

Clinical characteristics and prognostic analysis of patients with HIV and glioma: A case series and literature review

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Abstract. Cerebral glial tumors have become increasingly common in human immunodeficiency virus (HIV)-positive patients. The present study aimed to report a series of such cases, explore their clinical and pathological characteristics and subject all the reported cases to a survival analysis. The characteristics, management and prognosis of 10 HIV-positive patients with brain gliomas enrolled in a single hospital were investigated in detail. Immunohistochemical assessment of CD31, CD68 and CD163 was performed in the 10 HIV-positive patients with glioma and 18 HIV-negative patients with glioma. The relevant literature was also reviewed using relevant search terms. The potential predictive factors were screened by univariate and multivariate logistic regression analyses, and a nomogram was established based on the potential predictive factors. A total of 50 patients, including the 10 primary cases, were included in the survival analysis. The median survival time was 9 months. The gliomas of HIV-negative patients had a lower cell count of CD163⁺ cells than those of HIV-positive patients. High CD4⁺ T-cell count and the use of highly active antiretroviral therapy (HAART) tended to increase the median survival duration, although not significantly according to the log-rank analysis. In the univariate analysis, only surgery, radiotherapy (RT) and World Health Organization (WHO) tumor grade had significant associations with overall survival. In the multivariate analysis, only RT and WHO grade were independent predictors. In conclusion, gliomas may occur more frequently in HIV-positive populations than is currently recognized. The survival duration of most HIV-positive patients with glioma is determined by the tumor rather than HIV status. Adjuvant radiotherapy and the WHO grade of the

glioma are predicted to be independent prognostic factors. Surgical resection followed by RT plus regular HAART is recommended for patients with glioma who are HIV-positive.

Introduction

Approximately 10% of patients with human immunodeficiency virus (HIV) develop intracerebral mass lesions during the course of the infection. Most of these lesions are found to be either primary central nervous system lymphoma (PCNSL) or toxoplasma encephalitis (TE), both of which are considered acquired immune deficiency syndrome (AIDS)-defining diseases by the Centers for Disease Control (1). However, HIV-independent cerebral tumors can also arise, albeit less commonly. Since 1996, the survival time after HIV infection has been prolonged as the use of highly active antiretroviral therapy (HAART) can reduce the occurrence of opportunistic infections (2). Thus, an increasing population may live to experience non-AIDS-defining malignancies, including brain glial tumors. Glioma, particularly glioblastoma multiforme (GBM), is the most common primary brain tumor in general adults, which also accounts for a large number of intracerebral masses in HIV-positive patients (3,4). It has been reported that the incidence of glioma is higher in HIV-positive patients than in the general population (5). However, the pathogenesis is unclear and an insufficient number of patients with such an occurrence has been previously studied and details published. The immune system in HIV-positive patients is defective, which may cause the tumor development processes of elimination, equilibrium and/or escape to be ineffective. This may result in the more frequent clinical presentation of tumors in patients at a younger age. HIV itself can also lead to tumor formation. Specifically, transcriptional transactivator may upregulate transforming growth factor- β (TGF- β) and platelet-derived growth factor (PDGF) signaling to induce cell proliferation. In addition, TGF- β signaling may be increased by the envelope protein gp120. The downstream effect of PDGF signaling may be enhanced by matrix protein p17 through activation of C-X-C motif chemokine receptors 1 and 2. Finally, tumor protein p53 may be inhibited by accessory protein negative factor, leading to increased mutagenesis and impaired DNA repair (6).

The present study reports on 10 HIV-positive patients with intracranial glial tumors, preliminarily explores the

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pathogenesis of these tumors, and summarizes previously reported cases in the literature, to further characterize their clinical and pathological features and identify the prognostic factors in this group of patients.

Materials and methods

Patient recruitment and data collection. Participants were recruited consecutively between April 2016 and December 2021 at the Department of Neurosurgery of Beijing Ditan Hospital, an infectious disease hospital affiliated with Capital Medical University (Beijing, China). A total of 10 HIV-infected patients with concurrent cerebral gliomas were retrospectively analyzed in the study. Their presentations, scans, CD4⁺ T cell counts, HIV loads, pathology, treatments and prognoses were collected and analyzed. Immunohistochemical assessment of CD31, CD68 and CD163 was performed in the 10 HIV-positive patients with glioma and 18 HIV-negative patients with glioma (Table SI). The CD4⁺ T cell counts and HIV load data of 33 patients with AIDS-related PCNSL (AR-PCNSL) and CD4⁺ T cell count data of another 17 HIV-negative patients with glioma (Tables SII and SIII) were compared with those of the HIV-positive patients with glioma. The study was approved by the Ethics Committee of Beijing Ditan Hospital.

Immunohistochemical staining. The protein expression levels of CD31, CD68, CD163, isocitrate dehydrogenase 1 (IDH1) and Ki-67 were assessed by immunohistochemistry. The tumor tissues excised during surgery were immediately placed in 10% formalin for fixation for 12 h at room temperature, processed by the automation-tissue-dehydrating machine according to the operation manual (HistoCore PEGASUS; Leica Microsystems, Inc.), followed by paraffin embedding and sectioning (4- μ m). The tissues were then immersed in blocking reagent (H₂O₂) for 30 min at room temperature (diluted to 3% with distilled water). The primary antibodies CD31 (cat. no. ZA-0568), CD68 (cat. no. ZM-0060), CD163 (cat. no. ZM-0428), IDH1 R132H mutation-specific (cat. no. ZM-0447) and Ki-67 (cat. no. ZM-0166) were purchased from ZSGB-BIO (OriGene Technologies, Inc.) and used at a dilution of 1:100. All tissue sections were incubated with primary antibody at 4°C overnight. A BOND Polymer Refine Detection secondary antibody (cat. no. DS9800; Leica Microsystems, Inc.) was then incubated with the tissue sections at room temperature for 30 min. Immunohistochemistry experiments were performed with a LEICA BOND-MAX automatic immunohistochemistry staining system. Immunostaining was assessed based on the number of positive cells in the tissues (magnification, x200 for CD31; magnification, x400 for IDH1, Ki-67, CD68 and CD163). A total of three different fields of view were randomly selected and observed under a Leica SP8 confocal microscope. The average of the combined counts was then calculated. The results were interpreted by two neuropathologists independently.

Data collection from PubMed. To gain an improved understanding of the relationship between clinical characteristics, including CD4⁺T cell count and HAART treatment, and the prognosis of this disease, the PubMed database was searched for articles published before February 2022 and the available

literature on gliomas in patients with HIV was reviewed. The search strategy was [(HIV) OR (AIDS)] AND [(glioma) OR (astrocytoma) OR (oligodendroglioma) OR (glioblastoma multiforme)]. Cases eligible for further analysis were required to meet the following criteria: i) History of HIV before the diagnosis of glioma; and ii) confirmed histopathological diagnosis of glioma. The selection flow chart of the literature search is presented in Fig. S1.

The demographics (age and sex), CD4⁺ T cell count, the time interval between tumor and HIV diagnosis, lesion location, treatment [surgical resection (SR), stereotactic biopsy (SB), radiotherapy (RT) and chemotherapy (CTh)], pathological diagnosis, World Health Organization (WHO) tumor grade, critical events (alive or dead and the cause of death), and overall survival (OS) were extracted from the included articles. For analysis, the CD4⁺ T cell count was classified into two groups with a cut-off value of 200 cells/ μ l for AIDS diagnosis, and the WHO glioma grade was classified into two groups, specifically low-grade for WHO grades 1 and 2, and high-grade for WHO grades 3 and 4. Five cases with no recorded survival time were excluded from the survival analysis.

Statistical analysis. SPSS statistical package (version 24.0; IBM Corp.) was used to perform the statistical analysis. The Shapiro-Wilk method was used to determine the normality of the continuous data. Unpaired Student's t-test was used to analyze the normally distributed continuous CD31⁺, CD68⁺ and CD163⁺ cell counts. Kruskal-Wallis H test followed by Dunn-Bonferroni tests was used to analyze the non-normally distributed continuous CD4⁺ T cell counts of the AR-PCNSL, HIV-glioma and non-HIV-glioma cohorts. Mann-Whitney U two-sample test was used to analyze the non-normally distributed continuous variable of HIV load between the AR-PCNSL and HIV-glioma cohorts. Spearman correlation was used to test associations between CD4⁺ T cell count, HIV load and the histological WHO grade of tumors, and between the CD163⁺ cell count and the IDH1, Ki-67, WHO grade and the OS. The Kaplan-Meier method was used to estimate survival curves and the log-rank test was used for comparison. Univariate and multivariate analyses were performed using Cox regression models to screen potential predictive factors. Statistically significant risk factors ($P < 0.05$) in the univariate analysis and clinically important factors were considered for further multivariate analysis. Finally, the significant risk factors based on the multivariate analysis were included in the nomogram construction. The 0.5 and 1-year OS probabilities were estimated using the nomogram. Concordance index (C-index) and area under the receiver operating characteristic curve (AUC) were used to evaluate discriminative ability. Calibration plots were used to evaluate calibrating ability. R software (version 3.6.2; <http://www.r-project.org/>) was used to establish the nomogram. $P < 0.05$ was considered to indicate a statistically significant difference, and all tests were two-sided.

Results

Characteristics of patients. The 10 HIV-positive patients with glioma who were enrolled in the present study comprised

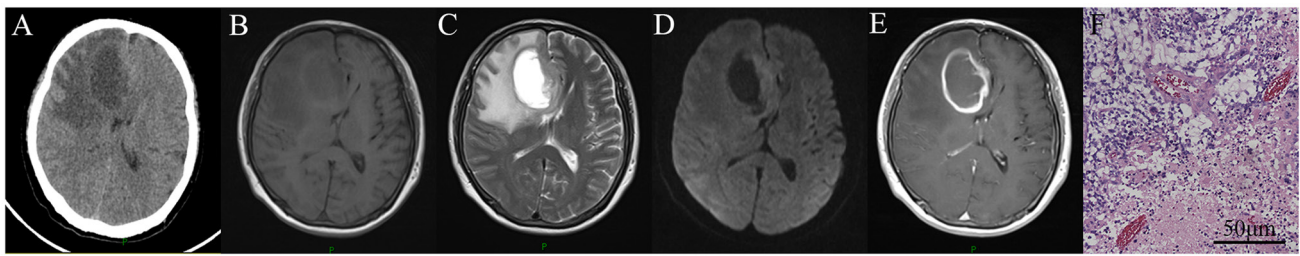


Figure 1. Radiological and pathological images of a 53-year-old male patient with human immunodeficiency virus and glioblastoma multiforme. (A) Computed tomography, (B) MRI-T1-WI, (C) MRI-T2-WI, (D) diffusion-WI and (E) contrast-enhanced T1-WI. (F) Hematoxylin and eosin staining. MRI, magnetic resonance imaging; WI, weighted imaging.

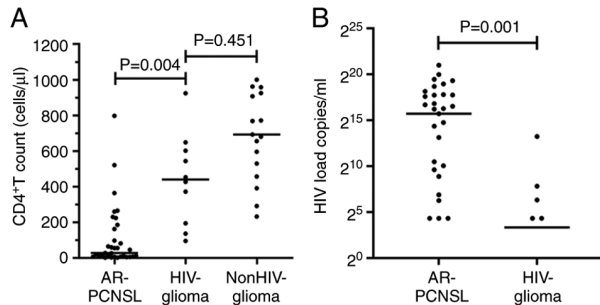


Figure 2. Comparison of CD4⁺ T-cell count and HIV load in different cohorts. (A) CD4⁺ T-cell count in HIV-positive patients with glioma (n=10) compared with patients with AR-PCNSL (n=33) and HIV-negative patients with glioma (n=17). (B) The HIV-positive glioma patient cohort had a lower HIV load than the patients with AR-PCNSL. HIV, human immunodeficiency virus; AR-PCNSL, acquired immunodeficiency syndrome-primary central nervous system lymphoma.

5 patients with GBM, 2 patients with anaplastic astrocytomas (AAs), 2 patients with anaplastic oligodendrogliomas and 1 case of astrocytoma. These patients represented 2.8% (10/3,631) of all patients infected with HIV, 12.5% (10/80) of all patients with HIV-associated focal mass lesions and 3.4% (10/294) of all patients with cerebral gliomas at the Department of Neurosurgery of Beijing Ditan Hospital. At the time of diagnosis, the patients comprised 9 men and 1 woman with a mean age of 36.7 years (range, 23-57 years). Seizures were reported by 4 patients at their initial presentation. The others presented with intracranial hypertension, limb hemiplegia or aphasia. All the brain lesions were supratentorial, with the majority located in the cerebral hemisphere, and only one in the paraventricular region and two at the basal ganglia. Lymphocyte profiles were available for all the patients. The median CD4⁺ T-cell count and HIV load at glioma presentation were 441 cells/µl (range, 96-925 cells/µl) and 10 copies/ml (range, 0-9,704 copies/ml), respectively. None of the patients had any pre-existing systemic tumors or had developed AIDS-defining diseases, such as Kaposi's sarcoma, PCNSL, TE or PML. In a number of these cases, the intracranial tumors were detected several years after HIV diagnosis, with an interval ranging from 50 days to 10 years, with a median of 4 years. All the patients received regular HAART treatment after the detection of HIV, with the exception of one who privately withdrew from the use of drugs after 2 years of regular medication and had a high HIV load of 9,704 copies/ml at glioma detection. The radiological and pathological images of the patients appeared

consistent with immunocompetent glioma (Fig. 1). The treatments received included SR, SB, RT and CTh, which differed from the standard algorithm for AIDS-defining diseases, such as the treatment of *Toxoplasma gondii* for TE and high-dose methotrexate-based chemotherapy for PCNSL. The therapeutic regimens of RT and CTh were applied according to the guidelines of the Chinese Glioma Cooperative Group, Society for Neuro-Oncology of China and Chinese Brain Cancer Association, and varied by taking into consideration the tumor grade, patient age, performance status and tumor molecular features (7). At the time of follow-up, half of the patients had died due to tumor progression. The median survival time was 7.5 months after tumor diagnosis. Patient characteristics, management and outcomes are summarized in Table I.

In the pathological analysis, there was a trend of longer survival in IDH1-positive patients compared with IDH1-negative patients (log-rank, $P=0.219$; Fig. S2A and B). In addition, there was no difference between the Ki-67 high expression group ($\geq 30\%$) and low expression group ($< 30\%$) (log-rank, $P=0.778$; Fig. S2C and D). The HIV-positive patients with glioma had a lower count of CD163⁺ cells compared with the 18 HIV-negative patients with glioma ($P=0.039$); however, no significant difference in CD68⁺ and CD31⁺ counts was detected ($P=0.162$ and $P=0.148$, respectively; Figs. S3 and S4). In further correlation analysis, no association between the CD163⁺ cell count and IDH1, Ki-67, WHO grade or OS was detected ($P=0.496$, $P=0.853$, $P=0.186$ and $P=0.159$, respectively). Compared with the 33 patients with AR-PCNSL, the HIV-positive patients with glioma had a higher CD4⁺ T-cell count (adjusted $P=0.004$; Fig. 2A) and lower HIV load ($P=0.001$; Fig. 2B). However, no significant difference in the CD4⁺ T-cell count of the HIV-positive patients with glioma and the 17 HIV-negative patients with glioma was observed (adjusted $P=0.451$; Fig. 2A). In addition, no significant association was identified between the CD4⁺ T-cell count and either the WHO histological grade of the tumor ($P=0.790$) or HIV load ($P=0.728$). Moreover, no association between CD4⁺ T-cell count and tumor outcome was identified ($P=0.815$), possibly because of the limited sample size. To explore the impact of CD4⁺ T-cell count on the prognosis of such patients and identify the other prognostic factors, the literature was searched to identify previous reports of HIV-positive patients with glioma.

Characteristics of previously published cases. A total of 658 articles were identified by a literature search for evaluation.

Table I. Characteristics of HIV-positive patients with brain glial tumors treated at Beijing Ditan Hospital.

No.	Age, years/ sex	CD4 ⁺ T-cell count, cells/ μ l	HIV load, copies/ml	Interval ^a / HAART, years	Tumor location	Clinical manifestation	Surgery	Tumor type	WHO grade	IDH1	Ki-67, %	RT	CTh	Survival, days	Cause of death
1	28/M	373	<20	5/1	R. fronto-temporal lobe	Intracranial hypertension	SR	AO	3	+	5	Y	Y	225	Tumor
2	33/M	96	228	3/3	L. basal ganglia	Limb hemiplegia and aphasia	SB	AA	3	-	5	N	N	31	Tumor
3	25/M	925	0	<1/<1	L. temporo-parietal lobe	Limb hemiplegia and aphasia	SR	GBM	4	-	40	N	N	30	Tumor
4	43/M	454	80	5/5	L. basal ganglia	Seizure and intracranial hypertension	SR	GBM	4	-	20	N	N	18	Tumor
5	57/M	137	0	6/6	L. paraventricular region	Limb hemiplegia and aphasia	SR	GBM	4	-	30	Y	Y	189	Alive
6	53/M	195	0	10/10	R. frontal lobe	Limb hemiplegia	SR	GBM	4	-	80	Y	Y	75+	Alive
7	40/M	602	<20	7/7	L. frontal lobe	Seizure	SR	AO	3	+	20	Y	Y	106+	Alive
8	23/M	428	9,704	3/2	L. frontal lobe	Seizure	SB	AA	4	+	25	Y	N	90+	Alive
9	36/F	545	0	3/2	R. fronto-temporal lobe	Intracranial hypertension	SR	GBM	4	+	10	N	N	30	Tumor
10	29/M	649	0	1/1	R. frontal lobe	Seizure	SR	A	2	+	3	Y	N	1,941+	Alive

^aInterval between HIV diagnosis and tumor presentation. HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; WHO, World Health Organization; IDH1, isocitrate dehydrogenase 1; RT, radiation therapy; CTh, chemotherapy; M, male; F, female; R, right; L, left; SR, surgical resection; SB, stereotactic biopsy; AO, anaplastic oligodendroglioma; AA, anaplastic astrocytoma; GBM, glioblastoma multiforme; A, astrocytoma; N, no; Y, yes.

Table II. HIV-positive patients with glioma reported in the literature.

First author/s, year	Age, years/sex	Interval ^a , years	CD4 count, cells/ μ l	HAART	Tumor location	Surgery	RT	CTh	Tumor type	WHO grade	Survival, days	Cause of death (Refs.)	
Gasnault <i>et al</i> , 1988	43/M	-	-	N	L. occipital lobe	SB	N	N	A	2	12	Intracerebral hematoma (8)	
Carrana <i>et al</i> , 1990 Ho <i>et al</i> , 1991 Kasantikul <i>et al</i> , 1992 Chappell <i>et al</i> , 1992 Chamberlain, 1994	19/M	-	-	N	L. parietal lobe	SB	Y	N	GBM	4	365	Tumor (9)	
	34/M	-	-	N	R. parietal lobe	SB	Y	N	AA	3	1,095	Tumor (10)	
	37/M	2	-	N	L. temporal lobe	SB	N	N	AA	3	30	CMV (11)	
	32/M	0.17	257	N	L. parieto-occipital lobe	SB	N	N	AA	3	3	Tumor (12)	
	-	-	-	N	-	SB	-	-	A	2	555	- (1)	
Moullignier <i>et al</i> , 1994	32/M	2	-	N	R. temporal lobe	SR	Y	Y	AA	3	570	Tumor (1)	
	38/M	4	-	N	R. frontal lobe	SR	Y	Y	GBM	4	300+	Alive	
	48/M	0	80	N	Bilateral frontal lobe	SB	N	N	GBM	4	180	Tumor (3)	
	30/M	1.08	605	N	R. parietal parasagittal	SB	N	N	A	2	- ^b	-	
	43/M	0.25	200	N	L. parieto-occipital lobe	SB	N	N	A	2	11	Pulmonary embolism	
Gervasoni <i>et al</i> , 1995	34/M	0	417	N	Subthalamic	SB	Y	N	A	2	210	Tumor (13)	
	-	-	54	N	L. parietal lobe	SB	N	N	AA	4	10	Tumor	
	-	-	54	N	L. parietal lobe and corpus callosum	SB	Y	N	A	2	270	Tumor	
	-	-	405	N	L. thalamus	SB	N	N	A	1	365	PCP	
	-	-	405	N	L. paraventricular parieto-occipital region	SB	Y	N	A	2	540+	Alive	
Neal <i>et al</i> , 1996	35/M	2	280	N	L. temporal lobe	SB	N	N	GBM	4	60	Tumor (14)	
Tacconi <i>et al</i> , 1996	22/M	-	-	N	L. temporal lobe	SB	Y	N	A	2	600	Tumor (4)	
	32/M	-	-	N	L. frontal lobe	SB	Y	N	A	2	300+	Alive	
	44/M	-	-	N	R. basal ganglia	SB	Y	Y	AA	3	210	PCP	
	38/M	-	-	N	R. frontal lobe	SB	Y	N	A	2	180+	Alive	
	28/M	-	270	N	-	SB	Y	N	A	2	270	Tumor (15)	
Monforte <i>et al</i> , 1997	34/M	-	436	N	-	SB	Y	N	A	2	450+	Alive	
	36/M	6	112	N	-	SRx2	Y	Y	GBM	4	270	- (5)	
	60/M	11	-	N	-	SB	Y	Y	GBM	4	450+	Alive	
	38/F	0	490	N	-	Necropsy?		N	N	GBM	4	1	Tumor
	44/M	4	-	Y	-	SR	Y	Y	GBM	4	270	-	
Blumenthal <i>et al</i> , 1999	41/M	11	408	N	-	SR	Y	Y	GBM	4	90	Tumor	
	38/M	0	225	N	-	SR	Y	N	A	2	4,320+	Alive	

Table II. Continued.

First author/s, year	Age, years/sex	Interval ^a , years	CD4 count, cells/ μ l	HAART	Tumor location	Surgery	RT	CTh	Tumor type	WHO grade	Survival, days	Cause of death	(Refs.)
Vannemreddy <i>et al</i> , 2000	29/M	-	-	N	Corpus callosum	SB	Y	N	GBM	4	120	Tumor	(16)
Wolff <i>et al</i> , 2002	31/M	-	-	N	Brainstem	SB	N	N	GBM	4	60	Tumor	(17)
Corti <i>et al</i> , 2004	31/F	-	42	Y	R. frontal lobe	SR	N	N	O	2	840+	Alive	(18)
Hall and Short, 2009	33/M	3	610	Y	L. frontal lobe	SRx2	Y	Y	GBM	4	390	Tumor	(19)
	50/F	10	600	Y	R. frontal lobe	SR	N	N	GBM	4	780+	Alive	
	43/M	-	400	Y	R. temporal lobe	SRx2	Y	Y	GBM	4	365	Tumor	
	42/F	-	-	N	L. basal ganglia	SB	N	N	GBM	4	60	Tumor	
	55/M	3	423	Y	Brainstem	SB	N	N	AA	3	30+	Alive	(20)
Brassco <i>et al</i> , 2013	16/F	16	-	-	Both frontal lobes	SB	Y	Y	GBM	4	90	Tumor	(21)
de Oliveira <i>et al</i> , 2014	42/F	0.5	66	Y	L. fronto-temporal lobe	Necropsy	N	N	GBM	4	30	Tumor	(22)
Wang <i>et al</i> , 2018	53/M	-	-	-	L. temporal lobe	SR	N	Y	GBM	4	240	-	(23)
	46/M	4	-	Y	R. parietal lobe	SR	Y	Y	GBM	4	450+	Alive	
Jokonya <i>et al</i> , 2018	29/F	-	81	Y	-	-	-	-	A	2	- ^b	-	(24)
	47/M	-	530	Y	-	-	-	-	A	2	- ^b	-	
	52/M	-	530	Y	-	-	-	-	GBM	4	- ^b	-	
	57/M	-	240	N	-	-	-	-	GBM	4	- ^b	-	

^aInterval between HIV diagnosis and tumor presentation; ^bcases removed from the survival analysis due to the lack of survival information. HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; RT, radiation therapy; CTh, chemotherapy; WHO, World Health Organization; M, male; F, female; N, no; Y, yes; R, right; L, left; SB, stereotactic biopsy; SR, surgical resection; A, astrocytoma; GBM, glioblastoma multiforme; AA, anaplastic astrocytoma; O, oligodendroglioma; PCP, *Pneumocystis carinii* pneumonia; CMV, cytomegalovirus.

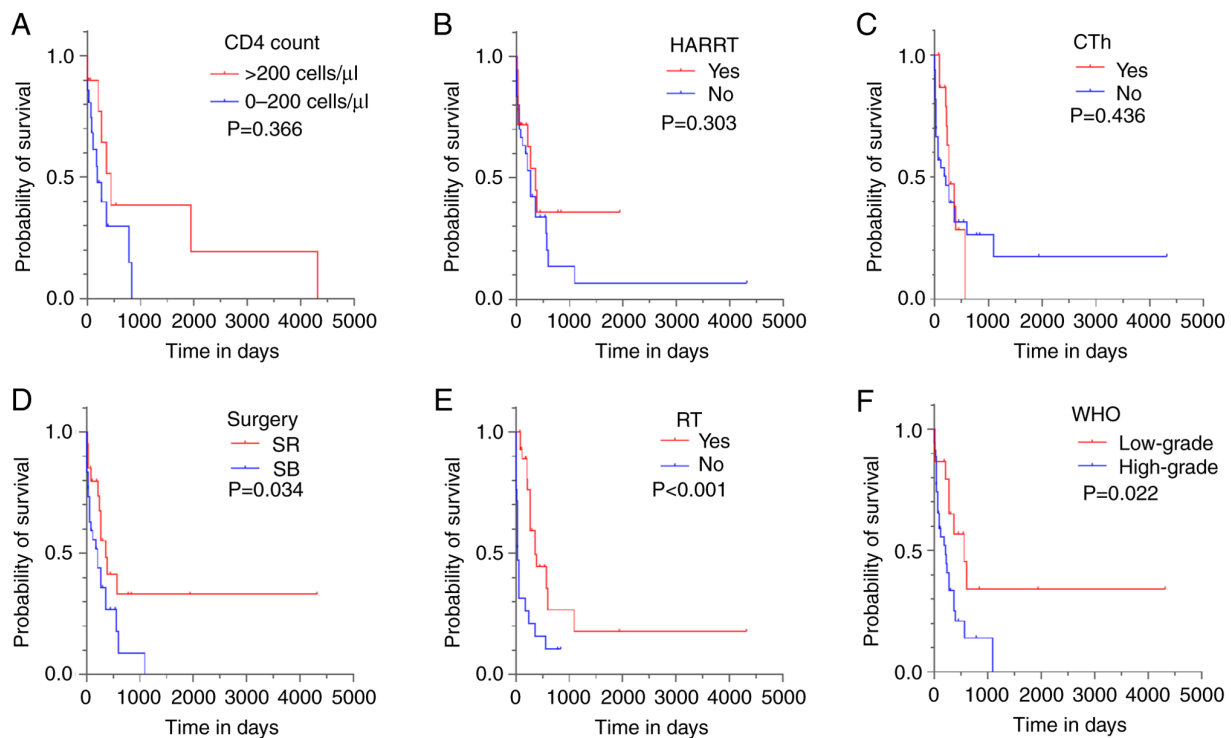


Figure 3. Kaplan-Meier curves for OS based on clinical parameters. Effects of different clinical parameters on the OS of human immunodeficiency virus-positive patients with glioma. Log-rank tests and Kaplan-Meier curves were used to compare differences between subgroups with regard to (A) CD4⁺ T-cell count, (B) HAART, (C) CTh, (D) surgery type, (E) RT and (F) WHO grade. OS, overall survival; HAART, highly active antiretroviral therapy; CTh, chemotherapy; SR, surgical resection; SB, stereotactic biopsy; RT, radiotherapy; WHO, World Health Organization.

Following selection according to the PRISMA guidelines, 21 publications from 1988 to 2018 were included (1,3-5,8-24), including 45 cases of gliomas with HIV infection (Table II). Among these tumors, there were 21 (46.6%) GBMs, 16 (35.6%) astrocytomas, 7 (15.6%) AAs and 1 (2.2%) oligodendroglioma. The mean age of the patients was 38.4 years (range, 16-60 years). Among the 40 patients whose sex was reported, 33 (82.5%) were male and the other 7 were female (17.5%). Patients were diagnosed HIV-positive a mean of 3.8 years (range, 0-16 years) prior to tumor presentation. At the time of glioma diagnosis, the mean CD4⁺ T-cell count was 316.2±189.9 cells/μl (range, 42-610 cells/μl). Most of the gliomas were located in the cerebral hemisphere. More than half of these patients (29/45, 64.4%) died during the follow-up period. Among the patients for which the cause of death was recorded, all but 5 died from the progressive effect of the brain tumor (20/25, 80%). In addition, 2 patients died from surgical complications, specifically, postoperative pulmonary embolism and intracerebral hematoma. The other 3 patients died due to opportunistic AIDS-associated infections: *Pneumocystis carinii* pneumonia in 2 cases and cytomegalovirus in 1 case. The 45 reviewed cases are summarized in Table II.

The mean OS of these patients was 23.7 months, whereas the median survival time was 9 months. This was slightly higher than that of the primary patient cohort, perhaps due to the lower proportion of high-grade gliomas (27/40, 67.5% vs. 9/10, 90%). A total of 50 cases, including the 10 cases reported in the present study and 40 cases in the published articles, excluding the 5 cases for which no survival time

was reported, were further subjected to a survival analysis. Seven parameters, namely the age of onset, CD4⁺ T-cell count (0-200 and >200 cells/μl), HAART treatment (no/yes), surgery (SB/SR), RT (no/yes), CTh (no/yes), and WHO grade (low-grade/high-grade) were analyzed for their association with OS.

CD4⁺ T-cell count and HAART. Patients were classified into two cohorts based on CD4⁺ T-cell count (0-200 and >200 cells/μl) and HAART (no/yes). The median survival was 180±89 days for patients with a low CD4⁺ T-cell count (n=10) and 270±75 days for patients with a high CD4⁺ T-cell count (n=21). The median survival was 365±109 days for patients treated with HAART (n=18) and 270±47 days for patients not treated with HAART (n=30). There was a trend of increased median survival with higher CD4⁺ T-cell count and HAART treatment; however, no statistically significant difference was detected between the subgroups according to the log-rank analysis of Kaplan-Meier curves (P=0.366 and P=0.303, respectively; Fig. 3A and B). The additional univariate analysis also found no statistically significant relationship of CD4⁺ T-cell count and HAART with OS (P=0.381 and P=0.318, respectively; Table III). However, in clinical practice, HAART is considered an important therapy for such patients. Therefore, this parameter was included in further multivariate Cox regression models.

Onset age, surgery, RT, CTh and WHO grade. Univariate analysis showed that onset age and CTh did not influence OS (P=0.534 and P=0.451, respectively; Table III). In addition, no

Table III. Univariate and multivariate analyses for risk factors of overall survival.

Variables	Subgroup	Frequency, n (%)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Onset age	-	-	0.988 (0.952-1.026)	0.534	-	-
CD4	0-200	10 (32.3)	0.659 (0.259-1.675)	0.381	-	-
	>200	21 (67.7)			-	-
HAART	No	30 (62.5)	0.674 (0.318-0.674)	0.318	0.582 (0.189-1.795)	0.346
	Yes	18 (37.5)				
Surgery	SB	28 (58.3)	0.460 (0.217-0.976)	0.043	0.548 (0.185-1.623)	0.278
	SR	20 (41.7)				
RT	No	28 (57.1)	0.257 (0.124-0.532)	<0.001	0.210 (0.092-0.480)	<0.001
	Yes	21 (42.9)				
CTh	No	33 (67.3)	0.739 (0.337-1.622)	0.451	-	-
	Yes	16 (32.7)			-	-
WHO grade	Low	15 (30.0)	2.455 (1.089-5.535)	0.030	3.079 (1.270-7.464)	0.013
	High	35 (70.0)				

HR, hazard ratio; HAART, highly active antiretroviral therapy; SB, stereotactic biopsy; SR, surgical resection; RT, radiation therapy; CTh, chemotherapy; WHO, World Health Organization.

trend of longer survival was observed in patients who received adjuvant therapy with CTh (log-rank $P=0.436$; Fig. 3C). The log-rank analysis of Kaplan-Meier curves based on surgery, RT and WHO grade showed significant differences between the subgroups ($P=0.034$, $P<0.001$ and $P=0.022$, respectively; Fig. 3D-F). In the univariate analysis, these three parameters also exhibited significant differences ($P=0.043$, $P<0.001$ and $P=0.030$, respectively).

Parameters related to OS. The three significant parameters, along with HAART, were included in the multivariate Cox regression model. Only RT and WHO grade were independent prognostic parameters ($P<0.001$ and $P=0.013$, respectively). High WHO tumor grade was identified as a factor that increased the risk of death by 3.079-fold with a 95% CI of 1.270-7.464. In addition, RT substantially reduced the risk of death by 0.210-fold (95% CI, 0.092-0.480).

Nomogram construction. A nomogram (Fig. 4A) for predicting the 0.5- and 1-year survival rates of such patients was established based on HAART (no/yes), surgery (SB/SR), RT (no/yes) and WHO grade (low-grade/high-grade). The nomogram had a high C-index of 0.774 (95% CI, 0.703-0.845) for assessment of the predictive model. Calibration plots and receiver operating characteristic curves for the nomogram model were established. The calibration curves indicated that the predicted 0.5- and 1-year survival rates were consistent with the actual results in the cohort (Fig. 4B and C). The AUC value of the nomogram for 0.5-year survival was 0.931 and for 1-year survival was 0.787 (Fig. 4D), suggesting that the model had good predictive ability.

Discussion

Neurological involvement is increasingly common in HIV-positive patients. It has been reported that 40-60% of patients with AIDS have concurrent neurological disorders (25). In addition to the most commonly identified focal intracerebral pathological entities, which include cryptococcosis, tuberculoma, PML, PCNSL and TE, other entities should be considered in the differential diagnosis of lesions that affect the central nervous system (CNS) in HIV-positive patients due to divergent treatment options and prognosis. The survival duration of patients with HIV has increased by a large margin due to the use of HAART which can reduce opportunistic infections. In 2017, the incidence rate of HIV infection in China was estimated to be 0.025-0.50 per 1,000 population (26). The prevalence of glioma in individuals who are not infected with HIV was reportedly 0.05-0.06% worldwide from 2010 to 2014 (7,27); by comparison, its prevalence in HIV-positive individuals in the present study was ~2.8%, which is considerably higher than that in the immunocompetent population. Among patients with HIV-related focal mass lesions, glioma was detected 6% in two cohorts in the 1990s before the utilization of HAART (3,4), and in 12.5% of the patients enrolled in the current study. These data indicate that the presence of glioma in HIV-positive patients with focal mass lesions may be more common than is currently recognized, particularly in the era after the introduction of HAART. This may be due to the survival time after infection with HIV being prolonged (2).

The pathogenesis of glioma in HIV-positive individuals was explored in the present study via analysis of the

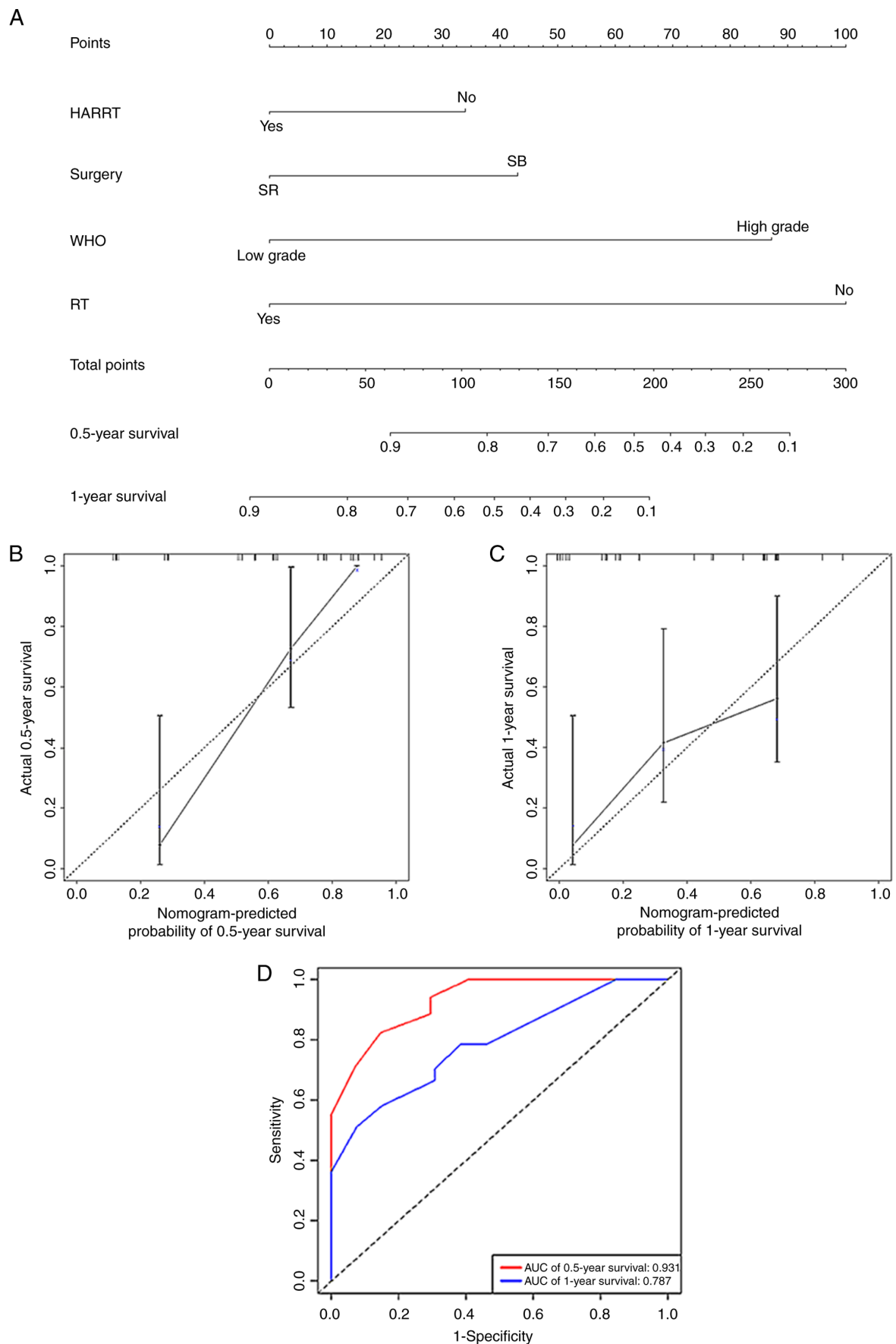


Figure 4. Nomogram construction, calibration plot and ROC curves of the nomogram model for human immunodeficiency virus-positive patients with glioma. (A) Nomogram for the prediction of 0.5- and 1-year survival rates of patients based on four independent prognostic factors: HAART, surgery type, WHO grade and RT. Calibration plots of the nomogram model for (B) 0.5 and (C) 1-year survival. (D) ROC curves of the nomogram model. ROC, receiver operating characteristic; HAART, highly active antiretroviral therapy; WHO, World Health Organization; SR, surgical resection; SB, stereotactic biopsy; RT, radiotherapy; AUC, area under the receiver operating characteristic curve.

macrophage markers CD68 and CD163, and the endothelial cell marker CD31. The gliomas of HIV-positive patients had a lower cell count of CD163⁺ cells but no difference in CD68⁺ and CD31⁺ cell counts compared with those of HIV-negative patients. CD163 is a differentiation marker of M2 phenotype tumor-associated macrophages (TAMs). Therefore, the results suggest that HIV-positive glioma may have a lower proportion of M2-phenotype TAMs which are considered to create a supportive stroma for tumor growth (28). In a previous study, CD163 expression was found to have a positive association with the malignant grade of glioma and IDH wild-type glioma, and higher CD163 expression indicated a significantly poor survival in patients with gliomas (28). In the patients of the present study, however, no association between CD163⁺ cell count and IDH1, Ki-67, WHO grade or OS was detected, possibly because of the limited sample size. Further analysis with a larger sample size is necessary to further investigate this.

In the total cohort in the present study, the majority of deaths were tumor-related (25/30, 83.3%), and the median survival time was only 9 months, which is much lower than that of immunocompetent patients with glioma. The poor prognosis of these patients may be due to the presumptive diagnosis of PCNSL or TE for HIV-positive patients with focal cerebral mass lesions. These patients received empiric treatment, instead of undergoing diagnosis by biopsy or resection surgery, particularly when the CD4⁺ T lymphocyte count was <200 cells/ μ l. The poor prognosis of these cases may be associated with a delay in the establishment of the correct diagnosis and ineffective empiric treatment, which caused the optimal opportunity for the most appropriate therapy to be missed. The establishment of a correct diagnosis is crucial before the initiation of further treatment. Therefore, in atypical cases or cases with no clinical or neuroradiological remission following empirical treatment for TE or PCNSL, an immediate aggressive approach is required to confirm the diagnosis.

Among all the cases in the present study, more patients who underwent conservative surgery via SB than SR (58.3 vs. 41.7%). According to log-rank analysis, SR resulted in a longer survival than SB ($P=0.034$). However, univariate and multivariate logistic regression analysis showed that surgery type was a predictive rather than an independent factor ($P=0.043$ and $P=0.278$, respectively). Postoperative RT was found to be an independent predictor ($P<0.001$) for OS. However, there was no trend of longer survival in patients who received CTh, possibly due to the limited number of samples from patients who received CTh (16 cases). These results indicate that SR followed by RT should be recommended for HIV-positive patients with glioma, as it is in the general population, particularly those with high-grade glioma, since a high tumor grade is also an independent risk factor for a shorter survival time. It is well known that the WHO grade in glioma plays an important role in prognosis prediction. However, it has not been well studied in HIV patients with concurrent glioma. Furthermore, not enough samples are available for a separate analysis for the rare concurrence of these two diseases. Also, previous studies have analyzed different graded of glioma together when looking for prognostic factors (29,30).

Most of the patients who participated in the survival analysis were younger than non-HIV infected glioma patients, with a mean age of ~37 years. At the time of glioma diagnosis, patients had a low CD4⁺ T-cell count with a median interval from HIV diagnosis of 3 years (50 days-11 years). This suggests that gliomas may occur earlier and more frequently in this population. Hajjar *et al* (31) showed that the incidence of non-AIDS-defining malignancies in patients with AIDS was 5.4-fold higher than that of the general population. This phenomenon may be due to the inhibitory effect of HIV infection on immune surveillance accelerating the development of malignant tumors (32). However, in the current univariate logistic regression analysis, CD4⁺ T-cell count and HAART status did not affect OS, and only a trend of increased median OS with high CD4⁺ T-cell count and HAART treatment was observed. This may be due to the majority of the patients succumbing to tumor-related factors (25/30, 83.3%) before lethal AIDS-related complications developed. However, there were some patients (3/50, 6%) who died due to AIDS complications. Therefore, it remains strongly recommended to regularly administer HAART, particularly protease inhibitors, to such patients to inhibit HIV replication and restore their immune function. Moreover, protease inhibitors can promote the inhibition of vascular endothelial growth factors and reduce angiogenesis, which is the main mechanism of malignant tumor growth (33).

The present study reports the largest series of patients with concurrent HIV infection and glioma. The clinical characteristics, management and prognosis of 10 patients were evaluated and the relevant literature on gliomas in HIV/AIDS patients was also reviewed. A total of 45 cases were extracted from 21 different articles and survival analysis with a sample of 50 cases was conducted. The analysis found that early age of onset and CTh were not associated with OS in this population, although these factors are commonly recognized as being beneficial in immunocompetent patients with glioma; this may be due to the limited sample size. At the initial diagnosis of glioma, the CD4⁺ T-cell count and HAART status were not found to affect OS, but a trend of increased median survival with high CD4⁺ T-cell count and HAART treatment was identified. Adjuvant RT and the WHO grade of the glioma were found to be independent prognostic factors. The results also indicate that glioma may occur more commonly than is currently recognized in this population. Therefore, in addition to the most common AIDS-defining diseases, glioma should be included in the differential diagnosis of contrast-enhanced CNS lesions in patients with HIV. When the diagnosis remains uncertain, SB or direct SR should be performed in selective cases to avoid inappropriate treatment. When the diagnosis of glioma is confirmed, the approach to the management of the tumor should be the same as that in the general population. SR followed by RT plus regular HAART is recommended for the treatment of HIV-positive patients with glioma. Tumor progression, as opposed to AIDS-related complications, determines patient survival and is the leading cause of mortality. Despite multiple aggressive therapies, the median survival time after diagnosis is <1 year. In the present study, a nomogram containing four factors that performed well in predicting the 0.5- and 1-year survival rates was developed. As evidenced by the calibration plot and its discriminative ability, the nomogram provides accurate survival probability, which

can assist clinicians, patients and families in decision-making and prognosis prediction for cases with concurrent HIV infection and glioma.

There are several limitations of the present study. This retrospective study was based on a small sample population due to the rare incidence of the concurrence of HIV and glioma. Patients who succumbed to HIV infection and surgical complications were not excluded, which may have contributed to some statistical bias. Future studies with larger cohorts and molecular pathological analyses are required to corroborate the effect of HIV infection on the development of gliomas. Furthermore, the nomogram model was based only on treatment strategies and WHO grade risk factors. Other promising risk factors, such as molecular features observed in immunocompetent glioma patients, may be included to further improve the performance of the model.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XD, TL and EF were responsible for conceptualization. XD and BL curated the data. TL and EF acquired funding. BL, TL and EF performed the investigations. XD and XZho were responsible for methodology. TL and EF performed project administration. XZhe and FW contributed to the acquisition of clinical data. XZho, HG and JC contributed to the acquisition of experimental data. XD was responsible for software. TL and EF supervised the study. EF validated and visualized the results. XD wrote the original draft of the manuscript, and BL and TL reviewed and edited the manuscript. EF and TL 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 study was approved by The Ethics Committee of Beijing Ditan Hospital (approval no. KY 2022-029-001). Written informed consent was obtained from all the patients included in the study.

Patient consent for publication

The patient or their parent, guardian or next of kin provided written informed consent for the publication of any associated data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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