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Clinical Significance of Various Classification Standards of Age Groups in Predicting Survival of Patients with Glioblastoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Xingwang Zhou*
ABCDEF Xiaodong Niu*
ABCEF Qing Mao
ABCDEF Yanhui Liu

Department of Neurosurgery, West China Hospital, Chengdu, Sichuan, P.R. China

* Xingwang Zhou and Xiaodong Niu contributed equally to this work

Corresponding Authors: Qing Mao, e-mail: maoqing@scu.edu.cn, Yanhui Liu, e-mail: yhliu2001@163.com
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Background: The present study aimed to assess the association of various age groups with survival in patients with glioblastoma.

Material/Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to extracted data on new diagnoses of glioblastoma between 2005 and 2015. Four age models were constructed according to the age at diagnosis.

Results: A total of 28 734 patients with glioblastoma (16 823 men and 11 911 women) were enrolled in the study. In multivariate analysis, variables including sex, race, tumor, and clinical information were identified as confounding factors to adjust 4 age models. In model 1, ages 39–58, 59–78, and 79+ years were risk factors of survival compared with age 0–18 years. In model 2, ages 18–65, 66–79, and 80+ years were prognostic factors of shorter survival compared with ages 0–17 years. In model 3, ages 45–59, 60–74, and 75+ years were associated with poor prognosis, while ages 18–44 years was associated with favorable clinical outcomes compared with ages 0–17 years. In model 4, ages 18–53, 54–64, and 65+ years were associated with poor prognosis.

Conclusions: The differences in prognoses in different age groups of glioblastoma patients suggest that clinicians should incorporate age into routine clinical assessments and develop appropriate treatment strategies.

MeSH Keywords: Age Groups • Glioblastoma • Prognosis • SEER Program

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Background

Glioblastoma is the most common malignant tumor of the central nervous system in adult patients [1]. Although tumor resection followed by adjuvant radiotherapy and chemotherapy or TTFields were performed, the clinical outcome remained poor [2]. Therefore, the identification of parameters correlated with the prognosis of patients with glioblastoma may facilitate individualized treatment and improve patient prognosis.

Growing evidence indicates that IDH1, MGMT, TERT, P53, EGFR, and age at diagnosis are associated with clinical outcome in patients with glioblastoma [3–6]. The age at diagnosis has a pivotal role in predicting the clinical outcome of several malignant tumors, including hormone receptor-positive breast cancer, glioma, thyroid cancer, and cervical cancer [7–11], while the prognostic role of age in glioblastoma is conflicting [7,8,12,13]. Chen et al. [8] conducted a retrospective analysis with 125 high-grade gliomas to evaluate the prognostic effect of 3 age groups (≤50 and >50 years old; ≤60 and >60 years old; ≤45 and 45–65 and ≥65 years old) and their results showed that older patients had worse clinical survival. However, Gately et al. reviewed the clinical data of 165 glioblastoma multiforme (GBM) patients to assess the influence of age group (≤60 and 60–70 and ≥70 years old) on the prognosis of patients, and they found that age was not associated with survival of GBM patients [13]. Furthermore, the age cut-offs employed to predict the clinical outcome of glioblastoma patients were different, and controversial results may be associated with a small sample size [8,12,13]. Thus, the impact of age in glioblastoma patients should be clarified in a larger population, and the cut-offs of age used to predict survival should be redefined. Our study aimed to assess the impact of different age groups on prognosis in patients with glioblastoma.

Material and Methods

Data and Patients

The Surveillance, Epidemiology, and End Results (SEER) database was used to extract data on new diagnoses of glioblastoma between 2005 and 2015 in the era of temozolomide (TMZ) via SEER*stat software (version 8.3.4) [14]. SEER contains cancer incidence and survival data from 18 registries in different region of US: California, Kentucky, Louisiana, New Jersey, Greater Georgia, San Francisco-Oakland, Connecticut, Detroit, Hawaii, Iowa, Atlanta, San Jose-Monterey, Los Angeles, Alaska Natives, Rural Georgia, New Mexico, Seattle, and Utah [15]. Patients with glioblastoma (International Classification of Diseases for Oncology Third Edition [ICD-O-3] histology code 9440-9442) and location in the brain (CT71.0-71.9) were enrolled in this study [16]. The diagnostic confirmation of patients with clinical diagnosis only, direct visualization without microscopic confirmation, radiography without microscopic confirmation, and unknown were excluded. Patients identified based on the death certificate or autopsy only also were excluded. This study was performed using public data from the SEER database and did not include personal identifying information or human subjects use; therefore, ethics committee approval and informed consent were not required.

Primary endpoint and parameters

The primary endpoint was overall survival (OS), which was defined as the duration from the month of diagnosis to the date of death or the last follow-up. The demographic data including sex, age, race (white and non-white) and marital status (married, single, separated, divorced, widowed, and unknow) were recorded. The imaging data, including tumor location and tumor size, were recorded. We also recorded the clinical data, including the extent of tumor resection, whether the patient accepted radiotherapy and chemotherapy, and the vital status (alive or dead).

Classification of standard age groups

Classification of standard age groups was performed based on the following methods (Supplementary Figure 1). First, the X-tile was used to identify the cut-off of age for prognosis in patients with glioblastoma, and this was model 1. Second, based on the World Health Organization (WHO)'s latest criteria for age classification, patients enrolled in the present study were classified into juveniles (<18 years), young people (18–65 years), middle-aged person (66–79 years) and the aged (80+ years), and this age group was used in model 2. Third, previous criteria of age classification by WHO also used to divide all patients into 5 groups – juveniles (<18 years), young people (18–44 years), middle-aged person (45–59 years), young-old people (60–74 years), and the aged (75+ years) – and this age group was used in model 3. Finally, another age group (<18 years, 18–53 years, 54–65 years, 65+ years) used in this study was mainly based on published research which assessed the potential age-specific genetic effects in those different ages of patients with GBM [17], and this age group was used in model 4.

Statistical analysis

All statistical analyses were performed in Statistical Package for the Social Sciences version 19.0, X-tile, and GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA). The comparison of variables in different age groups were made using the chi-square test for categorical variables and the *t* test for continuous variables. A statistically significant difference was defined as a two-sided p value less than 0.05. Survival was evaluated via Kaplan-Meier models and multivariate Cox

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proportional hazards model. Hazard ratios (HR) were used to evaluate the prognostic role of these models in patients with glioblastoma. A hazard is the rate at which an event occurs, so that the probability of an event happening in a short time interval is the length of time multiplied by the hazard. The survival curves presented in this study were generated by GraphPad Prism 5. X-tile determined the cut-off of age in predicting the OS of glioblastoma patients. We used correspondence analysis to assess the association between 7 intervals of OS and these models of age [18].

Results

A total of 28 734 patients with glioblastoma, including 16 823 men and 11 911 women, were enrolled (Table 1). Of these patients, 25 570 were white and 3164 were non-white. Regarding marital status, 18 204 patients were married, 4189 were single, 5183 were separated/divorced/widowed, and the marriage status of 1158 was unknown. The distribution of patients in the 4 different age groups is summarized in Table 1. The most common tumor location was frontal lobe (8102) followed by temporal (7268), parietal (4645), overlapping lesion of the brain (4095), occipital (1256), cerebrum (1054), cerebellum (222), brain stem (157), and ventricle (120). The total numbers of patients with tumor size <5 cm, 5–7 cm, and >7 cm were 14 371, 7749, and 6614, respectively. Gross total resection was performed on 9209 patients, subtotal resection in 13 844 patients, the extent of resection of 308 patients was unknown, and 5373 patients did not undergo tumor resection. There were 18 059 patients who received radiotherapy and 19 554 patients received chemotherapy. At last follow-up, 24 300 were dead.

The results of the X-tile showed that the optimal cut-off of age in predicting OS for patients with glioblastoma was ages 0–18, 19–38, 39–58, 59–78, and 79+years. In univariate analysis (Table 2), sex and tumor location were not correlated with prognosis (p>0.05), while white race (HR: 0.871; 95% CI: 0.836–0.908), gross total resection (HR: 0.822; 95% CI: 0.808–0.837), and married (HR: 0.865; 95% CI: 0.849-0.883) were associated with increasing OS. However, large tumor size (HR: 1.070; 95% CI: 1.054–1.087), not receiving chemotherapy (HR: 1.828; 95% CI: 1.781–1.876), and not receiving radiotherapy (HR: 2.470;95% CI: 2.404–2.538) were associated with decreased OS (all p<0.001). In model 1, patients ages 19–38 years (HR: 0.694; 95% CI: 0.604–0.797) had a longer OS compared with patients ages <18 years old, while patients age 39–58 years old (HR: 1.189; 95% CI: 1.053-1.343), 59–78 years old (HR: 1.924; 95% CI: 1.706-2.170), and 79+ years old (HR: 4.076; 95% CI: 3.598-4.616) had shorter OS (all p<0.01, Table 2). The median OS for patients with ages 59–78 and 79+ years were 7 and 3 months, respectively, which were shorter than the median OS of 15 months in patients ages 0–18 years (all p<0.05), while the median OS of patients ages 19–38 years was 24 months, which was longer than in patients ages 0–18 years old. For patients ages 39–58 years, the median OS was 15 months. In model 2, older patients continued to show shorter OS than young patients (all p<0.005, Table 2). The median OS of patients ages 18–65, 66–79, and 80+ years were 13, 6, and 3 months, respectively, which were shorter than for patients ages 0–17 years, with a median OS of 15 months (all p<0.005). In model 3, patients age 45–59, 60–74, and 75+ years had shorter OS than patients 0–17 years old, while patients ages 18–44 years had longer survival (all p≤0.002). The median OS for patients ages 45–59, 60–74, and 75+ years were 14, 8, and 3 months, respectively, which were shorter than the median OS of 15 months in patients age 0–17 years. However, patients age 18–44 years had a longer median OS than patients age 0–17 years old (20 *vs.* 15 months). In model 4, older patients, except for ages 18–53 years, had shorter survival than patients ages 0–17 years (p<0.001, Figure 1). The median OS for patients ages 18–53, 54–64, and 65+ years were 17, 12, and 5 months, respectively.

In multivariate analysis (Table 3), the variables sex, race, tumor, and clinical information were identified as confounding factors to adjust the 4 age models. In model 1, ages 39–58 (HR=1.326, p<0.001), 59–78 (HR=2.127, p<0.001), and 79+ (HR=3.842, p<0.001) years were risk factors of survival compared with age 0–18 years. In model 2, ages 18–65 (HR=1.316, p<0.001), 66–79 (HR=2.316, p<0.001), and 80+ (HR=3.658, p<0.001) years were prognostic factors of shorter survival compared with ages 0–17 years old. In model 3, ages 45–59 (HR=1.374, p<0.001), 60–74 (HR=2.006, p<0.001), and 75+ (HR=3.384, p<0.001) years was associated with poor prognosis, while age 18–44 years (HR=0.835, p<0.001) was associated with better clinical outcome compared with age 0–17 years. In model 4, ages 18–53 (HR=1.066, p<0.001), 54–64 (HR=1.544, p<0.001), and 65+ years (HR=2.501, p<0.001) were associated with poor prognosis. We performed multivariate analysis to evaluate the association between the 4 age models and OS. The results showed that the 4 age models can predict OS of glioblastoma patients (Supplementary Table 1). Also, fewer older patients received radiotherapy and chemotherapy than younger patients (Table 4, all p<0.05).

Correspondence analysis was used to assess the relationship between 7 intervals of OS and model 1–4. The association between model 1 and the survival intervals was χ^2=3696.009 (P<0.0001), and the cumulative proportion of inertia explained by this model was 91.6%. The association of model 2 and survival intervals was χ^2=3346.345, (P<0.0001), and the cumulative proportion of inertia explained by this model was 98.1%. The χ^2 and P for the relationship between model 3 and survival intervals were 4036 and <0.0001, respectively, and the

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Table 1. Characteristics of patients with glioblastoma.

Parameter	Value	
Number of patients	28734	
Sex		
Male	16823	(58.55%)
Female	11911	(41.45%)
Race		
White	25570	(88.99%)
Non-white	3164	(11.01%)
Age		
Model1		
Age 0–18	357	(1.24%)
Age 19–38	1184	(4.12%)
Age 39–58	8859	(30.83%)
Age 59–78	15219	(52.97%)
Age 79+	3115	(10.84%)
Model2		
Age 0–17	332	(1.16%)
Age 18–65	16044	(55.84%)
Age 66–79	9736	(33.88%)
Age 80+	2622	(9.12%)
Model3		
Age 0–17	332	(1.16%)
Age 18–53	6335	(22.05%)
Age 54–64	8853	(30.80%)
Age 65+	13214	(45.99%)
Model4		
Age 0–17	332	(1.16%)
Age 18–44	2298	(8.00%)
Age 45–59	8604	(29.94%)
Age 60–74	11959	(41.61%)
Age 75+	5541	(19.29%)
Marital status		
Married	18204	(63.35%)
Single	4189	(14.58%)
Separated, divorced, widowed	5183	(18.04%)
Unknow	1158	(4.03%)
Tumor size		
<5 cm	14371	(50.01%)
5–7 cm	7749	(26.97%)
>7 cm	6614	(23.02%)
Tumor location		
Frontal	8102	(28.20%)
Temporal	7268	(25.29%)
Parietal	4645	(16.17%)
Occipital	1256	(4.37%)
Ventricle	120	(0.42%)
Brain stem	157	(0.55%)
Cerebellum	222	(0.77%)
Cerebrum	1054	(3.67%)
Overlapping lesion of the brain	4095	(14.25%)
NOS	1815	(6.32%)
Radiation		
Yes	18059	(62.85%)
No	10675	(37.15%)
Extent of resection		
No surgery	5373	(18.70%)
Complete resection	13844	(48.28%)
Uncomplete resection	9209	(32.05%)
Unknow	308	(1.07%)
Chemotherapy		
Yes	19554	(68.05%)
No	9180	(31.95%)
Vital status		
Death	24300	(84.57%)
Alive	4434	(15.43%)

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Table 2. The univariate analysis of 4 age models in predicting the prognosis of glioblastoma.

Variable	HR (95% CI)		p
Sex	1.019	(0.993–1.045)	0.152
Race	0.871	(0.836–0.908)	<0.001
Married	0.865	(0.849–0.883)	<0.001
High tumor size	1.070	(1.054–1.087)	<0.001
Tumor location	0.996	(0.991–1.000)	0.072
Gross total resection	0.822	(0.808–0.837)	<0.001
Non-radiation	1.828	(1.781–1.876)	<0.001
Non-chemotherapy	2.470	(2.404–2.538)	<0.001
Model1			
Age 0–18		1	Reference
Age 19–38	0.694	(0.604–0.797)	<0.001
Age 39–58	1.189	(1.053–1.343)	0.005
Age 59–78	1.924	(1.706–2.170)	<0.001
Age 79+	4.076	(3.598–4.616)	<0.001
Model2			
Age 0–17		1	Reference
Age 18–65	1.218	(1.075–1.380)	0.002
Age 66–79	2.203	(1.943–2.497)	<0.001
Age 80+	4.121	(3.619–4.694)	<0.001
Model3			
Age 0–17		1	Reference
Age 18–44	0.777	(0.681–0.888)	<0.001
Age 45–59	1.217	(1.073–1.380)	0.002
Age 60–74	1.790	(1.580–2.029)	<0.001
Age 75+	3.366	(2.965–3.382)	<0.001
Model4			
Age 0–17		1	Reference
Age 18–53	0.978	(0.862–1.110)	0.732
Age 54–64	1.407	(1.241–1.595)	<0.001
Age 65+	2.388	(2.107–2.705)	<0.001

cumulative proportion of inertia explained by this model was 91.8%. The association between model 4 and survival intervals was χ^2=3467.280 (P<0.0001), and the cumulative proportion of inertia was 95.8%. Supplementary Tables 2 and 3 show the percentages of participation of each level after matching for models of age and survival intervals. Supplementary Table 4 presents the scores calculated for each dimension and the contributions to mass and inertia by each of the age groups in the 4 age models. The Supplementary Table 5 summarizes the scores calculated for each dimension, and the contributions to mass and inertia survival intervals with age models.

Discussion

Age is one of the primary risk factors for development of cancer and cancer-associated death [19]. Some studies suggested that cancer patients ≥65 years old have a higher mortality rate than patients <65 years old [20]. As mentioned before, age at diagnosis was a strong prognostic factor for patients with several malignant tumors such as hormone-receptor-positive breast cancer, thyroid cancer, and cervical cancer [9–11]. In glioma patients, most previous studies also suggested that younger patients had a better prognosis than older patients [9–11], but this is controversial because results of studies conducted in Australia [13] did not support this conclusion.

Furthermore, most studies divided all patients into 2 groups according to the cut-off ages of 55 or 60 and 64.4 years old [8,21]. A few models of age as a continuous variable were conducted in glioblastoma patients. Although some studies explored the prognostic role of the age group (≤45 and 45–65 and ≥65 years old) and group (≤60 and 60–70 and ≥70 years old) in glioblastoma patients, the prognostic effect of WHO criteria for age classification and cut-offs of age identified by statistical software such as X-tile were unknown. In the present study, we used the SEER dataset to assess the prognostic role of age in patients with glioblastoma. X-tile identified the cut-offs of age in predicting OS. WHO criteria for age classification and the cut-off provided by other published research were also used. Four different age groups were conducted and named model 1, model 2, model 3, and model 4. In model 2 and model 4, older patients always had a poorer prognosis than young patients. In model 1 and model 3, patients age 19–38 years or 18–44 years had significantly better prognosis than any other age groups.

Over half of all glioblastomas are diagnosed in patients older than 60 years. Published reports found that the incidence and mortality rates of gliomas increased with age [22]. In the present study, 62.1% of patients with glioblastoma were older than 60 years. As a result, studies to assess the prognostic role of age based on cut-offs of 60 or 50 years may make it impossible to obtain an objective conclusion because of the high bias of age distribution. Our results show that younger patients had longer survival than older patients with glioblastoma, which is consistent with the previous study. Although some studies were conducted to explore the age-specific genome-wide

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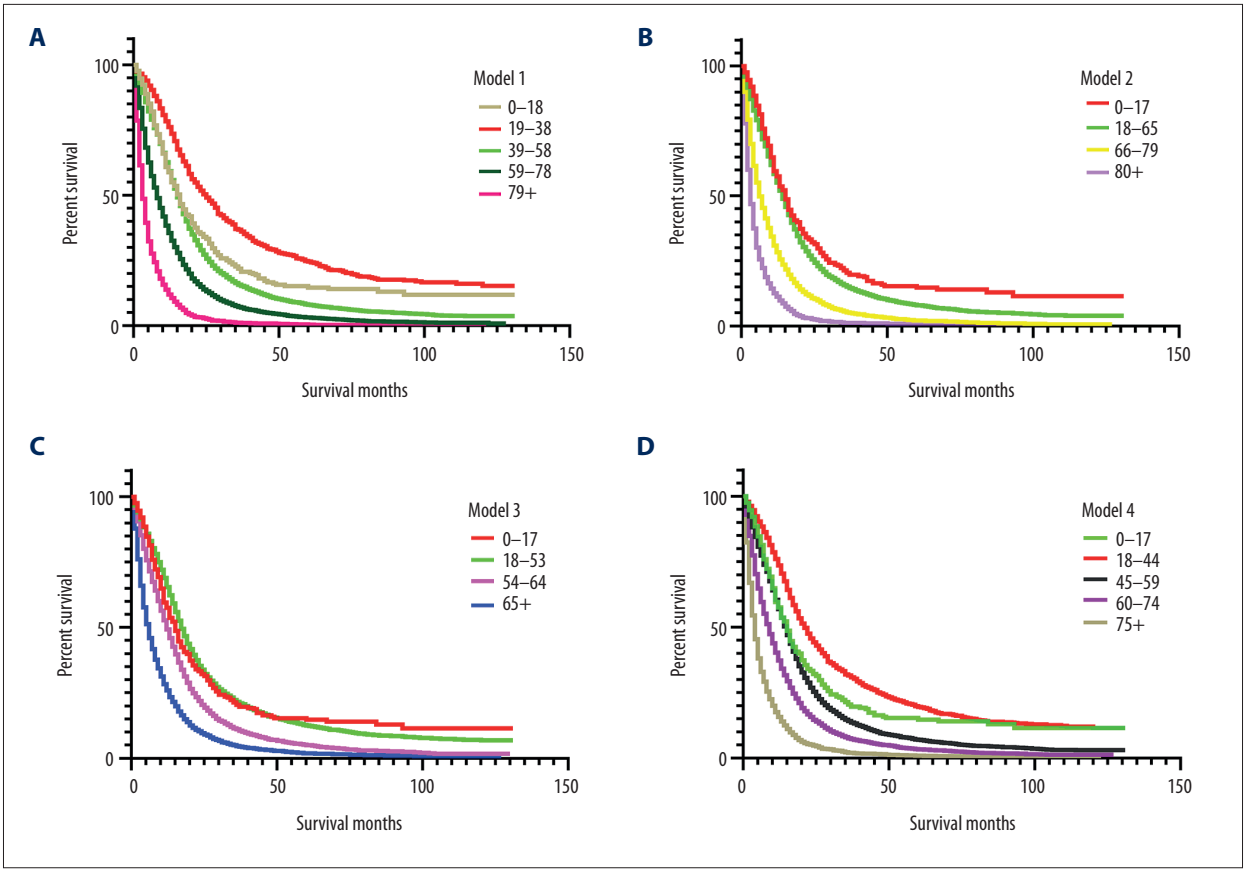

Figure 1. (**A–D**) The prognostic role of 4 age models in glioblastoma.

association in glioblastoma, the biological mechanism underlying the prognostic effect of age in glioblastoma is poorly understood. A genome-wide association study [23] by Walsh et al. indicated that genetic variants in telomerase-related genes such as risk alleles in TERT and RTEL1 were correlated with older age at diagnosis, while risk alleles in CCDC26 and PHLDB1 were associated with younger age, which may result in different clinical outcomes due to the different biomolecular mechanisms. Another study [17] on age-related genome-wide association in glioblastoma also suggested that a high frequency of germline variants related to "low-grade glioma (LGG)"-like tumor characteristics in glioblastoma patients ages 18–53 years old, as compared with patients ages 54–64 and 64+ years old, respectively, which indicated that the LGG-like tumor characteristic in younger patients may be responsible for the favorable prognosis in glioblastoma.

Furthermore, results from the TCGA GBM dataset showed that patients diagnosed at ages 18–53 years had a high frequency of IDH1 mutation than the subsets ages 54–64 and 64+ years old, while the rate of TERT mutation was higher in older patients than in younger patients [17]. The former was associated with favorable prognosis in patients with glioblastoma, while the latter was associated with poor clinical outcome [3,6]. Aging can influence the clinical outcome of glioblastoma patients by decreasing immune system effectiveness [24]. Aging can also suppress normal immunosurveillance via programmed-death-ligand 1 (PD-L1), immunosuppressive indoleamine 2,3 dioxygenase 1 (IDO), and CD11c, which can decrease the therapeutic efficacy against glioblastoma and improve the progression of malignant glioma cell [24,25].

In addition to the molecular difference between younger and older glioblastoma patients, therapeutic regimen followed by tumor resection might have a pivotal role in the clinical outcome. In the present study, older patients received less radiotherapy and chemotherapy than younger patients regardless of in any age model, which may be one of the main reasons for poor prognosis in older GBM patients.

In the present study, we first employed several age models to evaluate the prognostic role of age in glioblastoma patients. The model 1 was conducted on the cut-offs of age identified by the X-tile and the model 1 also showed the variate prognosis of each age stage. The model 2 and 3 were based on the WHO criteria for age classification, which may consider the relationship between human physiological function and age. As a result, the model 2 and 3 may show the physiological

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Table 3. The multivariate analysis of 4 age models in predicting the prognosis of glioblastoma.

Variable	HR (95% CI)	p
Model1		
Age 0–18	1	Reference
Age 19–38	0.712 (0.620–0.818)	<0.001
Age 39–58	1.326 (1.173–1.500)	<0.001
Age 59–78	2.127 (1.882–2.405)	<0.001
Age 79+	3.842 (3.381–4.365)	<0.001
Model2		
Age 0–17	1	Reference
Age 18–65	1.316 (1.160–1.492)	<0.001
Age 66–79	2.316 (2.039–2.631)	<0.001
Age 80+	3.658 (3.203–4.177)	<0.001

Variable	HR (95% CI)	p
Model3		
Age 0–17	1	Reference
Age 18–44	0.835 (0.730–0.954)	0.008
Age 45–59	1.374 (1.210–1.560)	<0.001
Age 60–74	2.006 (1.767–2.277)	<0.001
Age 75+	3.384 (2.974–3.851)	<0.001
Model4		
Age 0–17	1	Reference
Age 18–53	1.066 (0.938–1.211)	<0.001
Age 54–64	1.544 (1.360–1.754)	<0.001
Age 65+	2.501 (2.203–2.840)	<0.001

Table 4. The characteristics of radiotherapy and chemotherapy by 4 age models.

Variable	Radiotherapy (Yes/No)	P	Chemotherapy (Yes/No)	P
Model1		<0.001		<0.001
Age 0–18	229/128		248/109	
Age 19–38	789/395		892/292	
Age 39–58	6108/2751		6712/2141	
Age 59–78	9587/5632		10312/4907	
Age 79+	1346/1769		1384/1731	
Model2		<0.001		<0.001
Age 0–17	213/119		228/104	
Age 18–65	10915/5129		11973/4071	
Age 66–79	5847/3889		6247/3486	
Age 80+	1084/1538		1106/1516	
Model3		<0.001		<0.001
Age 0–17	213/119		228/104	
Age 18–44	1565/733		1757/541	
Age 45–59	5908/2696		6493/2111	
Age 60–74	7688/4271		8279/3680	
Age 75+	2685/2856		2797/2744	
Mdodel4		<0.001		<0.001
Age 0–17	213/119		228/104	
Age 18–53	4361/1968		4853/1476	
Age 54–64	5985/2868		6509/2344	
Age 65+	7494/5720		7958/5265	

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status with aging and indirectly reflect the relationship between physiological function status and survival indirectly. The model 4 has been used by previous study [17] to evaluate the potential age-specific genetic effects in those different ages of patients with GBM. To some extent, the model 4 might show the different prognosis in those different ages of patients with GBM, which also result from the potential age-specific genetic effects in those different ages of patients. All these age models can predict the prognosis of glioblastoma patients. It is difficult to say which model of the age is the best model that could be used in the clinical practice for the prognostic stratification of patients. Clinicians may select the appropriate age model to evaluate the prognosis according to the clinical situation. In addition, there were some limitations that should be considered. For one thing, we could not include the common molecular information such as IDH1 and MGMT into analysis due to the SEER dataset without this molecular information. For another, SEER data lack of specific details on chemotherapy, including length and response to chemotherapy. As a result, patients with different length of chemotherapy may have a diverse prognosis.

Conclusions

Four age models were constructed to assess the prognostic role in glioblastoma patients by using the SEER dataset. In model 1, ages 39–58, 59–78, and 79+ years were risk factors of survival compared with age 0–18 years. In model 2, ages 18–65, 66–79, and 80+ years old were prognostic factors of shorter survival compared with age 0–17 years. In model 3, ages 45–59, 60–74, and 75+ years old were associated with poor prognosis, while ages 18–44 years old were associated with favorable clinical outcomes compared with ages 0–17 years. In model 4, ages 18–53, 54–64, and 65+ years were associated with poor prognosis. Therefore, clinicians should incorporate age into routine clinical assessments and develop appropriate treatment strategies, which could improve the prognosis of patients with glioblastoma.

Conflicts of interest

None.

Supplementary Data

Supplementary Table 1. The prognostic role of the 4 age models in patients without chemotherapy.

Variable	HR(95% CI)	p
Model5		
Age 0–18	1	Reference
Age 19–38	0.916 (0.708–1.185)	0.503
Age 39–58	1.680 (1.340–2.107)	<0.001
Age 59–78	2.623 (2.095–3.285)	<0.001
Age 79+	3.851 (3.050–4.845)	<0.001
Model1		
Age 0–17	1	Reference
Age 18–65	1.698 (1.350–2.136)	<0.001
Age 66–79	2.789 (2.213–3.515)	<0.001
Age 80+	3.717 (2.937–4.705)	<0.001

Variable	HR(95% CI)	p
Model2		
Age 0–17	1	Reference
Age 18–44	1.088 (0.851–1.390)	0.501
Age 45–59	1.758 (1.394–2.217)	<0.001
Age 60–74	2.518 (2.000–3.172)	<0.001
Age 75+	3.656 (2.896–4.616)	<0.001
Mdodel4		
Age 0–17	1	Reference
Age 18–53	1.391 (1.101–1.756)	0.006
Age 54–64	1.906 (1.512–2.404)	<0.001
Age 65+	3.012 (2.391–3.793)	<0.001

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Supplementary Table 2. The percentages patients matching at each level the corresponding age model and OS intervals (horizontal direction).

Models	Survival intervals							
	0–6 months	7–12 months	13–18 months	19–24 months	25–30 months	31–36 months	>36 months	Active margin
Model1								
0–18	.255	.238	.151	.087	.078	.031	.160	1.000
19–38	.177	.178	.156	.105	.090	.048	.245	1.000
39–58	.295	.208	.181	.114	.063	.034	.105	1.000
59–78	.503	.210	.125	.064	.035	.016	.047	1.000
79+	.778	.132	.054	.016	.007	.005	.008	1.000
Mass	.452	.200	.136	.076	.043	.022	.070	
Model2								
0–17	.265	.241	.157	.087	.072	.027	.151	1.000
18–65	.326	.211	.170	.103	.059	.029	.101	1.000
66–79	.574	.200	.103	.049	.026	.014	.034	1.000
80+	.795	.122	.050	.016	.006	.004	.008	1.000
Mass	.452	.200	.136	.076	.043	.022	.070	
Model3								
0–17	.265	.241	.157	.087	.072	.027	.151	1.000
18–44	.204	.178	.171	.112	.085	.042	.210	1.000
45–59	.309	.213	.180	.111	.061	.032	.094	1.000
60–74	.479	.216	.131	.069	.037	.017	.050	1.000
75+	.730	.149	.063	.024	.011	.007	.015	1.000
Mass	.452	.200	.136	.076	.043	.022	.070	
Model4								
0–17	.265	.241	.157	.087	.072	.027	.151	1.000
18–53	.253	.193	.180	.118	.070	.038	.148	1.000
54–64	.364	.226	.167	.093	.054	.024	.072	1.000
65+	.612	.184	.094	.045	.023	.012	.030	1.000
Mass	.452	.200	.136	.076	.043	.022	.070	

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Supplementary Table 3. The percentages patients matching at each level the corresponding age model and OS intervals (vertical direction).

Models	Survival intervals							
	0–6 months	7–12 months	13–18 months	19–24 months	25–30 months	31–36 months	>36 months	Mass
Model1								
0–18	.007	.015	.014	.014	.022	.018	.028	.012
19–38	.016	.037	.047	.056	.086	.091	.143	.041
39–58	.201	.321	.411	.460	.449	.473	.461	.308
59–78	.589	.556	.485	.446	.425	.395	.355	.530
79+	.186	.072	.043	.023	.018	.024	.012	.108
Active margin	1.000	1.000	1.000	1.000	1.000	1.000	1.000	
Model2								
0–17	.265	.241	.157	.087	.072	.027	.151	1.000
18–65	.326	.211	.170	.103	.059	.029	.101	1.000
66–79	.574	.200	.103	.049	.026	.014	.034	1.000
80+	.795	.122	.050	.016	.006	.004	.008	1.000
Active margin	.452	.200	.136	.076	.043	.022	.070	
Model3								
0–17	.007	.014	.013	.013	.019	.014	.025	.012
18–44	.036	.071	.100	.117	.156	.153	.238	.080
45–59	.205	.320	.396	.435	.419	.436	.401	.299
60–74	.441	.451	.401	.374	.358	.331	.296	.416
75+	.311	.144	.090	.061	.047	.065	.041	.193
Active margin	1.000	1.000	1.000	1.000	1.000	1.000	1.000	
Model4								
0–17	.007	.014	.013	.013	.019	.014	.025	.012
18–53	.123	.214	.292	.340	.354	.387	.462	.220
54–64	.248	.348	.377	.377	.383	.338	.317	.308
65+	.622	.424	.317	.270	.244	.261	.196	.460
Active margin	1.000	1.000	1.000	1.000	1.000	1.000	1.000	

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Supplemenatry Table 4. Overview of the scores calculated for each dimension and the contributions to mass and inertia assigned to each of the age group.

Models	Mass	Score in dimension		Inertia	Contribution				Total
					of point to inertia dimension		of dimension to inertia of piont		
		1	2		1	2	1	2	
Model1									
0–18	.012	.776	–.411	.003	.022	.022	.856	.068	.923
19–38	.041	1.273	–1.205	.029	.194	.619	.797	.201	.998
39–58	.308	.585	.145	.037	.307	.067	.972	.017	.989
59–78	.530	–.228	.111	.010	.080	.067	.904	.060	.963
79+	.108	–1.120	–.448	.049	.396	.225	.951	.043	.993
Active total	1.000			.129	1.000	1.000			
Model2									
0–17	.012	.700	–.175	.002	.017	.008	.818	.006	.825
18–65	.558	.471	–.056	.042	.367	.042	.998	.002	1.000
66–79	.339	–.478	.231	.027	.229	.429	.972	.028	1.000
80+	.091	–1.198	–.490	.045	.388	.521	.980	.020	1.000
Active total	1.000			.116	1.000	1.000			
Model3									
0–17	.012	.697	–.296	.002	.016	.010	.862	.044	.906
18–44	.080	1.085	–.855	.040	.262	.570	.849	.150	1.000
45–59	.299	.501	.200	.029	.209	.117	.945	.043	.987
60–74	.416	–.146	.173	.005	.025	.121	.662	.263	.925
75+	.193	–.953	–.311	.065	.488	.182	.969	.029	.998
Active total	1.000			.140	1.000	1.000			
Model4									
0–17	.012	.711	–.234	.002	.017	.009	.849	.019	.867
18–53	.220	.825	–.306	.052	.442	.300	.973	.027	1.000
54–64	.308	.268	.374	.010	.065	.626	.718	.282	1.000
65+	.460	–.593	–.098	.055	.476	.064	.995	.005	1.000
Active total	1.000			.121	1.000	1.000			

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Supplemenatry Table 5. Overview of the scores calculated for each dimension, and the contributions to mass and inertia assigned to each of the 7 OS intervals associated with age models.

Models	Mass	Score in dimension		Inertia	Contribution				Total
					of point to inertia dimension		of dimension to inertia of piont		
		1	2		1	2	1	2	
Model1									
0–6 months	.452	–.582	–.119	.053	.446	.066	.987	.012	.999
7–12 months	.200	.112	.264	.003	.007	.144	.285	.443	.727
13–18 months	.136	.443	.324	.011	.078	.148	.861	.130	.991
19–24 months	.076	.652	.329	.012	.094	.086	.910	.065	.975
25–30 months	.043	.794	–.087	.009	.080	.003	.995	.003	.998
30–35 months	.022	.841	–.155	.005	.045	.005	.972	.009	.982
>36 months	.070	1.104	–.866	.035	.250	.547	.851	.147	.999
Active total	1.000			.129	1.000	1.000			
Model2									
0–6 months	.452	–.601	–.077	.055	.483	.063	.998	.002	1.000
7–12 months	.200	.175	.363	.003	.018	.626	.641	.343	.984
13–18 months	.136	.517	.036	.012	.108	.004	.994	.001	.994
19–24 months	.076	.701	–.097	.013	.111	.017	.988	.002	.991
25–30 months	.043	.774	–.141	.009	.077	.020	.995	.004	.999
30–35 months	.022	.708	–.044	.004	.032	.001	.995	.000	.995
>36 months	.070	.905	–.400	.020	.171	.268	.968	.024	.992
Active total	1.000			.116	1.000	1.000			
Model3									
0–6 months	.452	–.599	–.122	.059	.452	.066	.988	.012	1.000
7–12 months	.200	.121	.312	.004	.008	.190	.291	.556	.847
13–18 months	.136	.479	.301	.013	.087	.121	.894	.101	.995
19–24 months	.076	.672	.280	.013	.096	.059	.935	.046	.982
25–30 months	.043	.823	–.083	.011	.082	.003	.997	.003	1.000
30–35 months	.022	.790	–.106	.005	.038	.002	.968	.005	.973
>36 months	.070	1.099	–.902	.036	.237	.560	.837	.161	.998
Active total	1.000			.140	1.000	1.000			
Model4									
0–6 months	.452	–.576	–.109	.051	.442	.078	.993	.007	1.000
7–12 months	.200	.082	.292	.002	.004	.248	.264	.672	.935
13–18 months	.136	.480	.253	.011	.092	.126	.945	.053	.997
19–24 months	.076	.680	.105	.012	.104	.012	.988	.005	.992
25–30 months	.043	.776	.098	.009	.077	.006	.996	.003	.999
30–35 months	.022	.780	–.307	.005	.039	.030	.961	.030	.992
>36 months	.070	1.081	–.698	.030	.242	.499	.921	.078	.999
Active total	1.000			.121	1.000	1.000			

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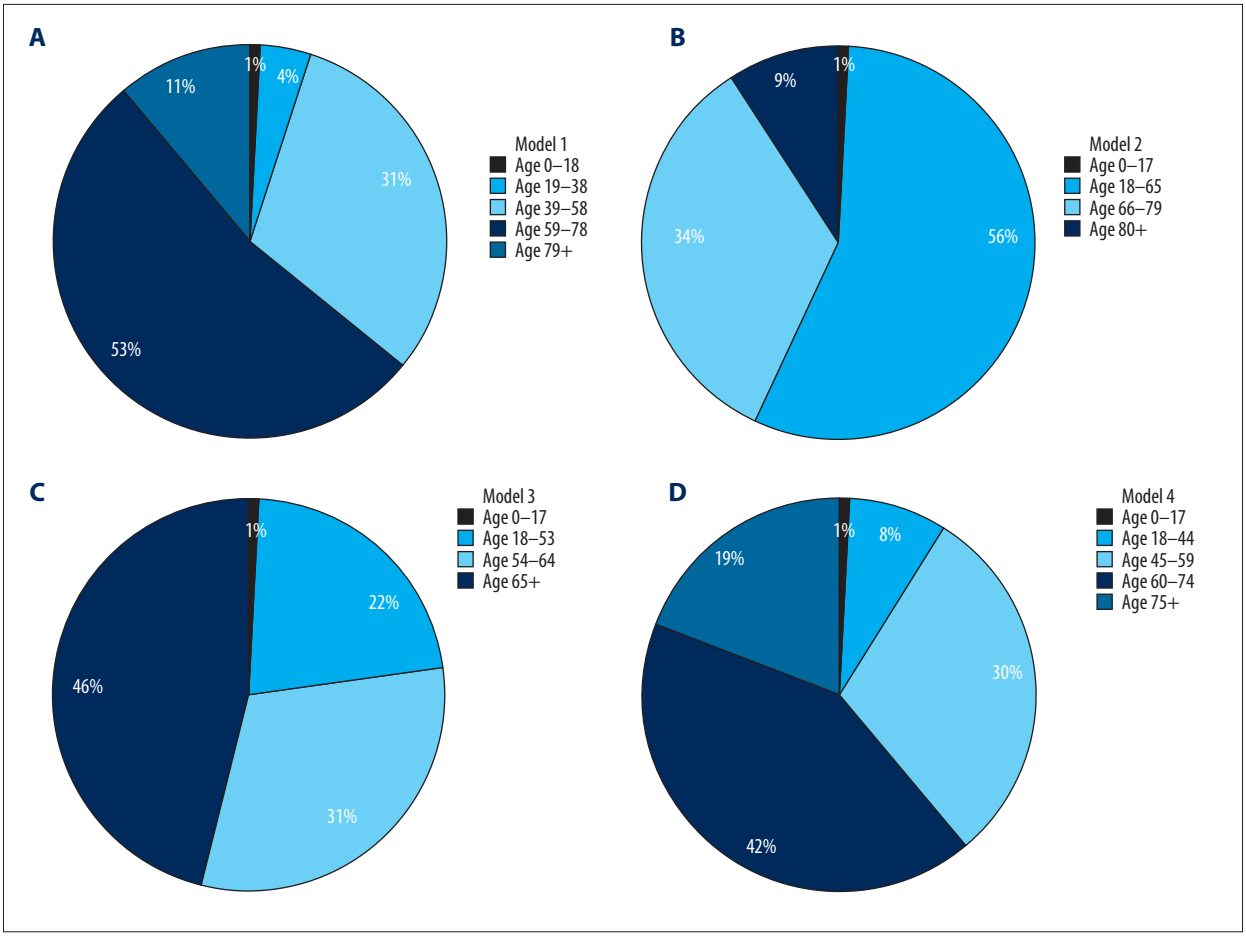

Supplementary Figure 1. (**A–D**) The distribution of age models in glioblastoma patients.

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