; PTV, planning target volume; MU, monitor unit.

independent-sample *t*-test, Chi-square test, and Mann-Whitney *U* test, no distinct differences were found between the two groups in the dexamethasone dose during radiotherapy, BMI before and after radiotherapy, weight loss >3 kg within 3 months, HGB after radiotherapy, ALB after radiotherapy, proportion of MGMT methylation, IDH mutation, tumour site, ECOG score, postoperative tumor volume, PTV dose, brain V10, brain V15, brain V20, brain V25, brain V30, brain V35, brainstem V10, brainstem V15, brainstem V20, brainstem V25, brainstem V30, brainstem V35, brainstem V50, and total MU (all P>0.05). The age, male ratio, PTV volume, mean brain dose, brain V50, brain volume, mean brainstem dose, and brainstem volume in the high FLR group were significantly higher than those in the low FLR group (P<0.05) (please refer to *Table 2*).

Cox regression analysis for factors influencing PFS of patients

Univariate Cox regression analysis

In the univariate analysis, male gender, age, ECOG score, PTV volume, mean brain dose, brain V25, brain V30, brain V35, brain volume, mean brainstem dose, brainstem volume, FIB and FLR after radiotherapy were positively associated with the risk of poor PFS (*Table 3*).

Multivariate Cox regression analysis

The variables with statistical significance in univariate analysis were further included in a multivariate model wherein male sex, higher PTV volume, mean brain dose, and mean brainstem dose were independently prognostic factors for poor PFS (*Table 4*).

Cox regression analysis for factors influencing OS of patients

Univariate Cox regression analysis

In the univariate analysis, male sex, age, ECOG score, PTV volume, mean brain dose, brain V25, brain V30, brain V35, brain volume, mean brainstem dose, brainstem volume, FIB and FLR after radiotherapy were positively associated with the risk of poor OS of patients, whereas the total MU exhibited a negative association (*Table 5*).

Multivariate Cox regression analysis

The variables with statistical significance in univariate analysis were further included in a multivariate model. It was demonstrated that higher PTV volume, mean

Table 2 Comparison for clinical data between high and low FLR groups

Variables	FLR <1.92 (n=22)	FLR ≥1.92 (n=82)	χ^2/t/z value	P value
Age (years)	45.86±12.56	53.55±13.44	–2.413	0.01
Gender			5.017	0.02
Male	9 (40.9)	55 (67.1)		
Female	13 (59.1)	27 (32.9)		
Dose of dexamethasone (mg)	23.86±20.52	19.56±18.60	0.943	0.34
BMI before radiotherapy (kg/m^2)	23.01±3.43	23.09±2.89	–0.119	0.90
BMI after radiotherapy (kg/m^2)	23.13±3.24	22.33±2.86	1.132	0.26
Weight loss >3 kg within 3 months	2 (9.1)	21 (25.6)	1.873	0.17
HGB after radiotherapy (g/L)			0.340	0.84
≥100	20 (90.9)	75 (91.5)		
80–99	2 (9.1)	6 (7.3)		
<80	0	1 (1.2)		
ALB after radiotherapy (g/L)			–	>0.99
≥30	22 (100.0)	79 (96.3)		
20–29	0	3 (3.7)		
MGMT methylation	11.26±12.56	11.11±13.60	0.046	0.96
IDH mutation	1 (4.5)	6 (7.3)	<0.001	>0.99
Tumor site			3.247	0.35
Parietal lobe	5 (22.7)	31 (37.8)		
Frontal lobe	8 (36.4)	17 (20.7)		
Temporal lobe	7 (31.8)	23 (28)		
Occipital lobe	2 (9.1)	11 (13.4)		
ECOG score	1.23±0.43	1.37±0.48	–1.308	0.19
Postoperative residue	13 (59.1)	55 (67.1)	0.488	0.48
PTV dose (Gy)	58.73±2.92	59.38±2.48	–1.054	0.29
PTV volume (mL)	343.50±305.33	779.13±208.45	–6.309	<0.001
Brain				
Mean dose (Gy)	26.84±2.92	38.60±2.29	–2.074	0.04
V10 (Gy)	76.05 (64.25, 95.45)	82.2 (69.38, 90.20)	–0.020	0.98
V15 (Gy)	68.70 (49.10, 90.25)	78.15 (60.68, 86.33)	–0.716	0.47
V20 (Gy)	58.45 (41.93, 82.53)	68.85 (53.65, 79.2)	–0.800	0.42
V25 (Gy)	47.50 (33.85, 75.15)	59.15 (43.18, 71.73)	–0.764	0.44
V30 (Gy)	38.1 (24.7, 65.75)	49.55 (35.48, 62.68)	–1.142	0.25
V35 (Gy)	29.75 (16.65, 52.3)	42.60 (30.58, 51.63)	–1.668	0.09
V50 (Gy)	18.25 (5.33, 32.23)	28.40 (20.05, 34.45)	–2.352	0.01

Table 2 (*continued*)

Table 2 (*continued*)

Variables	FLR <1.92 (n=22)	FLR ≥1.92 (n=82)	χ^2/t/z value	P value
Brain volume (mL)	1,358.54±173.29	1,469.98±167.07	−2.757	0.007
Brainstem				
Mean dose (Gy)	29.22±4.37	34.82±6.97	−6.444	<0.001
V10 (Gy)	69.55 (35.53, 93.75)	60.95 (33.35, 89.75)	−0.430	0.66
V15 (Gy)	64.6 (29.15, 90.85)	55.7 (24, 86.63)	−0.326	0.74
V20 (Gy)	60.2 (21.15, 88.33)	51 (14.33, 84.83)	−0.350	0.72
V25 (Gy)	55.5 (10.78, 87.13)	47.3 (8.43, 81.05)	−0.450	0.65
V30 (Gy)	45.35 (4.78, 84.18)	40.7 (4.55, 73.73)	−0.642	0.52
V35 (Gy)	37.3 (2.6, 76.25)	24.9 (1.83, 59.05)	−0.747	0.45
V50 (Gy)	8.7 (0, 19.53)	2.65 (0, 23.93)	−0.052	0.95
Brainstem volume (mL)	38.52±22.26	71.38±44	−3.380	0.001
Total MU	479.36±146.53	433.7±97.36	1.740	0.08

Measurement data with normal distribution were obtained as mean ± standard deviation and compared using a two independent-sample *t*-test; otherwise, data were expressed by median (interquartile range) and compared with the Mann-Whitney U test. Numerical data were presented by frequency (percentage) and compared using the Chi-square test. FLR, fibrinogen-to-lymphocyte ratio; BMI, body mass index; HGB, haemoglobin; ALB, albumin; MGMT, O6-methylguanine-DNA methyl-transferase; IDH, isocitrate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; PTV, planning target volume; MU, monitor unit.

Table 3 Univariate Cox regression analysis for PFS

Factors	Wald value	P value	HR value	95% CI
Age	6.713	0.01	1.021	1.005, 1.037
Male	3.925	0.048	1.541	1.005, 2.362
Dose of dexamethasone	1.135	0.28	1.006	0.995, 1.017
BMI before radiotherapy	0.183	0.66	1.014	0.951, 1.082
BMI after radiotherapy	0.002	0.96	1.001	0.937, 1.070
Weight loss >3 kg within 3 months	0.025	0.87	0.961	0.584, 1.581
HGB after radiotherapy				
<80 g/L	Reference			
80–99 g/L	0.185	0.66	0.630	0.077, 5.173
≥100 g/L	0.387	0.53	0.533	0.073, 3.874
ALB after radiotherapy				
20–29 g/L	Reference			
≥30 g/L	0.143	0.70	1.249	0.394, 3.954
MGMT methylation	1.295	0.25	0.991	0.975, 1.007
IDH mutation	0.992	0.31	1.525	0.664, 3.502

Table 3 (*continued*)

Table 3 (*continued*)

Factors	Wald value	P value	HR value	95% CI
Tumor site				
Occipital lobe	Reference			
Parietal lobe	0.028	0.86	1.058	0.547, 2.047
Frontal lobe	0.603	0.43	0.755	0.371, 1.535
Temporal lobe	0.041	0.83	0.932	0.472, 1.841
ECOG score	4.566	0.03	1.588	1.039, 2.428
Postoperative residue	0.019	0.88	0.970	0.632, 1.489
PTV dose	3.015	0.08	1.083	0.990, 1.185
PTV volume	28.516	<0.001	1.002	1.001, 1.003
Brain				
Mean dose	13.744	<0.001	1.003	1.001, 1.004
V10	2.317	0.12	1.011	0.997, 1.026
V15	3.282	0.07	1.011	0.999, 1.023
V20	3.837	0.050	1.011	1.000, 1.022
V25	5.917	0.01	1.014	1.003, 1.025
V30	8.084	0.004	1.016	1.005, 1.028
V35	11.376	0.001	1.021	1.009, 1.033
V50	1.144	0.28	1.001	0.999, 1.002
Brain volume	12.924	<0.001	1.002	1.001, 1.003
Brainstem				
Mean dose	26.943	<0.001	1.026	1.016, 1.036
V10	0.008	0.92	1.000	0.994, 1.006
V15	0.006	0.93	1.000	0.994, 1.006
V20	0.001	0.97	1.000	0.994, 1.006
V25	0.018	0.89	1.000	0.995, 1.006
V30	0.070	0.79	1.001	0.995, 1.007
V35	0.091	0.76	1.001	0.995, 1.007
V50	1.606	0.20	1.006	0.997, 1.015
Brainstem volume	8.769	0.003	1.004	1.002, 1.007
Total MU	1.886	0.170	0.999	0.997, 1.001
FIB	16.257	<0.001	1.299	1.144, 1.474
FLR	7.731	0.005	1.101	1.029, 1.178

PFS, progression-free survival; BMI, body mass index; HGB, haemoglobin; ALB, albumin; MGMT, O6-methylguanine-DNA methyltransferase; IDH, isocitrate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; PTV, planning target volume; MU, monitor unit; FIB, fibrinogen; FLR, fibrinogen-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

Table 4 Multivariate Cox regression analysis for PFS

Factors	Wald value	P value	HR value	95% CI
Age	0.787	0.37	1.010	0.988, 1.032
Male	3.926	0.048	1.642	1.005, 2.682
ECOG score	0.208	0.64	0.877	0.499, 1.541
PTV volume	4.104	0.04	1.001	1.000, 1.003
Brain				
Mean dose	5.529	0.01	1.003	1.000, 1.005
V25	0.128	0.72	0.987	0.921, 1.058
V30	0.028	0.86	0.992	0.900, 1.093
V35	0.746	0.38	1.030	0.963, 1.103
Brain volume	3.459	0.06	1.001	1.000, 1.003
Brainstem mean dose	5.026	0.02	1.017	1.002, 1.032
Brainstem volume	0.005	0.94	1.000	0.994, 1.006
FIB	2.675	0.10	0.808	0.626, 1.043
FLR	2.374	0.12	1.082	0.979, 1.197

PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; PTV, planning target volume; FIB, fibrinogen; FLR, fibrinogen-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

brain dose, and mean brainstem dose were independent prognostic factors for poor OS (*Table 6*).

Spearman correlation analysis

Association between FIB and clinical indicators

The PTV volume, mean brain dosage, mean brainstem dose, and brainstem volume were all inversely correlated with the changes in FIB from before to after radiotherapy. ($P<0.05$).

Association between FLR and clinical indicators

The PTV volume, mean brain dosage, mean brainstem dose, and brainstem volume were all inversely correlated with the changes in FLR before and after radiation. ($P<0.05$).

Discussion

Studies have increasingly proved that the inflammatory response is closely associated with multiple stages of tumour occurrence and development (12), and has significant implications for the body's immune function, patient response to therapy, and prognosis, etc. (13-15). FIB is the most abundant plasma coagulation factor that is synthesised by the liver, and participates in tissue inflammation, infection, or tissue damage repair through conversion to fibrin in the presence of thrombin. Besides its role in coagulation, FIB is crucial for infiltration, metastasis, and inflammatory response in multiple tumours (16,17). A high level of FIB is an indicator of coagulation and fibrinolysis, and is a prognostic marker for progression of various tumours, such as head and neck tumours, oesophageal carcinoma, breast and colon cancer (18). Sheng *et al.* (19) retrospectively analysed the preoperative FIB levels of 110 laryngeal cancer patients who were scheduled for tumour resection and found that higher levels of preoperative plasm FIB (>4.00 g/L) were predictive of shorter OS and disease-free survival (DFS), and an advanced tumour stage in these patients. In a different retrospective analysis, 68 patients scheduled for radical oesophageal cancer resection and undergoing neoadjuvant therapy had significantly shorter DFS after surgery if they had preoperative hyperfibrinogenaemia and elevated plasma FIB during neoadjuvant therapy (20). In tumour patients with activation of the fibrinolytic system, it is frequently observed that the extent of activation is highly involved in the distant metastasis, progression, and prognosis of diverse malignancies. The clinical significance of FIB in

Table 5 Univariate Cox regression analysis for OS

Factors	Wald value	P value	HR value	95% CI
Age	9.237	0.002	1.027	1.010, 1.045
Male	4.355	0.03	1.630	1.030, 2.580
Dose of dexamethasone	0.032	0.85	0.999	0.988, 1.010
BMI before radiotherapy	0.719	0.39	1.030	0.962, 1.102
BMI after radiotherapy	0.001	0.97	1.001	0.993, 1.074
Weight loss >3 kg within 3 months	0.342	0.55	1.169	0.693, 1.973
HGB after radiotherapy				
<80 g/L	Reference			
80–99 g/L	0.783	0.37	0.385	0.046, 3.191
≥100 g/L	1.657	0.19	0.269	0.036, 1.987
ALB after radiotherapy				
20–29 g/L	Reference			
≥30 g/L	0.071	0.79	1.210	0.297, 4.926
MGMT methylation	0.285	0.59	0.996	0.979, 1.012
IDH mutation	3.333	0.06	2.181	0.944, 5.039
Tumor site				
Occipital lobe	Reference			
Parietal lobe	1.400	0.23	1.567	0.745, 3.297
Frontal lobe	0.014	0.90	0.953	0.428, 2.121
Temporal lobe	0.104	0.74	1.135	0.525, 2.456
ECOG score	4.242	0.03	1.603	1.023, 2.512
Postoperative residue	1.076	0.30	1.279	0.803, 2.038
PTV dose	2.388	0.12	1.078	0.980, 1.185
PTV volume	50.435	<0.001	1.004	1.003, 1.005
Brain				
Mean dose	18.124	<0.001	1.003	1.002, 1.004
V10	0.283	0.59	1.004	0.989, 1.020
V15	3.612	0.057	1.012	1.000, 1.025
V20	3.785	0.052	1.012	1.000, 1.024
V25	4.482	0.03	1.013	1.001, 1.024
V30	6.972	0.008	1.016	1.004, 1.027
V35	11.292	0.001	1.022	1.009, 1.034
V50	0.590	0.44	1.000	0.999, 1.002
Brain volume	20.491	<0.001	1.003	1.002, 1.004

Table 5 (*continued*)

Table 5 (*continued*)

Factors	Wald value	P value	HR value	95% CI
Brainstem				
Mean dose	48.145	<0.001	1.045	1.032, 1.058
V10	0.002	0.96	1.000	0.993, 1.007
V15	0.023	0.87	1.001	0.994, 1.007
V20	0.041	0.83	1.001	0.994, 1.007
V25	0.063	0.80	1.001	0.995, 1.007
V30	0.231	0.63	1.002	0.995, 1.008
V35	0.407	0.52	1.002	0.995, 1.009
V50	2.086	0.14	1.007	0.998, 1.016
Brainstem volume	13.654	<0.001	1.005	1.002, 1.007
Total MU	5.448	0.020	0.997	0.995, 1.000
FIB	47.092	<0.001	1.671	1.443, 1.934
FLR	20.918	<0.001	1.162	1.089, 1.239

OS, overall survival; BMI, body mass index; HGB, haemoglobin; ALB, albumin; MGMT, O6-methylguanine-DNA methyl-transferase; IDH, isocitrate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; PTV, planning target volume; MU, monitor unit; FIB, fibrinogen; FLR, fibrinogen-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

Table 6 Multivariate Cox regression analysis for OS

Factor	Wald value	P value	HR value	95% CI
Age	3.287	0.07	1.024	0.998, 1.050
Male	2.514	0.11	1.600	0.895, 2.860
ECOG score	0.428	0.51	0.802	0.414, 1.553
PTV volume	11.882	0.001	1.003	1.001, 1.004
Brain				
Mean dose	5.477	0.01	1.003	1.000, 1.005
V25	0.069	0.79	0.990	0.916, 1.069
V30	0.001	0.97	1.002	0.906, 1.108
V35	0.079	0.77	1.011	0.939, 1.088
Brain volume	3.606	0.058	1.002	1.000, 1.003
Brainstem mean dose	14.354	<0.001	1.036	1.017, 1.056
Brainstem volume	0.007	0.93	1.000	0.994, 1.005
Total MU	1.866	0.17	0.998	0.996, 1.001
FIB	0.053	0.81	1.034	0.781, 1.368
FLR	1.173	0.27	1.064	0.951, 1.190

OS, overall survival; ECOG, Eastern Cooperative Oncology Group; PTV, planning target volume; MU, monitor unit; FIB, fibrinogen; FLR, fibrinogen-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

glioblastoma has not been reported yet. The present study found that the mean PFS and OS of patients in the high FIB group after radiotherapy were 10.9 and 14.8 months, respectively, which was significantly lower than those in the low FIB group (P<0.05) and is consistent with the aforementioned studies. The mechanism underlying the association between FIB and tumour progression remains indescribable but there are three theories: (I) FIB binds with multiple growth factors, such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and neurotrophic factor, which are involved in various tumour pathophysiological processes (e.g., tumour development, inflammatory response, tumour microenvironment) via regulation of tumour cell growth and inhibition of the function of natural killer (NK) cells, thereby promoting proliferation, invasion, and migration of tumour cells (21); (II) FIB stimulates tumour angiogenesis through promoting vascular endothelial cell chemotaxis and enhancing the proangiogenic effects of vascular endothelial growth factor (VEGF) and FGF, which is conducive for tumour microenvironment remodelling (11); and (III) FIB can be synthesized by tumour cells and can augment the blockade of activated immune cells, which may help tumour cells escape from host immune surveillance, leading to more active proliferation, invasion, and migration in tumour cells; (IV) FIB can protect tumor cells from NK cell-mediated cytotoxicity by accumulating around them and forming a dense fibrin layer (22). FIB may therefore have a significant role in the development and spread of tumours. Furthermore, FIB-like proteins, which have structural similarities to FIB, can inhibit antigen-mediated T cell responses and evade immune surveillance (23). High expression has been detected in solid tumors such as liver cancer and lung cancer, and it has been shown that it can lead to poor therapeutic effects of immune checkpoint inhibitors and affect the development process of tumors. However, it plays a role in mediating tumor immune escape in the tumor microenvironment. The mechanism of action has not been clearly studied (10). Glioblastoma is more invasive and capable of neovascularization than tumours with lesser malignancy, and it has a higher blood vessel density than glioblastoma multiforme. Brain oedema is a secondary, multivariate, extremely complex pathophysiological condition that usually develops in glioblastoma patients following surgery. After brain cancer surgery, brain oedema is linked to chronic thrombin release, which increases FIB and fibrin synthesis and promotes the growth of tumours (24,25). No study has investigated radiotherapy-induced FIB changes, possibly attributable to the increasing rate and sensitivity of fibrin hydrolysis. In the present study, we found that the age, male ratio, PTV volume, mean brain dose, brain V15, brain V20, brain V25, brain V30, brain V35, brain V50, brain volume, mean brainstem dose, and brainstem volume were significantly higher in the high FIB group than those in the low FIB group (P<0.05), whereas the total MU was significantly lower (P<0.05). Furthermore, changes in FIB from before to after radiotherapy was negatively associated with the PTV volume, mean brain dose, mean brainstem dose, and brainstem volume (P<0.05). Since this study is a retrospective study, we adopted the 4th edition staging criteria from 2016. However, the 2021 WHO classification for CNS tumors no longer defines IDH-mutant astrocytomas as glioblastomas but rather as astrocytomas, IDH-mutant, WHO grade 4. Furthermore, low hemoglobin and anemia can directly affect tumor cell sensitivity to radiation, leading to decreased survival rates. Low ALB levels are a common manifestation of malnutrition in tumor patients and are associated with prognosis in various types of cancer (26). Considering that patients with glioblastoma require concurrent postoperative radiochemotherapy, their blood and biochemical indicators should not exceed more than twice the normal values before radiotherapy. Otherwise, they would not meet the criteria for receiving concurrent radiochemotherapy. Our study results indicate that no differences between the high and low FIB groups were detected for dexamethasone dose, BMI before and after radiotherapy, weight loss <3 kg within 3 months, HGB after radiotherapy, ALB after radiotherapy, proportion of MGMT methylation, IDH mutation, tumour site, ECOG score, and postoperative tumor volume. Thus, FIB changes caused by radiotherapy-associated dose-volume parameters (especially target region volume and dose volume of involved organs) correlated to a poor prognosis, though target region dose was not statistically significant for FIB changes, possibly because a standard dose was used in both groups. Furthermore, our study revealed a significantly lower total MU in the high FIB group, which might be attributable to the morphology of the single target region of radiotherapy for glioblastoma that facilitates planned dose optimisation, whereas the dose distribution in a large target volume does not necessarily need more complicated subfields and multi-leaf collimator (MLC) sequence.

Lymphocytes are a routine hematologic index of the immune status of patients during tumour-related treatment. Multiple traditional inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-

to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), are known potential prognostic biomarkers for various tumours (27). For instance, Liu *et al.* (28) retrospectively analysed 139 patients with small cell lung cancer and reported that high NLR (>4.55) and high PLR (>148) were mortality predictors, and high NLR was associated with a poor prognosis. Zhang *et al.* (29) found that preoperative serum NLR could be used as a prognostic indicator of EGFR mutation-positive stage Ⅳ non-small cell lung cancer (NSCLC) patients receiving EGFR tyrosine kinase inhibitors (EGFR-TKIs). Hirahara *et al.* (30) demonstrated that NLR/PLR was closely associated with tumour progression in patients with advanced gastric cancer, and could be used clinically as a novel hematologic predictor of tumour response to first-line therapy. Lymphocytes are sensitive to radiotherapy though they are not actively in mitosis (31). Besides directly damaging DNA in tumour cells, radiotherapy can lead to apoptosis by enhancing immunogenicity through promoting inflammation and releasing tumour antigens, or affect the host anti-tumour immune response via specifically recognizing and releasing a series of cytokines. Preoperative lymphocyte count reduction indicates an immunosuppressed status, whereas a low peripheral lymphocyte count indicates poor immune response that results in a decreased treatment effect. Nevertheless, the association between the decrease in lymphocytes and the reduction in tumour response to therapy is extremely complicated and needs validation in further experiments. Radiotherapy can directly kill lymphocytes to reduce their number, though different degrees of reduction may induce interindividual differences in anti-tumour immune functions. Differences in immune functions might mediate varying outcomes in tumour patients who maintain the same stage after identical treatment (32). Moreover, the target volume, radiation dose, segmentation mode (including conventional fractionated radiotherapy, hypofractionated radiotherapy, hyperfractionated radiotherapy, etc.), and the irradiated site, have significant implications for the decreased lymphocyte count after radiotherapy. A significant relationship between the irradiated tumour volume and the change of total lymphocyte count has been reported. In a study of 711 NSCLC patients receiving radiotherapy, a larger irradiated tumour volume was associated with a distinct decrease in the lymphocyte count after radiotherapy, possibly due to the exposure of more circulating cells to radiation and destruction of normal lymphocytes (26). In another study, 183 patients with high-grade glioma (HGG) were treated with radiotherapy + TMZ, 53 patients (29%) developed acute severe lymphopenia (ASL). Patients with ASL had significantly worse OS than those without (median: 12.5 *vs.* 20.2 months, respectively; P<0.001). Higher brain V25Gy are significant predictors of ASL during radiotherapy + TMZ therapy for HGG (33). Yovino *et al.* (34) showed that after a single dose of 2 Gy, approximately 5% of circulating blood cells will be exposed to 0.5 Gy. Although this dose is relatively low compared with the total dose received by the bulk tumor, it is still enough to cause a large number of lymphopenia: 62%, 92%, and 99% of circulating blood cells received at least 0.5 Gy after 10, 20, and 30 fractions of radiotherapy, respectively, which also suggests that lymphopenia is cumulative with radiotherapy dose-fractionation effects are closely related. FLR was first reported by Fan *et al.* (35), who found that oesophageal carcinoma patients with high preoperative FLR tended to have a low survival rate. Consistently, our study demonstrated that the mean PFS and OS of patients in the high FLR group after radiotherapy were significantly lower than those of patients in the low FLR group. Multiple studies have explored the role of FLR in the prognosis of lung, head and neck, and liver cancer (36-38). To our knowledge, FLR on prognosis in glioblastoma has not been reported yet. In the present study, FLR, which combines the FIB level and lymphocyte count, was evaluated as a prognostic indicator in glioblastoma patients receiving radiotherapy. We noted that the age, male ratio, PTV volume, mean brain dose, brain V50, brain volume, mean brainstem dose, and brainstem volume were significantly higher in the high FLR group than those in the low FLR group (P<0.05). Compared to the high FLR group, brain V15, 20, 25, 30, 35 were missing in the low FLR group, possibly due to the varying degrees of lymphocyte decrease after radiotherapy. However, we did not include the degree of lymphocyte decrease in the analysis, which is a limitation of the study. Moreover, the changes in FLR before and after radiotherapy were negatively associated with the PTV volume, mean brain dose, mean brainstem dose, and brainstem volume (P<0.05), which is consistent with the changing trend of FIB. Furthermore, larger PTV volume, mean brain and brainstem doses were independent prognostic factors for poor PFS and OS of patients. These findings imply that the FLR could be used as a clinical index for predicting the prognosis and sensitivity to radiotherapy in patients with glioblastoma.

Conclusions

In conclusion, the dose and volume parameters related to radiotherapy will affect the changes in FIB and FLR, thus affecting the prognosis. Shortening the irradiation time and optimizing the radiotherapy plan without changing the total irradiation dose and compromising the treatment effect to reduce the irradiated dose and volume of surrounding normal organs will remain an area of active research interest. The FLR, which combines the FIB level and lymphocyte count, is simple to measure and may have useful clinical applications. To develop more suitable, standardised cut-off values for FLR to direct clinical use in glioblastoma patient prognostication, however, large-scale, multi-centre prospective investigations are further warranted which can provide a basis for individualized treatment of patients.

Acknowledgments

Funding: This study was supported by the 2021 Science and Technology Development Plan Project of Henan Province (212102310663).

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2271/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2271/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2271/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2271/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital ethics committee (No. 2022-541-001) and individual consent for this retrospective analysis was waived.

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Cite this article as: Huang R, Lu X, Sun X, Wu H. Prognostic significance of alterations in fibrinogen level and fibrinogen-to-lymphocyte ratio after radiotherapy on survival outcomes in glioblastoma. Transl Cancer Res 2024;13(4):1887-1903. doi: 10.21037/tcr-23-2271

