Overexpression of EZH2 is associated with clinicopathological parameters and poor prognosis in gliomas

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Abstract. The histone methyltransferase enhancer of zeste homolog 2 (EZH2), which is primarily localized in the nucleus, mediates Polycomb repressive complex activity by trimethylating lysine 27 of histone H3 (H3K27me3), thereby leading to transcriptional silencing. EZH2 plays a crucial role in cell proliferation, differentiation and apoptosis. Its overexpression is frequently observed in various cancers and contributes to tumor progression. A potential prognostic role for EZH2 in glioma has been suggested. The present study aimed to evaluate the clinicopathological and prognostic significance of EZH2 expression in glioma. EZH2 mRNA levels in tumor and normal tissues were assessed using the TIMER2.0 and The Cancer Genome Atlas databases. The prognostic value of EZH2 mRNA expression was analyzed using the Kaplan-Meier plotter. Immunohistochemistry was performed on 147 clinical glioma samples to evaluate EZH2 protein expression. Cox proportional hazards models and Kaplan-Meier survival curves were used to examine the associations between EZH2 expression, clinicopathological parameters and overall survival (OS). EZH2 was significantly upregulated and amplified in tumor tissues across multiple cohorts. In high-grade gliomas, elevated EZH2 expression was significantly associated with poorer OS, disease-specific survival and progression-free interval. The results of the present study indicated that EZH2 expression may serve as a valuable prognostic biomarker in glioma.

Introduction

Glioma is the most common primary intracranial tumor, accounting for ~22.2% of all central nervous system malignancies (1). The World Health Organization (WHO) classifies gliomas into grades I-IV, with grades I-II considered low-grade gliomas (LGG) and grades III-IV considered high-grade gliomas (HGG) (2). Histopathological features are closely correlated with the degree of malignancy (3,4). HGGs are associated with high morbidity, therapeutic resistance, frequent recurrence and poor survival, thereby imposing a substantial burden on patients and society (5-7). Surgical resection remains the primary treatment; however, its efficacy is limited and adjuvant radiotherapy and chemotherapy are often required (8-10). Despite multimodal therapy, recurrence rates remain high (11). The median survival of patients with LGG is ~10 years, whereas that of untreated patients with HGG is <20 months (12), with only a minority surviving beyond 3 years after surgery (13). Therefore, understanding the molecular mechanisms underlying glioma progression is essential for identifying novel diagnostic biomarkers and therapeutic targets.

Primarily localized in the nucleus, the histone methyltransferase EZH2 is integral to the assembly of the Polycomb repressive complex (14,15). This enzyme trimethylates lysine 27 of histone H3 (H3K27me3), leading to gene silencing through both canonical and non-canonical mechanisms, thereby exerting transcriptional repression or activation (16-18). EZH2 plays a crucial role in cell proliferation, differentiation and apoptosis and its functions are closely associated with the regulation of diverse targets and signaling pathways (19,20).

EZH2 has recently emerged as a significant regulator in various cancers (21), influencing cell proliferation, apoptosis, epithelial-mesenchymal transition, invasion and drug resistance in glioma and other malignancies (22-24). Suppression of EZH2 through small-molecule inhibitors or gene knockdown results in reduced growth and tumor formation in rectal cancer cells (25). Moreover, within the tumor microenvironment, EZH2 expression directly influences T-cell responses and is involved in the suppression of chemokine signaling and cytotoxic lymphocyte activity (26). In cancer, elevated EZH2 expression is associated with tumor aggressiveness, unfavorable prognosis and recurrence across multiple tumor types, thereby serving as a diagnostic marker (27-29). The present study investigated the prognostic relevance of EZH2 expression in glioma by integrating public database analyses [TIMER2.0, The Cancer Genome Atlas (TCGA)] with a large

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Chinese cohort of 147 patients, with detailed stratification by WHO grade, IDH status and 1p/19q co-deletion.

Materials and methods

Bioinformatics analysis. EZH2 mRNA expression levels across cancer samples were analyzed using TIMER 2.0 (http://timer.comp-genomics.org/). Its expression in normal brain tissues and glioma tissues was assessed using TCGA database (https://portal.gdc.cancer.gov/). Clinical and molecular data from patients with glioma were also extracted from TCGA for subsequent prognostic analysis. The prognostic significance of EZH2 mRNA expression was evaluated using an online tool (https://www.helixlife.cn/). The optimal cut-off value was determined by selecting the 'auto select best cut-off' option. Based on this cut-off, patients were stratified into high and low EZH2 expression cohorts and overall survival (OS), disease-specific survival (DSS) and progression-free interval (PFI) curves were generated.

Tissue samples and clinical data. The tissue samples used in the present study were obtained from Shanghai Outdo Biotech Company (China). A total of 149 human glioma tissue specimens were initially collected, of which 147 were included in the final analysis due to the availability of complete clinicopathological data. The tissue samples were collected (patient surgery dates) from February 2008 to October 2011. All immunohistochemistry staining, imaging, and data analysis were performed in the laboratory of Shanghai Outdo Biotech Company from January 2018 to June 2025. The present study was approved by the Ethics Committee of Shanghai Outdo Biotech Company (approval no. HBraG149Su01), which covers both sample collection and the experimental procedures. Written informed consent was obtained from all patients and/or their legal guardians prior to sample collection.

Immunohistochemical analysis. Tissue specimens were processed by formalin fixation [10% neutral buffered formalin, at room temperature (20-25˚C), for 24 h], dehydration (graded ethanol series: 75, 85, 95, 100 and 100% at room temperature, each for 1 h), clearing (xylene, at room temperature, two changes, each for 15 min), and paraffin embedding (molten paraffin at 60˚C, for 2 h) to obtain 4-μm-thick sections. Dewaxing was performed by baking at 70˚C for 3 h, followed by alcohol rehydration and antigen retrieval using a microwave in 0.01 M citrate buffer (pH 6.0) at 100˚C for 15 min. The sections were then treated with 3% H_2O_2 at room temperature for 15 min, washed three times with PBS (5 min each), and blocked with 5% bovine serum albumin (cat. no. A8020; Beijing Solarbio Science & Technology, Co., Ltd.) in PBS for 30 min at room temperature. The primary antibody used was a rabbit anti-EZH2 monoclonal antibody (1:50; cat. no. 5246; CST Biological Reagents Co., Ltd.), which was incubated overnight at 4˚C. The following day, the sections were washed three times with PBS, followed by incubation with biotinylated goat anti-rabbit secondary antibody (1:200 dilution; cat. no. PMK-016-001M; Wuhan Pumike Biotechnology Co., Ltd.) for 30 min at room temperature. After incubation, the sections were rinsed with PBS. Visualization was achieved using DAB, followed by counterstaining with hematoxylin. The sections were then dehydrated, treated with xylene, and mounted with neutral gum. Finally, immunohistochemistry images were captured using a digital section scanning system (KF-PRO-005; Ningbo Jiangfeng Bioinformatics Technology Co., Ltd.).

EZH2 exhibited nuclear staining with a brownish-yellow color. Immunohistochemical results were scored based on staining intensity and the percentage of cells at each intensity. Staining intensity was semi-quantitatively assessed using the H-score method, categorized into four grades: 0 (no staining), 1+ (weak staining), 2+ (moderate staining), or 3+ (strong staining). The percentage of cells at each staining intensity was determined, and a staining score was calculated by multiplying the percentage by the corresponding intensity score. The total score ranged from 0 (no staining) to 300 (100% of cells with staining intensity 3+). Two experienced pathologists, blinded to the patients' clinical information, independently evaluated all immunohistochemical results. Inter-observer differences were averaged, and the median value was used to classify final expression as high or low.

Statistical analysis. The association between EZH2 expression and clinicopathological data was assessed using univariate survival analysis with the Cox proportional hazards model, and Pearson's χ^2 test was applied. Variables that were significant in univariate analyses were subsequently included in multivariate analysis, in which hazard ratios (HRs), log-rank P-values, and 95% confidence intervals (CIs) were calculated. Kaplan-Meier survival curves were generated to estimate survival probabilities, and statistical significance was assessed using the log-rank test. All statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp.) and GraphPad Prism version 9.0 (Dotmatics). $P<0.05$ was considered to indicate a statistically significant difference

Results

EZH2 mRNA expression and prognosis in glioma. Analysis of TIMER 2.0 data revealed significantly elevated EZH2 mRNA expression in 19 cancer types, including glioblastoma, compared with normal tissues ($^{***}P<0.001$, Fig. 1A). Similarly, EZH2 expression was higher in glioma tissues than in normal brain tissues in the CGGA dataset ($^{***}P<0.001$, Fig. 1B). Using TCGA data, Kaplan-Meier analysis demonstrated that high EZH2 mRNA expression was significantly associated with shorter OS, DSS and PFI in patients with glioma ($P<0.001$, Fig. 1C-E).

Correlation between EZH2 mRNA expression and clinicopathological features. Univariate Cox analysis of 673 TCGA patients with glioma indicated that high EZH2 expression was significantly associated with age, WHO grade and sex (Table I). EZH2 expression was significantly higher in isocitrate dehydrogenase (IDH) wild-type tumors than in IDH-mutant tumors, and lower in tumors with 1p/19q co-deletion (Table I).

Association between EZH2 protein expression and WHO grade. WHO grade is closely associated with patient prognosis, with higher grades indicating significantly worse outcomes than lower grades. In the analysis of the present study a total

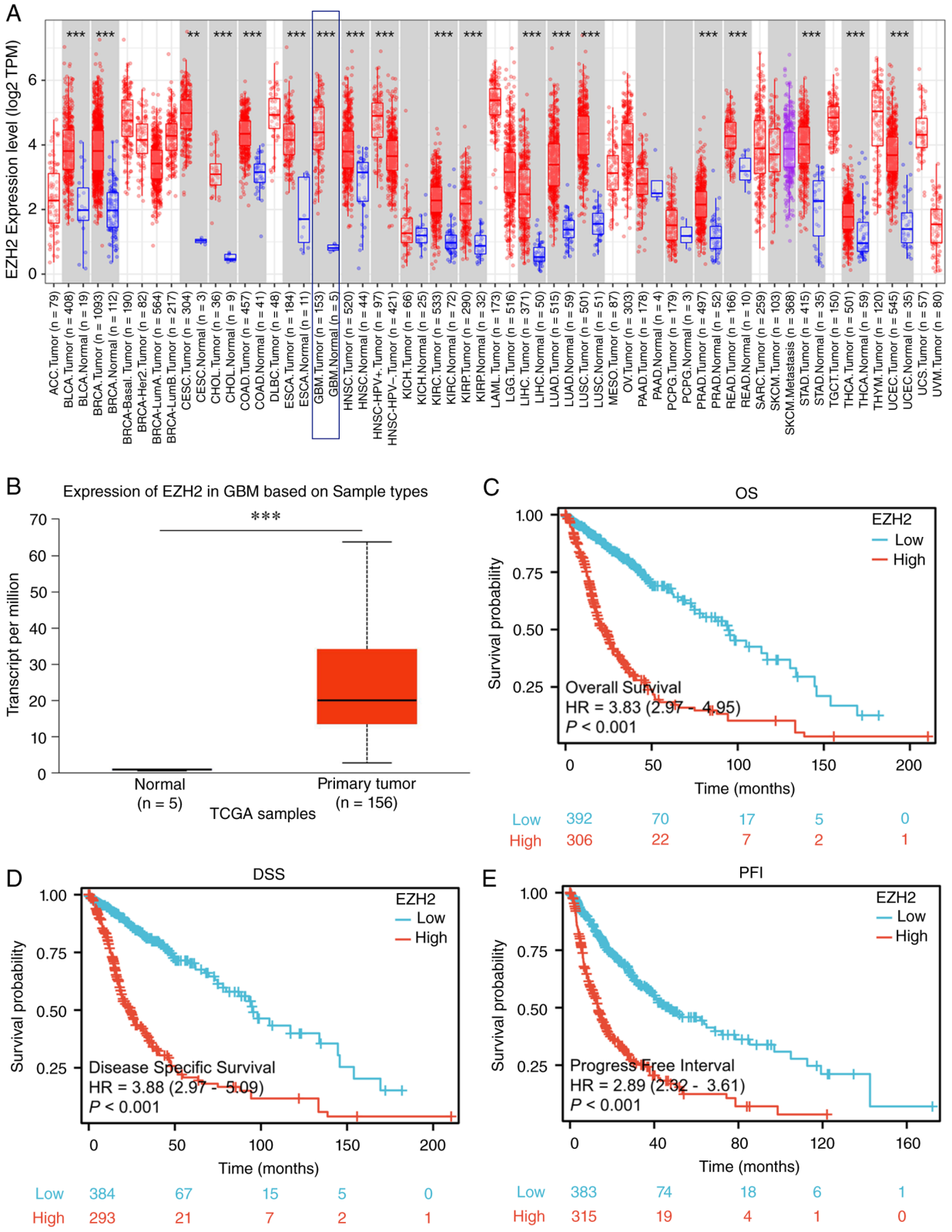

Figure 1. Public database analysis of EZH2 expression in patients with glioma. (A) Expression of EZH2 at the mRNA level in Pan cancer in an analysis using the timer 2.0 database. (B) In the TCGA database, EZH2 mRNA levels were found to be significantly higher in 156 primary tumor tissues compared with 5 normal brain tissues. (C-E) Kaplan-Meier curves of (C) OS, (D) DSS and (E) PFI showed that EZH2 mRNA levels were significantly associated with the survival of patients with glioma. **P<0.01 and ***P<0.001. EZH2, enhancer of zeste homolog 2; TCGA, The Cancer Genome Atlas; OS, overall survival; DSS, disease-specific survival; PFI, progression-free interval.

of 147 glioma tissue samples, the correlation between EZH2 expression and WHO grade was assessed using immunohistochemical staining. The results demonstrated that EZH2 was predominantly localized in the nucleus and its expression increased markedly with advancing WHO grade (Fig. 2A). Notably, EZH2 protein expression was significantly higher

Table I. Association between EZH2 mRNA expression and clinicopathological characteristics of glial patients.

Clinicopathological characteristics	Expression level of EZH2		Pearson χ^2	P-value
	Low, n (%)	High, n (%)		
n	336	337		
Age, years			27.222	<0.001
≤60	294 (43.7)	240 (35.7)		
>60	42 (6.2)	97 (14.4)		
Sex			0.940	0.332
Male	188 (27.9)	201 (29.9)		
Female	148 (22)	136 (20.2)		
WHO grade			165.320	<0.001
G1	31 (4.6)	27 (4.0)		
G2	169 (25.1)	47 (7.0)		
G3	118 (17.5)	121 (18.0)		
G4	18 (2.7)	142 (21.1)		
IDH status			110.400	<0.001
WT	54 (8.1)	183 (27.6)		
Mut	279 (42)	148 (22.3)		
1p/19q codeletion, n (%)			51.027	<0.001
Non-codel	210 (31.5)	288 (43.2)		
Codel	125 (18.7)	44 (6.6)		

EZH2, enhancer of zeste homolog 2; WHO, World Health Organization.

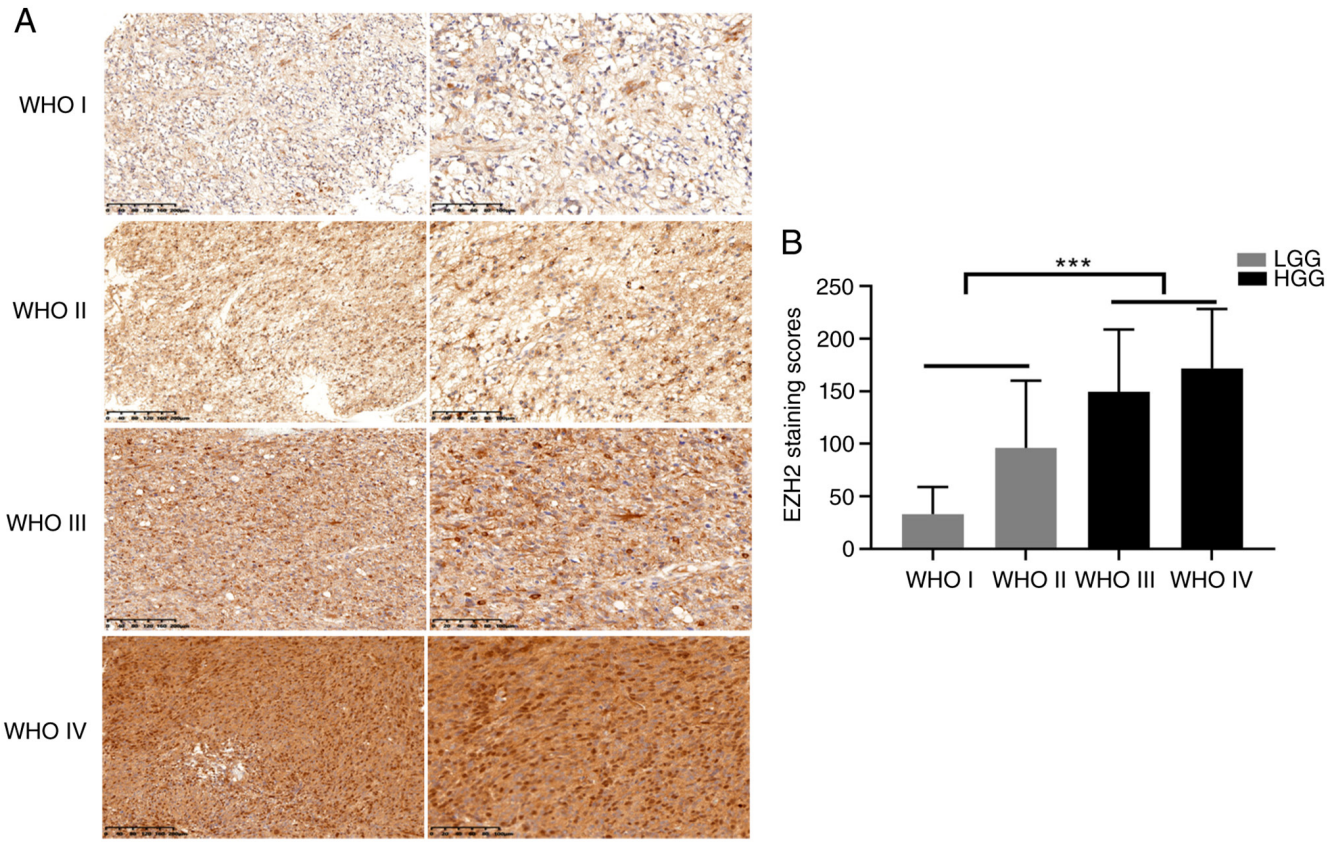

Figure 2. Analysis of EZH2 expression in all grades of glioma tissues. (A) Immunohistochemical staining was performed to detect EZH2 protein expression in glioma tissues of each WHO grade. (Magnification, x200 μm on the left, x100 μm on the right). (B) Results of quantitative expression of EZH2 by Immunohistochemistry in WHO grade glioma. ***P<0.001. EZH2, enhancer of zeste homolog 2; WHO, World Health Organization.

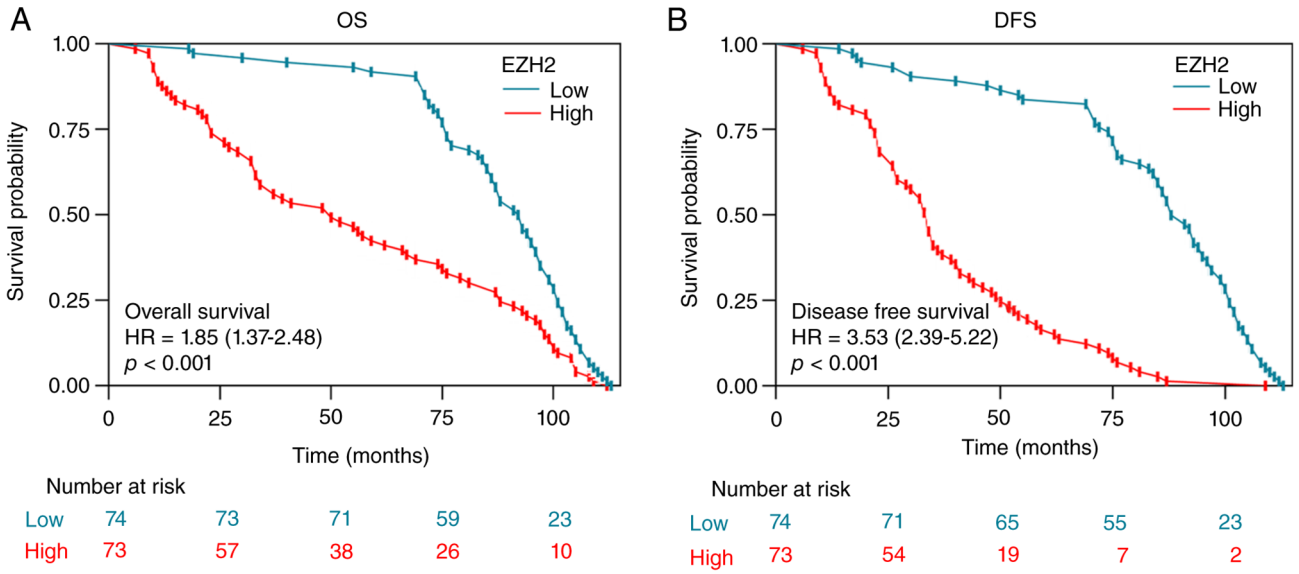

Figure 3. Analysis of EZH2 protein expression and patient prognosis in patients with glioma. (A and B) The Kaplan-Meier curves for (A) OS and (B) DFS demonstrated a significant association between EZH2 protein expression levels and the survival of patients with glioma. EZH2, enhancer of zeste homolog 2; OS, overall survival; DFS, disease free survival; HR, hazard ratio.

in the WHO high-grade group than in the LGG (***P<0.001, Fig. 2B), indicating a positive association between elevated EZH2 expression, advanced tumor grade and poorer prognosis.

Association between EZH2 expression levels and patient prognosis in glioma tissue samples. Clinical data from 147 patients with glioma were analyzed using Kaplan-Meier survival curves and the log-rank test. The results demonstrated that patients in the high EZH2 expression group had significantly shorter OS and DFS than those in the low expression group (P<0.001, Fig. 3A and B).

The relationship between EZH 2 expression levels in glioma tissue samples and the clinicopathological features of patients with glioma. Analysis of clinicopathological parameters from 147 patients with glioma revealed a significant correlation between high EZH2 protein expression and age, WHO grade and recurrence, but not gender (Table II). These findings were consistent with data derived from the TCGA database, further supporting the prognostic relevance of EZH2 expression. Additionally, univariate Cox regression analysis indicated that EZH2 expression, sex, age and WHO grade were all associated with patient outcomes (Table III). Furthermore, multivariate Cox regression analysis confirmed that EZH2 expression, age and WHO grade were independent risk factors for survival in patients with glioma (Table III).

Discussion

Gliomas represent the most prevalent primary tumors of the central nervous system (1,30,31), with glioblastoma accounting for 60-75% of cases (32). Despite the establishment of combined surgical resection, localized fractionated radiotherapy, and adjuvant temozolomide as the standard first-line therapy, the 5-year survival rate for patients with glioblastoma remains strikingly low at 6.8% (33,34). This highlights the critical need to identify novel and reliable prognostic biomarkers to improve survival prediction and optimize therapeutic strategies for patients with glioma.

EZH2, a histone methyltransferase, is frequently overexpressed in multiple cancers and is consistently associated with poor prognosis (35-38). Mechanistically, EZH2 exerts its oncogenic effects through both canonical and non-canonical pathways. Canonically, it catalyzes H3K27 trimethylation (H3K27me3), leading to transcriptional silencing of tumor suppressor genes such as CDKN2A, CDKN1C and RUNX3 (39). Non-canonically, EZH2 can regulate gene expression or methylate non-histone proteins independently of its methyltransferase activity (40). Moreover, crosstalk between EZH2 and several signaling pathways, including PI3K/AKT and Notch, has been implicated in pancreatic neuroendocrine neoplasm cell proliferation, maintenance of stemness, and therapy resistance (41). Previous studies have shown that EZH2 inhibition impairs glioma cell self-renewal *in vitro*, reduces tumorigenicity *in vivo*, and enhances chemo-radio-sensitivity, ultimately improving survival (42-44). Despite these findings, the association between EZH2 expression and key clinicopathological features, including glioma grade, IDH mutation status, 1p/19q co-deletion, and prognosis, had not been comprehensively characterized prior to the present study.

In the present study, EZH2 expression in glioma was systematically evaluated using both public databases and the present clinical cohort. Analysis of TIMER2.0 and TCGA data demonstrated that EZH2 mRNA expression was significantly upregulated in glioma tissues compared with normal brain tissue and was highly expressed across multiple cancer types. In the TCGA cohort, high EZH2 mRNA expression was strongly associated with higher WHO grade, aggressive histological subtypes, IDH wild-type status, and the absence of 1p/19q co-deletion. Kaplan-Meier analysis showed that elevated EZH2 mRNA expression was associated with shorter OS, DSS, and PFI. To validate these findings at the protein

Table II. Relationship between the protein expression of EZH2 and clinicopathological characteristics of patients with glioma (n=147).

Clinicopathological characteristics	Total, n	Expression level of EZH2		Pearson χ^2	P-value
		Low, n (%)	High, n (%)		
n		74	73		
Sex				0.396	0.529
Male	95	46 (48.4)	49 (51.6)		
Female	52	28 (53.8)	24 (46.2)		
Age, years				5.961	0.015
≤40	61	38	23		
>40	86	36	50		
WHO stage				35.277	<0.001
G1 + G2	110	71 (48.3)	39 (26.5)		
G3 + G4	37	3 (2.0)	34 (23.1)		
Recurrence rate				88.226	<0.001
No recurrence	65	61 (41.5)	4 (2.7)		
Recurrence	82	13 (8.8)	69 (46.9)		

EZH2, enhancer of zeste homolog 2; WHO, World Health Organization.

Table III. Analysis of prognostic parameters for overall survival of patients with glioma.

Clinicopathological characteristic	Univariate analysis		Multivariate analysis	
	P-value	HR (95% CI)	P-value	HR (95% CI)
EZH2 expression: High vs. low	<0.01	8.111 (3.962-16.606)	0.038	2.399 (1.048-5.492)
Sex: Male vs. female	0.041	0.532 (0.291-0.975)	0.274	0.705 (0.378-1.318)
Age, years: ≤40 vs.40	<0.01	1.034 (1.017-1.052)	0.001	1.032 (1.013-1.052)
WHO stage: G1 vs. G2 vs. G3 vs. G4	<0.01	4.669 (3.409-6.395)	<0.01	3.694 (2.557-5.338)

HR, hazard ratio; CI, confidence interval; EZH2, enhancer of zeste homolog 2; WHO, World Health Organization.

level, immunohistochemistry was performed on 147 glioma specimens spanning WHO grades I-IV. The results demonstrated that higher WHO grade was associated with increased EZH2 protein expression. Conversely, lower EZH2 expression was associated with more favorable pathological features, lower histological grade, reduced recurrence, and longer survival. Univariate Cox regression analysis identified EZH2 expression level, patient age, sex, and WHO grade as significant prognostic factors. Subsequent multivariate analysis confirmed that EZH2 expression, age, and WHO grade were independent predictors of OS in patients with glioma. Collectively, these findings indicate a strong association between elevated EZH2 expression and higher tumor grade, with increased expression levels predicting poorer prognosis.

Beyond its prognostic value, EZH2 is emerging as a promising therapeutic target. The EZH2 inhibitor tazemetostat has received FDA approval for epithelioid sarcoma and follicular lymphoma, and preclinical studies have evaluated its efficacy in glioma models (45,46). In glioblastoma cell lines and xenograft models, EZH2 inhibition suppresses proliferation, induces differentiation, and sensitizes tumors to temozolomide and radiotherapy (47,48). However, the clinical translation of EZH2 inhibitors for glioma faces considerable challenges, including the blood-brain barrier and intratumoral heterogeneity. Nevertheless, these findings support further exploration of EZH2 not only as a biomarker for patient stratification but also as a candidate for combination therapy with current standard-of-care regimens.

Limitations and future directions: Several limitations of the present study should be acknowledged. First, the molecular mechanisms by which EZH2 promotes glioma progression were not experimentally investigated. *In vitro* or *in vivo* functional assays were not performed (for example, knockdown or overexpression of EZH2) to establish causality or dissect the downstream signaling pathways. Second, multi-factor interaction analyses incorporating other clinically relevant molecular markers, such as MGMT promoter methylation and TERT mutations, were not conducted, as these data were not available for all patients in the present retrospective cohort. Consequently, the authors could not assess whether

EZH2 expression adds independent predictive value beyond these established markers or evaluate its role in treatment response prediction. Third, the tissue samples were obtained from a single commercial source (Shanghai Outdo Biotech Company), which may introduce selection bias and limit the generalizability of the findings of the present study to other populations or clinical settings. Finally, the retrospective design inherently carries the risk of unmeasured confounding. Future studies should prospectively validate the findings of the present study in larger, multi-center cohorts with comprehensive molecular profiling to enable robust multi-factor interaction analyses. Mechanistically, gain-of-function and loss-of-function approaches are urgently needed to elucidate the canonical and non-canonical pathways of EZH2 in glioma. Additionally, the therapeutic potential of combining EZH2 inhibitors with temozolomide and radiotherapy warrants further investigation, particularly in the context of overcoming chemo-radio-resistance.

In summary, the present study provided robust evidence that EZH2 expression is closely associated with glioma grade, molecular subtype and patient survival. The consistency between mRNA and protein expression data, its independent prognostic value in multivariate analysis, and its biological plausibility based on established mechanisms collectively support EZH2 as a clinically useful prognostic biomarker in glioma. Further independent validation and mechanistic studies are warranted to facilitate translation of these findings into clinical practice.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CP, WC and RG performed experiments and data analysis. JY, LW and LL assisted with data acquisition. CP, WC and RG contributed to statistical analysis, figure preparation and manuscript drafting. CP revised the manuscript. RG designed and supervised the present study. CP and RG confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Shanghai Outdo Biotech Company (approval no. HBraG149Su01). All tissue samples were provided by Shanghai Outdo Biotech Company, and written informed consent was obtained from all patients and/or their legal guardians prior to sample collection.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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