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Prognostic analysis and nomogram construction for older patients with IDH-wild-type glioblastoma

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ABSTRACT

As many countries face an ageing population, the number of older patients with glioblastoma (GB) is increasing. Thus, there is an urgent need for prognostic models to aid in treatment decision-making and life planning. A total of 98 patients with isocitrate dehydrogenase (IDH)-wild-type GB aged ≥65 years were analysed from January 2012 to January 2020. Independent prognostic factors were identified by prognostic analysis. Using the independent prognostic factors for overall survival (OS), a nomogram was constructed by R software to predict the prognosis of older patients with IDH-wild-type GB. The concordance index (C-index) and receiver operating characteristic (ROC) curve were used to assess model discrimination, and the calibration curve was used to assess model calibration. Prognostic analysis showed that the extent of resection (EOR), adjusted Charlson comorbidity index (ACCI), O6-methylguanine-DNA methyltransferase (MGMT) methylation status, postoperative radiotherapy, and postoperative temozolomide (TMZ) chemotherapy were independent prognostic factors for OS. MGMT methylation status and subventricular zone (SVZ) involvement were independent prognostic factors for progression-free survival (PFS). A nomogram was constructed based on EOR, ACCI, MGMT methylation status, postoperative radiotherapy and postoperative TMZ chemotherapy to predict the 6-month, 12-month and 18-month OS of older patients with IDH-wild-type GB. The C-index of the nomogram was 0.72, and the ROC curves showed that the areas under the curve (AUCs) at 6, 12 and 18 months were 0.874, 0.739 and 0.779, respectively. The calibration plots showed that the nomogram was in good agreement with the actual observations in predicting the OS of older patients with IDH-wild-type GB. Older patients with IDH-wild-type GB can benefit from gross total resection (GTR), postoperative radiotherapy and postoperative TMZ chemotherapy. A high ACCI score and MGMT nonmethylation are poor prognostic factors. We constructed a nomogram including the ACCI to facilitate clinical decision-making and follow-up interval selection.

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1. Introduction

Glioblastoma (GB) is one of the most malignant primary central nervous system tumours. It often grows infiltrates and has strong invasiveness. The prognosis of GB patients is very poor. The 6-month overall survival (OS) is 42.4%, the median OS is only 14 months, and the 5-year OS is less than 5% [1]. The incidence rate of GB increases with age, with a median age of 65 years. According to The Central Brain Tumour Registry of the United States (CBTRUS) statistical data, in the tumour of neuroepithelial tissue, average annual age-specific incidence rates of glioblastoma were 12.98%, 15.29% and 9.06% in 65–74 years, 75–84 years and 85+ years, respectively. The estimated numbers of patients with glioblastoma were 6780 patients and 6950 patients in 2019 and 2020, respectively. Therefore, population ageing will lead to an increasing number of older patients being diagnosed with GB in the next few years [2]. The 2016 World Health Organization (WHO) classification of tumours of the central nervous system (CNS) classified GB into GB isocitrate dehydrogenase (IDH)-wild-type, IDH-mutant GB and GB not otherwise specified (NOS) [3]. A study showed that the 3-year OS rates of IDH1-mutant GB and IDH1-wild-type GB were 60% and 29%, respectively. The prognosis of IDH-wild-type GB is significantly worse than that of IDH-mutant GB [4]. The 2021 WHO classification of tumours of the CNS fifth edition regards IDH-wild-type GB as an independent type. Glioblastoma IDH mutant in the 2016 WHO CNS tumour classification was classified as adult diffusive gliomas in the 2021 WHO CNS tumour classification. Among them, IDH mutant astrocytoma with CDKN2A/B homozygous deletion was defined as WHO grade 4, even without microvascular proliferation and necrosis. IDH wild-type diffuse astrocytoma with EGFR amplification or TERT promoter mutation or +7/−10 chromosome copy number changes is defined as IDH-wild-type astrocytoma with glioblastoma molecular characteristics, WHO grade 4 [5]. A population-based study showed that the median OS of GB patients ≥65 years old was only 7.2 months, and the prognosis was significantly worse than that of nonolder patients with GB [6]. Because the organ functional reserve is reduced and the incidence of medical comorbidities is increased in older patients with GB [7], the tolerance to treatment of older patients with GB is reduced, the probability of adverse effects from therapy is higher [8], and a small portion of older patients with GB abandon further radiotherapy or chemotherapy after surgery [9,10], as well as probably a more aggressive biological phenotype in older GB. Differences in gene mutation and protein expression have been studied in younger (18–45 years) and elderly (≥70 years) patients with IDH-wild-type glioblastoma. TOPO1 is highly expressed in young patients, and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation often occurs in elderly patients. Mutations in PDGFRA, PTPN11, SMARCA4, BRAF and TP53 often occur in young patients [11]. A randomized phase III clinical trial indicated that short hypofractioned radiotherapy (40.5 Gy/15 fractions) combined with concurrent and up to 12 cycles of adjuvant temozolomide (TMZ) chemotherapy improved the OS and progression-free survival (PFS) of GB patients aged ≥65 years compared with patients who received only a short course of radiotherapy [12]. The Charlson comorbidity index (CCI) is an index for evaluating comorbidities. Its prognostic value is comparable to that of age and Karnofsky performance status (KPS) [13]. Charlson et al. established the age-adjusted Charlson comorbidity index (ACCI) to estimate the relative risk of death in patients undergoing surgery based on the CCI [14]. Nomograms have been used to evaluate the prognosis of GB [15–17]. However, the variable data used to construct the abovementioned nomograms for GB mainly came from nonolder patients with GB; thus, they are not representative enough for older patients with GB and have limited predictive value. There is an urgent need to build a nomogram prediction model based on the data of older patients with GB to predict the OS of these patients, improve the prediction performance of the individual survival rate, and provide consultation and risk assessment for treatment strategies and follow-up intervals. Hence, our study retrospectively analysed the clinical characteristics of older patients with IDH-wild-type GB, including comorbidities, histological and molecular pathological results, treatment methods and imaging features, identified important factors for predicting prognosis, and constructed a nomogram according to the independent prognostic factors identified to analyse the survival rate in older patients with GB.

2. Materials and methods

2.1. Selection of patients

This study included 98 older patients with IDH-wild-type GB treated at Xiangya Hospital of Central South University from January 2012 to January 2020. The inclusion criteria were as follows: 1) age ≥65 years; 2) received surgical treatment at Xiangya Hospital of Central South University; and 3) pathologically confirmed IDH-wild-type GB. This study strictly complied with the ethical requirements of the Helsinki Declaration and was approved by the ethics committee of Xiangya Hospital.

2.2. Pathological data

Before 2016, patients were diagnosed according to the 2007 WHO central nervous system tumour classification standard [18]. After 2016, patients were diagnosed according to the 2016 WHO classification of central nervous system tumours [3]. The expression of Ki67 and epidermal growth factor receptor (EGFR) was detected using immunohistochemistry (IHC). If the MGMT methylation status and IDH mutation status could not be detected by polymerase chain reaction (PCR), the results of IHC were used.

2.3. Treatment and data collection

The extent of resection (EOR) was assessed according to the Response Assessment in Neuro-Oncology (RANO) criteria [19] according to the T1 contrasted image in MRI before surgery and within 72 h of surgery or first early MRI after surgery. Tumour size was defined as the product of the maximum vertical diameter of the enhanced lesion (m^2), *EOR = preoperative lesion - postoperative*

lesion/preoperative lesion (%). According to the research of Lamborn et al. [20], gross total resection (GTR) was defined as resection greater than 90%, subtotal resection (STR) between 10% and 90% and biopsy less than 10%. The subventricular zone (SVZ) was defined as a 3–5 mm area from the lateral wall of the lateral ventricle [21]. Preoperative MRI was used to assess the involvement of the SVZ of the tumour, and contrast-enhancing tumour invasion of the SVZ in MRI T1 contrast-enhanced images was defined as SVZ involvement when the shortest distance from the tumour to the ventricle wall was less than 5 mm [22]. Some patients underwent intensity-modulated radiotherapy (IMRT) according to the European Organization for Research and Treatment of Cancer (EORTC) protocol [23], as well as concurrent and adjuvant TMZ chemotherapy. The following data were acquired for all patients: age at diagnosis, sex (male or female), KPS score before surgery (40–100), preoperative ACCI [24], expression of Ki67 and EGFR, IDH mutation status, MGMT methylation status, SVZ involvement status and progression and survival conditions. Tumour progression was diagnosed according to RANO criteria [19,25]. Complete response was defined as: complete disappearance of contrast-enhancing lesion sustained for 4 weeks, no new lesions; stable or improved nonenhancing (T2/FLAIR) tumour lesion; off corticosteroids or on physiologic replacement dose only; and stable or improved clinically; Partial response was defined as: ≥50% decrease in contrast-enhancing lesion sustained for 4 weeks, no progression of nonmeasurable disease; no new lesions; stable or improved non-enhancing (T2/FLAIR) tumour lesion without higher dose of corticosteroids compared with baseline scan; stable or reduced corticosteroid dose, and stable or improved clinically; Stable disease was defined as: does not qualify for complete response, partial response or progressive disease sustained for 4 weeks, stable nonenhancing (T2/FLAIR) tumour lesion without higher dose of corticosteroids compared with baseline scan and clinically stable status; Progressive disease was defined as: ≥25% increase in contrast-enhancing lesion sustained for 4 weeks, significant increase in nonenhancing (T2/FLAIR) tumour lesion without lower dose of corticosteroids; any new lesion; clear progression of nonmeasurable disease; or clear clinical deterioration due to tumour, not due to decrease in corticosteroid dose. PFS was calculated from the date of surgery to the date of the first progression of the tumour. OS was calculated from the date of surgery to the date of death. The end of follow-up was November 1, 2020, and the median follow-up time was 10.28 months.

2.4. Statistical analysis

The statistical software used was SPSS 26.0 (Chicago, IL) and R software 4.0.3. The measurement data are expressed as the mean ±

Table 1
Clinical characteristics of older patients with IDH-wild-type glioblastoma.

Characteristic		Number (N = 98)
Age		68.3 ± 3.8
Gender		
	Male	56 (57.1%)
	Female	42 (42.9%)
EOR		
	GTR	62 (63.3%)
	STR	36 (36.7%)
KPS		
	>60	78 (79.6%)
	≤60	20 (20.4%)
ACCI		
	≤6	87 (88.8%)
	>6	11 (11.2%)
Ki67		
	≤30%+	77 (78.6%)
	>30%+	21 (21.4%)
MGMT		
	Methylation	47 (48.0%)
	Unmethylation	51 (52.0%)
PostRT		
	Yes	55 (56.1%)
	No	43 (43.9%)
PostCT		
	Yes	58 (59.2%)
	No	40 (40.8%)
EGFR		
	–	9 (15.3%)
	+	50 (84.7%)
SVZ		
	non-involvement	49 (50.0%)
	Involvement	49 (50.0%)

EOR: Extent of resection; KPS: Karnofsky performance status; ACCI: Age-adjusted Charlson comorbidity index; MGMT: O6-methylguanine-DNA methyltransferase; GTR: Gross total resection; STR: Subtotal resection; PostRT: Postoperative radiotherapy; PostCT: Postoperative TMZ chemotherapy; EGFR: Epidermal growth factor receptor; SVZ: Subventricular zone.

standard deviation (x ± s), and the percentage (%) represents the count data. X-tile software (3.6.1; Yale University, USA) was used to select the best cut-off value. Survival curves were drawn by the Kaplan–Meier method and compared by the log-rank test. Factors with $P < 0.05$ in univariate Cox analysis were included in multivariate Cox analysis to identify independent prognostic factors. According to independent prognostic factors, the nomogram prediction model was constructed by using the R language rms package. The discrimination and calibration of the nomogram were evaluated by Harrell's concordance index (C-index) and the calibration curve. The standard of significant difference was $P < 0.05$.

3. Results

3.1. Patient characteristics and survival analysis

The characteristics of the patients are shown in Table 1. The age of the 98 patients with IDH-wild-type GB ranged from 65 to 79 years, with a median age of 68.3 years. A total of 63.3% of patients had GTR, and the rest had STR. It should be noted that only one older patient underwent biopsy and was diagnosed with IDH-mutant GBM. The best cut-off values for ACCI, KPS and the expression of Ki67 were 6, 60 and 30%, respectively, as calculated by X-tile software. Regarding preoperative ACCI, the base score was 4, and the maximum score was 8 when combined with other complications. There were 87 patients in the ACCI≤6 group and 11 patients in the ACCI>6 group. The patients had a minimum KPS score of 40 and a maximum of 90. The expression of Ki67 ranged from 4 to 60%, with 77 patients having a Ki67 index ≤30%+ and 21 patients having a Ki67 index >30%+. EGFR expression status was available in 59 patients, and EGFR expression was positive in 50 cases and negative in 9 cases. Fifty percent of patients had SVZ involvement, and 50% of patients did not have SVZ involvement. Patients with MGMT methylation accounted for 48.0% of the total, and patients with unmethylated MGMT accounted for 52.0% (Table 1). The MGMT methylation status and IDH mutation status of 93 patients were examined by PCR, and the MGMT methylation status and IDH mutation status of the remaining patients were examined by IHC. A total of 55 patients received IMRT, of whom 51 received conventional fractionated radiotherapy (60 Gy/2 Gy/30 f), 4 received short hypofractionated radiotherapy (40.5 Gy/2.7 Gy/15 f), and 1 refused further treatment after the radiation dose reached 37.5 Gy. A total of 58 patients received postoperative TMZ chemotherapy, of whom 11 received 2–5 TMZ chemotherapy cycles and 47 received 6 or more TMZ chemotherapy cycles. Thirty-one patients did not receive radiotherapy or chemotherapy. The median interval between surgery and chemoradiotherapy was 35 days, ranging from 18 to 250 days. According to the Common Terminology Criteria for Adverse Events 5.0 (CTC AE 5.0), we evaluated haematotoxicity and hepatorenal toxicity in patients with older IDH-wild type glioblastoma who were receiving chemoradiotherapy. Grade 1 leukopenia occurred in 23 cases, and grade 2 leukopenia occurred in 11 cases. Grade 1 thrombocytopenia had 10 cases, grade 2 thrombocytopenia had 7 cases, grade 1 anaemia had 8 cases, and grade 2 anaemia had 5 cases. Grade 1 increased blood creatinine was observed in 4 cases. Six patients had grade 1 hyperbilirubinemia. Eight patients had grade 1 increased alanine aminotransferase, and 7 patients had grade 1 increased aspartate aminotransferase.

3.2. Survival analysis

Kaplan–Meier analysis and the log-rank test showed that patients with GTR ($P = 0.011$), a Ki67 index >30% ($P = 0.024$), MGMT methylation ($P = 0.007$) and SVZ noninvolvement ($P = 0.004$) had higher PFS rates than patients with STR, a Ki67 index ≤30%, MGMT nonmethylation, and SVZ involvement, and these differences were statistically significant Fig. 1(a–d). Patients with GTR ($P = 0.002$), KPS >60 ($P = 0.014$), ACCI≤6 ($P = 0.000$), Ki67 index >30% ($P = 0.045$), MGMT methylation ($P = 0.026$), SVZ noninvolvement ($P = 0.032$), postoperative radiotherapy ($P = 0.002$), and postoperative TMZ chemotherapy ($P = 0.000$) had higher OS rates than patients with STR, KPS ≤60, ACCI>6, Ki67 index ≤30%, MGMT nonmethylation, SVZ involvement, no postoperative radiotherapy and no postoperative chemotherapy, and these differences were also statistically significant Fig. 2(a–h). By November 1, 2020, 87 of 98 patients had progressed, the 12-month PFS was 18.7%, the 18-month PFS was 9.7%, and the median PFS was 6.6 months Fig. 3(a).

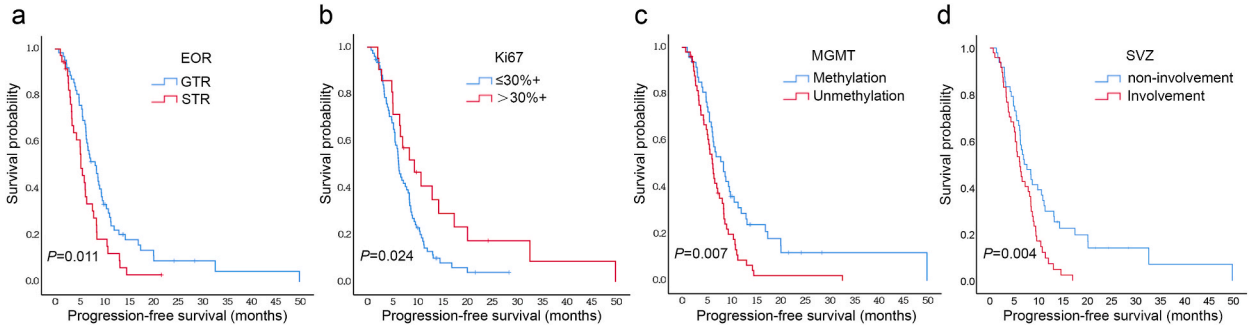

Fig. 1. Kaplan–Meier analysis of the progression-free survival rate in the subgroup of older patients with IDH wild-type glioblastoma. (a) EOR. (b) Ki67 expression. (c) MGMT methylation status. (d) SVZ involvement status.
EOR: Extent of resection. GTR: Gross total resection; STR: Subtotal resection; MGMT: O6-methylguanine-DNA methyltransferase; SVZ: Subventricular zone.

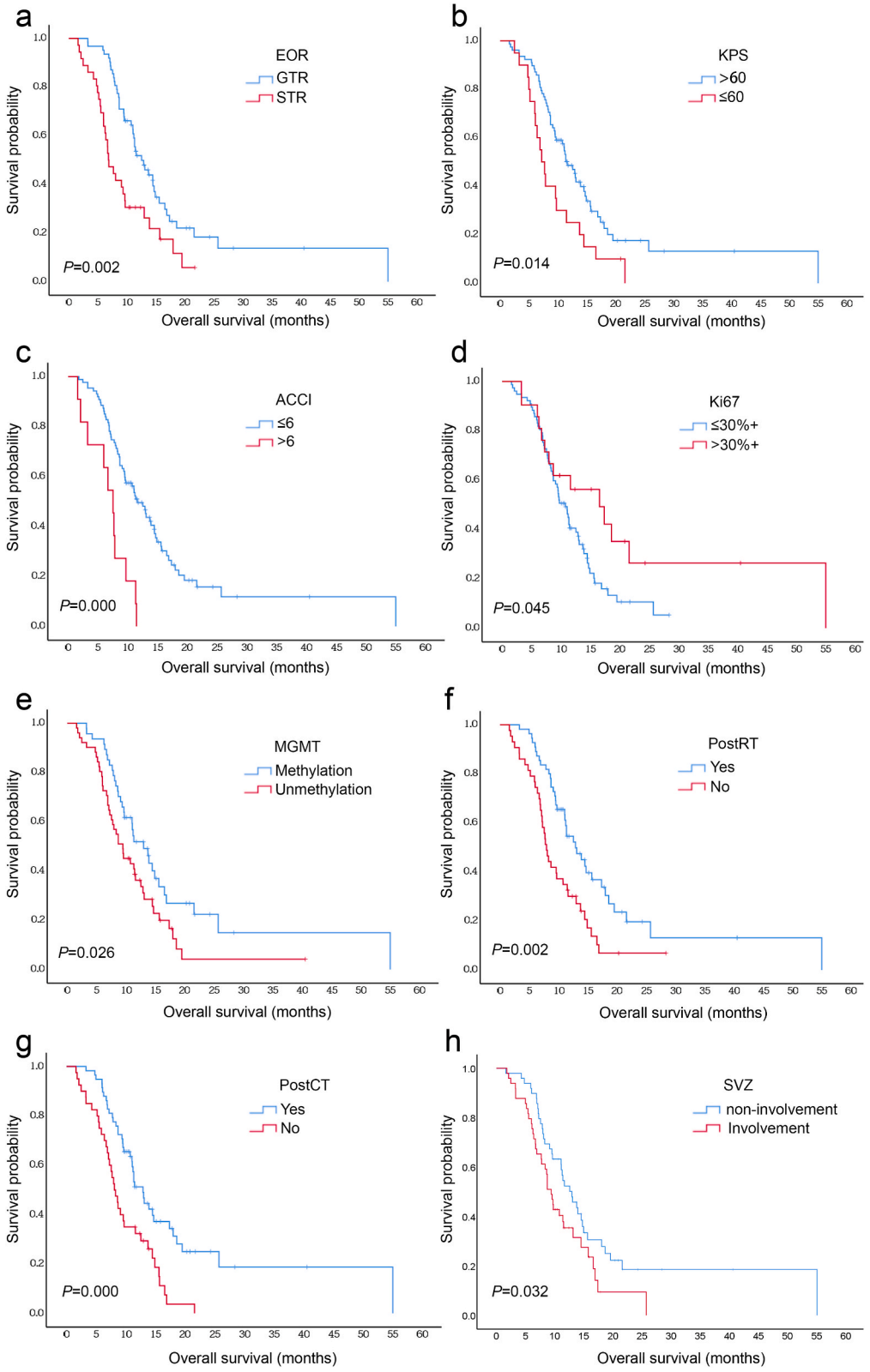

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Fig. 2. Kaplan–Meier analysis of overall survival in the subgroup of older patients with IDH-wild-type glioblastoma. (a) EOR. (b) KPS. (c) ACCI. (d) Ki67. (e) MGMT methylation status. (f) PostRT. (g) PostCT. (h)SVZ involvement status.
EOR: Extent of resection; GTR: Gross total resection; STR: Subtotal resection; KPS: Karnofsky performance status; ACCI: Age-adjusted Charlson comorbidity index; MGMT: O6-methylguanine-DNA methyltransferase; SVZ: Subventricular zone; PostRT: Postoperative radiotherapy; PostCT: Postoperative TMZ chemotherapy.

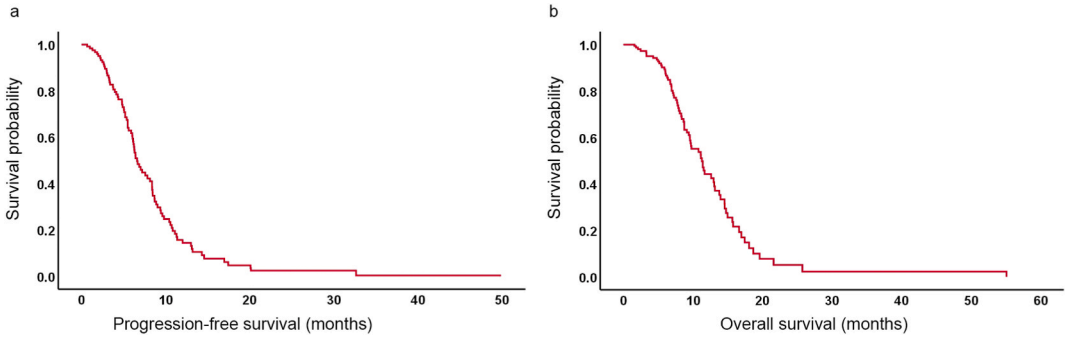

Fig. 3. (a)Progression-free survival. (b)overall survival of older patients with IDH-wild-type glioblastoma.

Twenty-three patients survived, and 75 died. The 12-month OS was 43.8%, the 18-month OS was 21.7%, and the median OS was 11.13 months Fig. 3(b).

Univariate Cox analysis showed (Table 2) that the factors associated with significant OS differences in older patients with IDH wild-type GB included the extent of resection (EOR) (GTR vs. STR), KPS (>60 vs. ≤60), ACCI (≤6 vs. >6), expression of Ki67 (≤30%+ vs.

Table 2
Univariate and multivariate Cox analysis of factors affecting OS of older patients with IDH-wild-type glioblastoma.

Characteristic		Univariate Cox analysis			Multivariate Cox analysis		
		P	HR	95%CI	*P*	HR	95%CI
Age		0.489	1.020	0.964-1.081			
Gender		0.122	0.689	0.430-1.105			
	Male						
	Female						
EOR		0.002	2.102	1.314-3.363	0.009	2.010	1.193-3.385
	GTR						
	STR						
KPS		0.016	1.905	1.127-3.218	0.164	1.573	0.831-2.976
	>60						
	≤60						
ACCI		0.000	3.512	1.798-6.863	0.042	2.253	1.030-4.931
	≤6						
	>6						
Ki67		0.048	0.540	0.293-0.994	0.198	0.656	0.346-1.246
	≤30%+						
	>30%+						
MGMT		0.028	1.686	1.059-2.683	0.002	2.231	1.346-3.697
	Methylation						
	Unmethylation						
PostRT		0.002	2.047	1.290-3.249	0.031	1.876	1.058-3.328
	Yes						
	No						
PostCT		0.001	2.256	1.412-3.602	0.049	1.756	1.002–3.077
	Yes						
	No						
EGFR		0.950	1.028	0.428-2.472			
	–						
	+						
SVZ		0.034	1.660	1.040-2.649	0.756	1.084	0.653-1.797
	non-involvement						
	Involvement						

OS: Overall survival; EOR: Extent of resection; KPS: Karnofsky performance status; ACCI: Age-adjusted Charlson comorbidity index; MGMT: O6-methylguanine-DNA methyltransferase; GTR: Gross total resection; STR: Subtotal resection; PostRT: Postoperative radiotherapy; PostCT: Postoperative TMZ chemotherapy; EGFR: Epidermal growth factor receptor; SVZ: Subventricular zone.

>30%+), MGMT methylation status (methylation vs. nonmethylation), SVZ involvement status (noninvolvement vs. involvement), postoperative radiotherapy (yes vs. no) and postoperative TMZ chemotherapy (yes vs. no). Factors with significant differences in PFS in univariate Cox analysis included EOR (GTR vs. STR), the expression of Ki67 (≤30%+ vs. >30%+), MGMT methylation (methylation vs. nonmethylation) and SVZ involvement status (noninvolvement vs. involvement). (Table 3). The above variables with $P < 0.05$ were included in the multivariate Cox analysis, and the independent prognostic factors of OS in older patients with IDH wild-type GB included EOR (GTR vs. STR), ACCI (≤6 vs. >6), MGMT methylation status (methylation vs. nonmethylation), postoperative radiotherapy (yes vs. no), and postoperative TMZ chemotherapy (yes vs. no). Patients who received GTR, ACCI score ≤6, MGMT methylation, postoperative radiotherapy and postoperative TMZ chemotherapy had longer OS. The independent risk factor for PFS was MGMT nonmethylation and SVZ involvement status.

3.3. Nomogram construction and evaluation

EOR, ACCI, MGMT methylation status, postoperative radiotherapy and postoperative TMZ chemotherapy were used to generate a nomogram to predict 6-month, 12-month, and 18-month OS in older patients with IDH-wild-type GB. The nomogram Fig. 4 showed that the ACCI was the most influential factor for OS in older patients with IDH-wild-type GB, followed by the EOR, MGMT methylation status, postoperative radiotherapy and postoperative TMZ chemotherapy. The nomogram was internally validated using bootstrapping and showed a C-index of 0.72. There was a 72% coincidence rate between the predicted survival and the observed survival. The nomogram can predict the OS of older patients with IDH-wild-type GB with reasonable accuracy. Moreover, the time-dependent receiver operating characteristic (ROC) curve Fig. 5(a–c) showed that the areas under the curve (AUCs) at 6 months, 12 months, and 18 months were 0.874, 0.739 and 0.779, respectively. The dashed line represents the reference line where an ideal nomogram would lie, namely, the ideal predictive value in the calibration chart. The X-axis represents the OS predicted by the nomogram, and the Y-axis represents the observed OS. The calibration plot of the nomogram Fig. 6(a–c) shows that the 6-month, 12-month and 18-month survival probabilities intersected with the dashed diagonal line. The nomogram predicted the 6-month, 12-month and 18-month OS probabilities, which corresponded well with the actual outcome.

Table 3
Univariate and multivariate Cox analysis of factors affecting PFS of older patients with IDH-wild-type glioblastoma.

Characteristic		Univariate Cox analysis			Multivariate Cox analysis		
		P	HR	95%CI	*P*	HR	95%CI
Age		0.950	1.002	0.949-1.057			
Gender		0.632	0.900	0.584-1.387			
	Male						
	Female						
EOR		0.012	1.768	1.135-2.754	0.129	1.426	0.902-2.253
	GTR						
	STR						
KPS		0.091	1.542	0.933-2.551			
	>60						
	≤60						
ACCI		0.062	1.968	0.967-4.002			
	≤6						
	>6						
Ki67		0.026	0.534	0.306-0.929	0.090	0.610	0.345-1.080
	≤30%+						
	>30%+						
MGMT		0.008	1.811	1.172-2.799	0.019	1.701	1.092-2.650
	Methylation						
	Unmethylation						
PostRT		0.090	1.452	0.943-2.235			
	Yes						
	No						
PostCT		0.128	1.403	0.908-2.168			
	Yes						
	No						
EGFR		0.890	0.945	0.423-2.112			
	–						
	+						
SVZ		0.005	1.895	1.211-2.963	0.030	1.650	1.050-2.594
	non-involvement						
	Involvement						

PFS: Progress-free survival; EOR: Extent of resection; GTR: Gross total resection; STR: Subtotal resection; KPS: Karnofsky performance status; ACCI: Age-adjusted Charlson comorbidity index; MGMT: O6-methylguanine-DNA methyltransferase; PostRT: Postoperative radiotherapy; PostCT: Postoperative TMZ chemotherapy; EGFR: Epidermal growth factor receptor; SVZ: Subventricular zone.

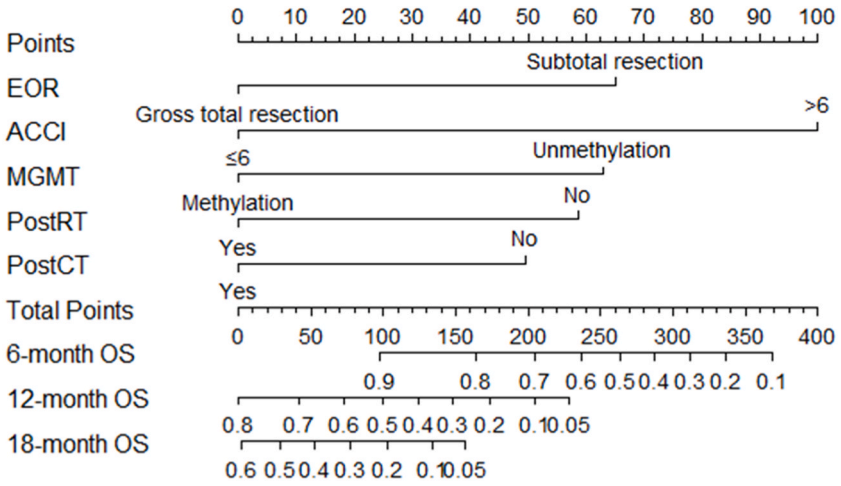

Fig. 4. Nomogram for predicting the overall survival of older patients with IDH-wild-type glioblastoma.
EOR: Extent of resection; ACCI: Age-adjusted Charlson comorbidity index; MGMT: O6-methylguanine-DNA methyltransferase; PostRT: Postoperative radiotherapy; PostCT: Postoperative TMZ chemotherapy; OS: Overall survival.

4. Discussion

The prognosis of older patients with IDH wild-type GB is worse than that of younger patients. Treatment selection is mainly limited by the reduced treatment tolerance of older patients, the higher probability of side effects to surgery and radiochemotherapy, and the great differences in tumour biological behaviour and treatment mode among individuals [6,26,27]. The use of nomogram models can further standardize the treatment of patients with GB and is conducive to promoting a more personalized medicine approach. Gittleman et al. [15,28] constructed and verified two nomograms according to the clinical trial data of Radiation Therapy Oncology Group (RTOG) 0525 and RTOG 0825 as well as the data of other American clinical trials, one for patients with GB and the other for patients with IDH-wild-type GB. Age is one of the predictors in the IDH-wild-type GB nomogram. The age ranges of patients in the training set (29–88 years) and the validation set (24–85 years) were very wide. Cheng et al. [29] validated the GB nomogram from Gittleman et al. based on the Chinese Glioma Genome Atlas (CGGA) and generated a nomogram including KPS, TMZ treatment, IDH mutation status, EOR and MGMT methylation status. The C-index of this nomogram was 0.69, which was higher than the C-index (0.61) of the nomogram constructed by Gittleman et al. ($P = 0.004$), indicating that their nomogram is more effective in the Chinese GB population. The above three nomograms were based on the data of adult and older patients with GB, and their value for older patients with GB remains to be verified. Therefore, Shen et al. [30] externally validated Gittleman's IDH-wild-type GB nomogram by using 63 patients with GB aged ≥70 years. The results showed that the nomogram had good performance in predicting the 12-month and 18-month survival rates but significantly overestimated the 24-month survival rate of patients. They suggested the inclusion of a narrow survival window, such as the 6-month survival rate, to increase the applicability to the population of older patients with GB. Therefore, the authors suggested that it is necessary to construct special nomograms to predict the prognosis of older patients with GB. Similar to the nomograms developed by Gittleman and Cheng, we used EOR, MGMT methylation status, postoperative radiotherapy and postoperative TMZ chemotherapy to generate a nomogram. The largest difference from the above existing nomograms is that we found the ACCI to be an independent prognostic factor of IDH-wild-type GB in older patients and included the ACCI in the nomogram. Comprehensive consideration of comorbidities may be conducive to treatment decision-making. The C-index of the nomogram in our study was 0.72, which shows that the model can predict the OS rate of patients with IDH-wild-type GB with reasonable accuracy. The calibration plot showed good consistency between the predicted OS probabilities at 6, 12 and 18 months and the actual observations. Moreover, the data are not from clinical trials and are more representative of clinical practice. The included factors are easy to collect in clinical work.

In this study, the ACCI was identified as the most influential independent prognostic predictor of OS in older patients with IDH-wild-type GB. The OS of patients in the ACCI> 6 group was less than 1 year, and the OS rates at 12 months and 18 months in the ACCI≤ 6 group were 49.6% and 24.6%, respectively ($P = 0.000$). However, caution should be taken in interpreting these data because only 11 of 98 patients (11.2%) had ACCI> 6 in this study. Balducci et al. [31] suggested that age is an important prognostic factor affecting the survival of GB patients, and they did not conclude that the CCI is a prognostic factor in older patients with GB. This may be related to the fact that they did not consider age and comorbidities comprehensively. It is necessary to consider ACCI in further research, especially for older patients with GB. A study on older patients with GB showed that the median OS of patients with ACCI <3 was 22 months, while the OS of patients with ACCI ≥3 was only 10 months ($P = 0.004$). The authors proposed that ACCI may be an appropriate tool for treatment decision-making for older patients with GB [32].

The difference between the physiological age and health status of older patients with GB may vary greatly. Factors such as comorbidities and treatment methods must be considered simultaneously to facilitate the stratification of patients and the development of more appropriate treatment plans. Minniti et al. [33] analysed 243 patients aged≥65 years with GB treated with standard-dose

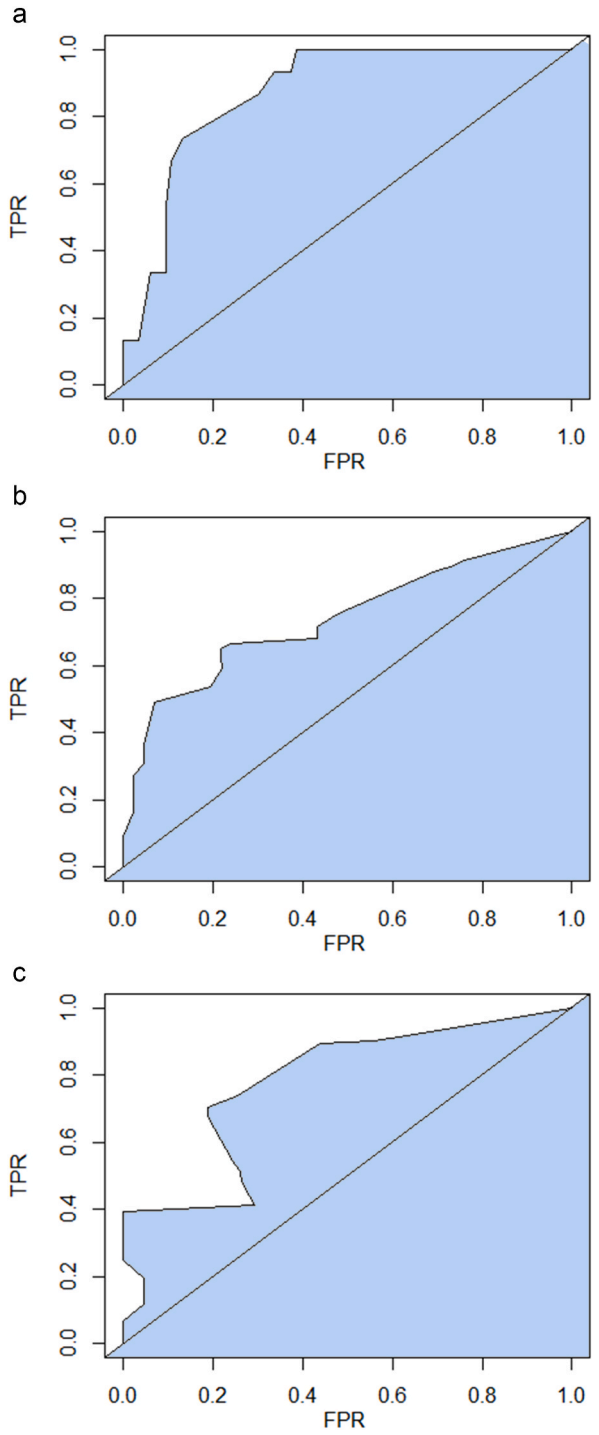

Fig. 5. The AUC calculated by the time-dependent ROC curve evaluated and predicted the discrimination accuracy of the nomogram for the OS of older patients with IDH-wild-type glioblastoma. (a) ROC curve for the prediction of 6-month OS, AUC = 0.874. (b) ROC curve for the prediction of 12-month OS, AUC = 0.739. (c) ROC curve for the prediction of 18-month OS, AUC = 0.779.
AUC, Area under the curve; ROC, Receiver operating characteristic; OS: Overall survival; TPR, True positive rate; FPR, False positive rate.

(60Gy) or short-course (40Gy) radiotherapy with concomitant and adjuvant TMZ chemotherapy, and age was not a prognostic factor for OS and PFS in multivariate analysis. The study of NOA-08 showed that age was not an independent prognostic factor for OS and PFS in 373 patients aged≥65 years with malignant gliomas receiving radiotherapy (60Gy) or dose-density chemotherapy (TMZ 100mg/m2, 7 days on, 7 days off) [34]. Our study found that univariate Cox analysis showed that age had no significant effect on OS (P

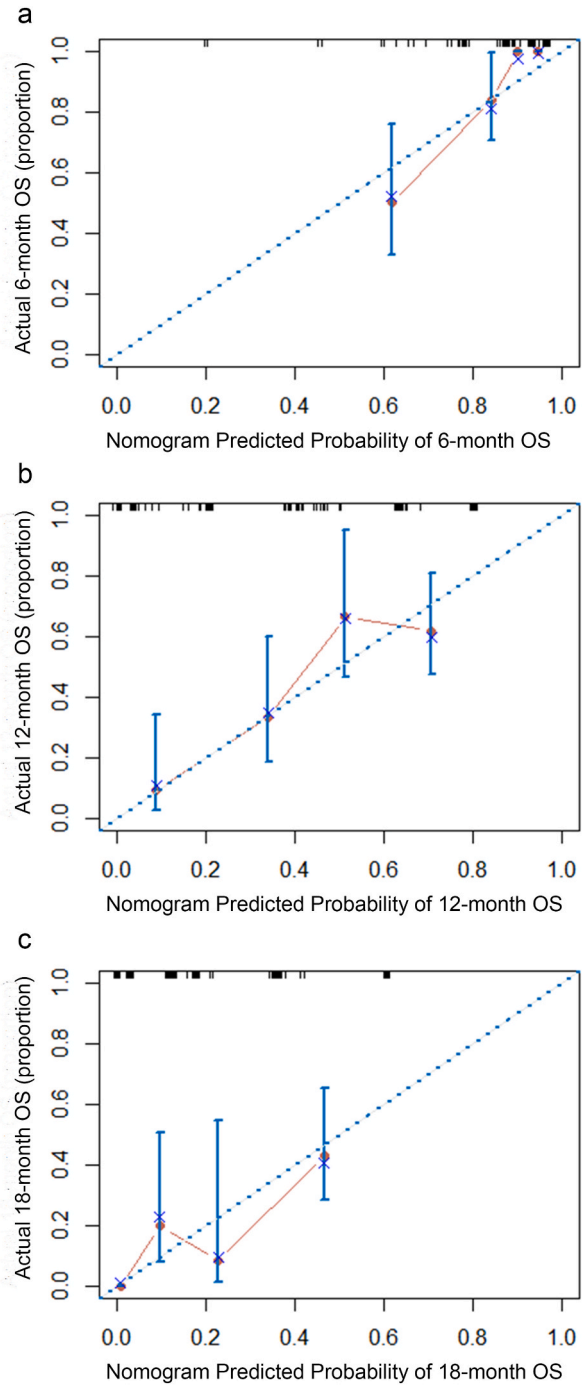

Fig. 6. Calibration chart of the nomogram for predicting the OS of older patients with IDH-wild-type glioblastoma. (a) Calibration of the nomogram for 6-month OS. (b) Calibration of the nomogram for 12-month OS. (c) Calibration of the nomogram for 18-month OS. The Y-axis shows OS, and the X-axis shows the nomogram-predicted probability of OS. The dashed line represents the reference line (namely, the ideal predictive value).
OS: overall survival.

= 0.489) or PFS (P = 0.950) in elderly patients with IDH-wild-type GB, which was not included in the multivariate COX analysis. Although our study did not conclude that age is related to the progression and prognosis of IDH-wild-type GB in older patients, age is indeed an important factor to be considered. A large number of studies have also shown that age is an important prognostic factor for patients with GB [6,26,35,36]. The most likely reason for the difference between the results of our study and those of other studies is the small number of patients enrolled and the short follow-up period. The bias inherent in a retrospective single-centre clinical study is

inevitable. This may reduce the prognostic value of the observed variables.

Deluche et al. [37] used the Geriatric-8 (G-8) to predict the prognosis of older patients with GB; 89 patients were divided into the high-score group (G-8 14.5–17), the intermediate-score group (G-8 10.5–14.5) and the low-score group (G-8<10.5), and patients in the high-score group had longer OS than those in the intermediate- and low-score groups ($P < 0.0001$); G-8 was an independent predictor of OS in older patients with GB. Kenis et al. [38] suggested that patients with malignant tumours should be assessed with a comprehensive geriatric assessment (CGA) if their G-8 ≤14/17. Lombardi et al. [39] conducted a single-centre retrospective study on 113 patients with GB aged ≥65 years. The prognostic value of CGA for GB was analysed. According to the CGA results, each patient was divided into fit, vulnerable or frail groups, and the median OS times were 16.5 months, 12.1 months and 10.3 months, respectively. Multivariate analysis showed that CGA was a predictor of mortality in older patients with GB. It was suggested that in the nomogram study on older patients with GB, G-8 and CGA should be included as variables on the basis of age and ACCI evaluation.

Several studies have shown that the maximum safe resection of tumours in older patients with GB is associated with longer OS [26,40–44]. In our study, multivariate analysis showed that EOR was an independent predictor of OS in older patients with IDH-wild-type GB, and GTR was an independent protective factor. It is worth noting that the size, location and proximity to functional areas of intracranial tumours may limit the scope of safe surgical resection, and it is still necessary to maximize tumour resection on the premise of ensuring safety. Karsy et al. [45] conducted a study to analyse the effect of EOR on the survival of 82 GB patients aged ≥75 years. The results showed that the therapeutic effect of GTR was limited by postoperative complications and KPS. Only patients without postoperative complications could benefit from GTR. Therefore, it is necessary to strike a balance between maximizing tumour resection and protecting neural function.

Postoperative adjuvant radiochemotherapy is an important part of the treatment of older patients with GB. For a long time, researchers have been exploring the optimal mode of radiotherapy and chemotherapy to reduce treatment-related toxicities and side effects in older patients with GB. A phase III randomized clinical trial conducted by the International Atomic Energy Agency (IAEA) further confirmed the feasibility and effectiveness of hypofractionated radiotherapy, which is related to better safety [46]. A Nordic phase III clinical trial [47] divided 291 patients with GB over 60 years old into the TMZ chemotherapy group (200 mg/m2, d1-5, 28 days as one cycle, 6 cycles total), hypofractionated radiotherapy group (34.0 Gy/3.4 Gy, 2 weeks total) and standard radiotherapy group (60.0 Gy/2.0 Gy, 6 weeks total). The median OS of the TMZ chemotherapy group was significantly longer than that of the standard radiotherapy group (8.4 months and 6 months, respectively). However, the standard radiotherapy group and hypofractionation radiotherapy group showed similar survival benefits. This study also showed that patients with MGMT methylation had improved OS after TMZ chemotherapy, but MGMT methylation was not related to prognosis in the radiotherapy group. MGMT methylation status is a powerful predictor of OS in patients treated with TMZ. The important finding of the NOA-08 study is that MGMT methylation status is a favourable prognostic factor in older patients with GB. Among the 412 older patients with malignant astrocytoma included in the study, the OS of MGMT methylation patients was 11.9 months, which was significantly longer than the 8.2 months observed for MGMT nonmethylation patients (HR 0.62, 95% CI 0.42–0.91, P = 0.014). Moreover, MGMT methylation patients benefited more from TMZ chemotherapy than radiotherapy, but MGMT nonmethylation patients showed the opposite trend [34,48]. Our results also showed that only MGMT methylation status was a predictor of PFS in older patients with IDH-wild-type GB. Therefore, in older patients with GB, MGMT methylation status is a predictor of the efficacy of TMZ chemotherapy and provides important information to determine the adjuvant treatment plan.

EGFR amplification occurred in approximately 45% of IDH-wild-type GB [49]. The significance of EGFR as a prognostic factor of glioblastoma remains controversial. Several studies have noted that EGFR gene amplification may indicate poor prognosis and shorter survival [50,51]. Other studies indicated that the correlation between EGFR and survival was not statistically significant [52,53]. and some even suggesting a favourable impact on patient survival [54–56]. Our study suggested that the expression of EGFR was not a prognostic factor for older IDH-wild-type GB. Hoffman et al. [57] reported 28 IDH-wild-type glioblastoma patients (18–45 years old), and EGFR copy number gain was a negative prognostic factor of OS in univariate and multivariate analyses with statistical significance but was not validated in The Cancer Genome Atlas (TCGA). Armocida et al. [58] divided 146 patients with IDH-wild-type glioblastoma into a younger adult group (18–45 years) and an adult group (>45 years). Bivariate analysis did not show a potential negative prognostic impact of EGFR overexpression in young adults (18–45 years) with IDH-wild-type glioblastoma. The prognostic value of EGFR in IDH-wild-type glioblastoma remains to be confirmed in large sample studies.

Tumour stem cells and brain neural stem cells in the SVZ are thought to promote tumour progression and recurrence in glioblastoma, and the SVZ is the reservoir of neural stem cells in the adult brain [59]. Research has shown that approximately 50–60% of glioblastomas involve the SVZ on contrast-enhanced T1 MRI [60]. Jungk et al. [61] carried out a retrospective survival analysis of 285 patients with IDH1-wild-type glioblastoma. The results showed that SVZ involvement was an independent predictor of worse prognosis. Our study showed that SVZ involvement is a negative prognostic factor of PFS for older IDH-wild-type glioblastoma in univariate and multivariate analyses and an unfavourable prognostic factor of OS in univariate analysis but not an independent prognostic factor of OS in multivariate analysis. Mistry et al. [62] analysed the relationship between the distance to the lateral ventricular wall from glioblastoma and the survival outcome of 502 glioblastoma patients, and the results showed a significantly decreased overall survival only when glioblastoma contacted the lateral ventricular wall. OS did not correlate with distance to the lateral ventricular wall from glioblastoma. Liang et al. [63] reported that SVZ invasion alone is not a prognostic factor of PFS and OS for glioblastoma, but joint invasion of the SVZ and corpus callosum is an adverse prognostic factor of PFS and OS for glioblastoma in multivariate analysis. When glioblastoma invaded the SVZ, planning the target volume in the postoperative radiotherapy plan inevitably included a part of the SVZ. The studies indicated that irradiation plans including the SVZ improved the results of high-grade glioma treatment [64–66].

In summary, we constructed a nomogram including the ACCI to predict the OS of older patients with IDH-wild-type GB. This nomogram was found to be beneficial for clinical decision making and follow-up interval selection. However, the sample size needs to

be further expanded, and further external verification is needed before the nomogram is used in a clinical setting.

Author contribution statement

Jidong Hong and Wenjun Cao: Conceived and designed the experiments; Wrote the paper.
Luqi Xiong, Wenjun Cao: Performed the experiments.
Chao Liu, Rui Wei, Liangfang Shen, Jidong Hong, Zhanzhan Li: Analysed and interpreted the data.
Lei Huo, Jun Wu, Tao Song, Li Meng and Zhongliang Hu: Contributed materials, analysis tools or data.

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Additional information

No additional information is available to this paper.

Declaration of competing interest

The authors declare no conflict of interest.

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