

# Establishment of age group classification for risk stratification in glioma patients

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## Research article

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# Abstract

**Objective:** Age is associated with the prognosis of glioma patients, but there is no uniform standard of age-group classification to evaluate the prognosis of glioma patients. In this study, we aimed to establish an age group classification for risk stratification in glioma patients.

**Methods:** A total of 1502 patients diagnosed with gliomas at Nanfang Hospital between 2000 and 2018 were enrolled. The WHO grade of glioma was used as a dependent variable to evaluate the effect of age on risk stratification. The evaluation model was established by logistic regression, and the Akaike information criterion (AIC) value of the model was used to determine the optimal cutoff points for age-classification. The differences in gender, WHO grade, pathological subtype, tumor cell differentiation direction, tumor size, tumor location, and molecular markers between different age groups were analyzed. The molecular markers included GFAP, EMA, MGMT, p53, NeuN, Oligo2, EGFR, VEGF, IDH1, Ki-67, 1p/19q, PR, CD3, H3K27M, and TS.

**Results:** The proportion of men with glioma was higher than that of women with glioma (58.3% vs 41.7%). Analysis of age showed that appropriate classifications of age group were 0-14 years old (pediatric group), 15-47 years old (youth group), 48-63 years old (middle-aged group), and  $\geq 64$  years old (elderly group). The proportions of glioblastoma and large tumor size (4-6 cm) increased with age ( $p = 0.000$ ,  $p = 0.018$ , respectively). Analysis of the pathological molecular markers across the four age groups showed that the proportion of patients with larger than 10% area of Ki-67 expression or positive PR expression increased with age ( $p = 0.000$ ,  $p = 0.017$ , respectively).

**Conclusion:** Age was effective evaluating the risk of glioblastoma in glioma patients. Appropriate classifications of age group for risk stratification were 0-14 years old (pediatric group), 15-47 years old (young group), 48-63 years old (middle age group) and  $\geq 64$  years old (elderly group). There was significant heterogeneity in WHO grade, tumor size, tumor location and some molecular markers among the four age groups.

## Introduction

Over the past 30 years, the incidence of primary malignant brain tumors has increased at an annual rate of 1%-2%, with an especially higher rate in the elderly population [1]. Glioma accounts for approximately 30% of all central nervous system (CNS) tumors and 80% of malignant primary brain tumors [2]. According to the 2016 World Health Organization (WHO) classification of tumors of the CNS, gliomas were classified into four grades (WHO grade I to IV) based on histologic criteria [3]. WHO grades I and II gliomas are recognized as low-grade gliomas (LGG) and grades III and IV are considered high-grade gliomas (HGG) [4]. In particular, glioblastoma (GBM, WHO grade IV) is the most common malignant tumor of the CNS, accounting for 45.2% of primary malignant the CNS tumors, and 54.0% of all gliomas [5]. The median survival of GBM patients is approximately 15 months, even after receiving multimodal therapies

that include maximal surgical resection with the preservation of neurological functions, followed by adjuvant radiotherapy and chemotherapy [6, 7].

Gliomas can occur at any age, with various incidences at different ages as reported in population-based studies [3, 8–10]. As glioma patients of different age groups have different characteristics, age has long been recognized as an important prognostic factor in glioma [11, 12]. LGG is the most common brain tumor in children, while HGG is the most frequent brain tumor in adults [13]. Tumors in the supratentorial areas of the brain (cerebral hemispheres and midline structures above the tentorium) were most frequent in adults, while subtentorial (brainstem and cerebellum) tumors were more common in young children than in adolescents and adults [10, 14]. There are also differences in prognosis among patients of different ages with the same diagnosis. A single-center review of 70 patients with intracranial anaplastic oligodendroglioma showed that the median survival time of patients younger than 50 years old was significantly longer than that of patients older than 50 years old [15]. Other studies have shown that age was an important prognostic factor in addition to KPS score, surgical scope and histology [16–18]. Therefore, for patients diagnosed with glioma by imaging examination and auxiliary examination, it is necessary to consider the age of the patients to perform personalized treatment for better outcomes.

However, there is no uniform age criterion for grouping glioma patients for personalized treatment [19]. In the published studies, some glioma patient cohorts were divided into different age groups according to fixed age intervals [5, 20], some were divided into two groups based on a certain age point [21], and others were divided based on the overall survival (OS) of the patients [22]. A number of studies have assessed age as a prognostic factor. Different criteria for age grouping have led to inconsistent conclusions regarding the prognostic value of age. Some studies have shown that age is not a prognostic factor in patients with glioma [23, 24]. A population-based glioblastoma study with age groups < 50 years, 50–59 years, 60–69 years, 70–79 years, and > 80 years, showed that the survival of young patients (< 50 years) (median, 8.8 months) was significantly longer than that for elderly patients (> 50 years; median, 4.1 months;  $p < 0.001$ ) [25]. However, the age grouping in this study did not subdivide glioma patients < 50 years of age and the number of patients was insufficient. Age-related studies involving a large number of glioma patients have yielded some relevant results [26, 27], but the age grouping criteria for these studies are influenced by several clinical factors, not objective clinical data. Therefore, there is an urgent need to establish a more appropriate age group classification criterion for better management of glioma patients.

For this purpose, we conducted a retrospective study collecting clinical data from 1502 patients with histologically proven gliomas in Nanfang Hospital between 2000 and 2018. Based on this cohort, we established a method of age group classification according to WHO grade for risk stratification in glioma patients, and investigated the characteristics of different age groups in terms of gender, WHO grade, pathological subtype, tumor cell differentiation direction, tumor size, tumor location, and pathological molecular markers.

## Materials And Methods

## Data collection

Unlike other types of cancer, primary brain cancer and other central nervous system tumors are not staged. They were classified according to the World Health Organization (WHO) 2000 Central nervous system tumor Classification, which was based on the predicted clinical behavior rating (grade I to IV). Although the WHO classification scheme was updated in 2007 and 2016, the central cancer registry (CCR) in the United States has not yet fully implemented these updated schemes. Although the latest version will not affect any cases included in this report, the updates made in 2007 may affect the diagnostic methods used to characterize individual tumors included in this report. With the improvement of the value of biomarkers in the histological classification of specific brain tumors, the WHO Central nervous system tumor Classification includes biomarkers in its 2016 revision.

A total of 1502 patients diagnosed with gliomas by pathological examination after surgery from 2000 to 2018 in Nanfang Hospital were enrolled in this study. The clinical data for age, gender, pathological diagnosis (according to the WHO 2000 Central nervous system tumor Classification), anatomic location of glioma, tumor size, and pathological molecular markers were collected (Table 1).

The terminology of the anatomic location of glioma used in this study was based on the Central Brain Tumor Registry of the United States (CBTRUS), Brain and other Central Nervous System Tumor Site Groupings. We recognize that with the 2016 WHO classification of central nervous system tumors, many of the histological diagnostic criteria have undergone major changes and steps have been taken to align their histological grouping scheme with the 2016 WHO standards.

The pathological diagnosis included histological classification, WHO grade, and molecular expression. The pathological molecular markers included Glial fibrillary acidic protein (GFAP, OriGene, monoclonal, 1:100 dilution), epithelial membrane antigen (EMA, OriGene, monoclonal, 1:100 dilution), O6-methylguanine-DNA methyltransferase (MGMT, OriGene, monoclonal, 1:100 dilution), neuronal nuclei (NeuN, OriGene, monoclonal, 1:100 dilution), oligodendrocyte transcription factor 2 (Oligo2, OriGene, monoclonal, 1:100 dilution), Epidermal growth factor receptor (EGFR, OriGene, monoclonal, 1:100 dilution), vascular endothelial growth factor (VEGF, OriGene, polyclonal, 1:100 dilution), isocitrate dehydrogenase 1 (IDH1, OriGene, monoclonal, 1:100 dilution), Ki-67 (OriGene, monoclonal, 1:100 dilution), ATRX chromatin remodeler (ATRX, OriGene, polyclonal, 1:100 dilution), CD34 molecule (CD34, OriGene, monoclonal, 1:100 dilution), Synaptophysin (Syn, OriGene, monoclonal, 1:100 dilution), BRAF V600E (Roche, monoclonal, 1:100 dilution), H3K27M (OriGene, polyclonal, 1:100 dilution), Neurofilament (NF, OriGene, monoclonal, 1:100 dilution), Chromogranin A (CgA, OriGene, monoclonal, 1:100 dilution), CD20 (OriGene, monoclonal, 1:100 dilution), Cytokeratin (CK, OriGene, monoclonal, 1:100 dilution), CD30 (OriGene, monoclonal, 1:100 dilution), Vimentin (OriGene, monoclonal, 1:100 dilution), Capicua (CIC, OriGene, monoclonal, 1:400 dilution), and Far upstream element binding protein 1 (FUBP1, OriGene, monoclonal, 1:400 dilution), Desmin (OriGene, monoclonal, 1:100 dilution), Progesterone receptor (PR, OriGene, monoclonal, 1:100 dilution), Leukocyte common antigen (LCA, OriGene, monoclonal, 1:100 dilution), Actin (OriGene, monoclonal, 1:100 dilution), CD3 (OriGene, monoclonal, 1:100 dilution),

Multidrug resistance protein (MRP, OriGene, monoclonal, 1:100 dilution), Lung cancer resistance protein (LRP, OriGene, monoclonal, 1:100 dilution), erb-b2 receptor tyrosine kinase 2 (Her2, OriGene, monoclonal, 1:100 dilution), Bcl2 apoptosis regulator (Bcl2, OriGene, monoclonal, 1:100 dilution), Thymidylate synthase (TS, OriGene, monoclonal, 1:100 dilution), P-glycoprotein (Pgp, OriGene, monoclonal, 1:100 dilution), Topoisomerase $\alpha$  (Top $\alpha$ , OriGene, monoclonal, 1:100 dilution), Glutathione-S-Transferase pi (GST- $\pi$ , OriGene, monoclonal, 1:100 dilution), and Neuron Specific Enolase (NSE, OriGene, monoclonal, 1:100 dilution)

### **Fluorescence in situ hybridization (FISH) Detection**

Dual-colour FISH was carried out on cytopins and matching FFPE tissue sections using the same commercial 1p/19q probes (Vysis paired probes 1p36/1q25 and 19q13/19p13, Abbott ). Briefly, 5- $\mu$ m-thick formalin-fixed, paraffin-embedded sections were deparaffinized, treated with saline sodium citrate and digested in pepsin solution. The probe mix (5 to 15  $\mu$ l) was added to each slide according to the manufacturer's instructions. Target DNA and probes were codenatured at 74°C for 5 minutes and incubated at 37°C overnight in a humidified hybridization chamber. Post-hybridization washes were performed in 2x SSC/0.3% NP-40 for 2 minutes at 75°C. Finally, the slides were air dried and counterstained with DAPI (4 ,6-diamidino-2-phenylindole).

### **Statistical analysis**

The SPSS statistical software package (version 25, IBM Corp.) was used for all analyses. The statistical significance level was set as  $p < 0.05$ . Note that reported percentages may not add up to 100% due to rounding. Categorical variables are shown numbers and percentages, while continuous variables are shown as the mean and standard deviation (SD). Pearson's chi-square test was performed to compare the categorical data. The established Dummy variables were taken as independent variables, and a logistic regression model was established according to whether high-grade glioma/WHO IV grade glioma was a dependent variable. The AIC was computed to determine the best cut-off point for age among all multivariate models. The model with the lowest AIC value was considered the best model.

## **Results**

### **Analysis of demographic and clinical characteristics**

The study population comprised 875 (58.3%) male patients and 627 (41.7%) female patients. The ratio of males to females was 1.4:1. The age range was 1 to 82 years old and the mean age was 37.7 years old (SD =17.7 years old). There were 137 patients were classified as WHO grade  $\text{I}$ , 530 patients were classified as WHO grade  $\text{II}$ , 381 patients were classified as WHO grade  $\text{III}$ , and 454 patients were classified as WHO grade  $\text{IV}$ . According to the 2016 WHO classification of tumors of the CNS, the 1502 glioma patients diagnosed and treated at Nanfang Hospital were subdivided into 23 histologically distinct types of primary glioma. Astrocytomas accounted for approximately 63.4% of all gliomas. The average diameter of glioma was 4.9 cm (SD = 2.0 cm). Gliomas mostly occurred in the frontal lobe (35.8%) and

temporal lobe (17.4%). Only a small number of gliomas were present in the spinal cord (10.4%). GBM represented the majority of gliomas (29.7%). The distribution of tumor sites showed that 1396 cases occurred in the brain, 99 cases occurred in the spinal cord and cauda equina, and 7 cases involved the spinal cord, cauda equina, and brain. Detailed information for this cohort of glioma patients is recorded in Table 1.

The median age at diagnosis for all primary glioma tumors was 38.0 years old. Compared to other pathological types of gliomas, diffuse astrocytoma, pilocytic astrocytoma, pleomorphic xanthoastrocytoma, anaplastic ependymoma and choroid plexus papilloma occurred at younger median ages. As shown by the cumulative curves of the proportion of gliomas across four WHO grades, gliomas of higher grades tended to be diagnosed at older ages (Fig. 1A,  $p < 0.05$ ). The average age at diagnosis of WHO grade IV glioma was 46.3, while WHO grade I gliomas were diagnosed at 21.9 years, with an age gap of more than 24 years (Fig. 1B). The average ages at diagnosis of WHO grade II and III were 33.6 and 38.9 years, respectively (Fig. 1B). In addition, we compared the average age at diagnosis of various pathological subtypes of glioma. We found that anaplastic astrocytoma (WHO grade III) was diagnosed at an older age than that of individuals diagnosed with astrocytoma (WHO grade II) (Fig. 1C and 1D, 43.0 vs 35.0 years, respectively,  $p < 0.05$ ). With a similar trend, anaplastic oligodendroglioma (WHO grade III) was diagnosed at a median age of 39.1 years, and oligodendroglioma (WHO grade II) was diagnosed at a median age of 34.8 years (Fig. 1E and 1F,  $p = 0.077$ ). In addition, oligodendroglioma (WHO grade II) and anaplastic oligodendroglioma (WHO grade III) were diagnosed at average ages of 34.0 and 42.5 years, respectively (Fig. 1G and 1H,  $p < 0.05$ ). Isocitrate dehydrogenase 1 (IDH1) is a vital marker for the molecular classification of glioma. In this cohort, when analyzing the average age at diagnosis of different IDH1 phenotypes by using the whole cohort, no significant differences were observed (Fig. S1A and S1B); however, IDH-wildtype (IDH-wt) glioblastoma was diagnosed at an older age than that of individuals diagnosed with IDH-mutant glioblastoma (Fig. S1C and S1D, 49.3 vs 43.2, respectively,  $p < 0.05$ ). These results indicated that the age at diagnosis was closely correlated with the WHO grade and pathological subtype of glioma.

### **Establishment of age group classification cut-off**

Age, Ki-67 and positive area of wt-p53 have great value for the diagnosis of WHO grade  $\geq$  glioma and high-grade glioma (Fig. 2A and 2B).

Dummy variables were established by age groups of 1-47 years old and  $\geq 48$  years old (I: any age between 2 and 81). The established dummy variables were considered as independent variables, and a logistic regression model was established according to whether the patients were high-grade glioma or WHO IV grade glioma, which were set as dependent variables. The AIC was calculated to determine the best cut-off point for age among all models. The model with the lowest AIC value was regarded as the best model. The results showed that the diagnostic age classification criterion was 0-47 years old and  $\geq 48$  years old. The probability of high-grade glioma or WHO IV grade glioma in the age group  $\geq 48$  years old was greater than that in the age group 0-47 years old (78.4% vs 45.2%, 50.2% vs 21.1%, respectively).

Owing to the differences in the epidemiology between adults and pediatric glioma patients, the differences in patient surgical tolerance and treatment regimens between middle-aged people and elderly people, and the various prognoses of the same diagnosis, only two age groups for the classification of glioma patients were not sufficient in clinical practice. Therefore, these two groups were subdivided into four groups. First, dummy variables were created by age groups of 0-1 years old and 1-47 years old (I: any age between 2 and 46). The established dummy variables were considered as independent variables, and a logistic regression model was set up according to whether glioma patients were high grade glioma or WHO IV grade glioma. The AIC value for each model was calculated. The model with the smallest AIC value was regarded as the best model. According to whether the patient suffered from WHO IV glioma, the diagnostic age classification criteria were 0-14 years old (pediatric group) and 15-48 years old (young group). According to whether the patient was suffered from high-grade glioma, the diagnostic age classification criteria were 0-31 years old (pediatric group) and 31-48 years old (young group). The evidence suggests that the difference between the biological spectrum of the disease may be reflected in diagnostic age, with the majority of the pediatric group belonging to the category described by Paugh et al [28]. Although some of the molecular abnormalities encountered in HGG in children are reminiscent of secondary glioblastomas, these tumors rarely originate from existing LGGs [29]. Finally, 15 years old was chosen as the age for distinguishing the pediatric group from the adult group.

Second, dummy variables as independent variables were established by age groups of 48-1 years old and  $\geq 1$  years old (I: any age between 49 and 80). The cut-off of the model with the minimum AIC value was calculated by the same method described above. The resulting diagnostic age classification criterion was 48-63 years old (middle-aged group) and  $\geq 64$  years old (elderly group). The probability of high-grade glioma or WHO IV grade glioma in the age group  $\geq 64$  years was greater than that of the age group 48-64 years old.

Collectively, glioma patients were divided into four age groups: 0-14 years old (pediatric group), 15-47 years old (youth group), 48-63 years old (middle-aged group) and  $\geq 64$  years old (elderly group). Notably, 12.3% of individuals were 0-14 years old (pediatric group), 56.3% were 15-47 years old (middle-aged group), 25.1% were 48-63 years old (youth group), and 6.3% were  $\geq 64$  years old (elderly group). The proportion of primary WHO grade IV gliomas and larger tumor sizes (larger than 4 cm) increased with age (Fig. 2C and 2D).

We used data from 650 patients in the CGGA database, according to 0-14 years old (pediatric group), 15-47 years old (young group), 48-63 years old (middle age group) and  $\geq 64$  years old (elderly group). The age group was used as a covariate, whether it was WHO grade IV as the dependent variable, using the prediction probability of 0.5 as the classification cutoff, and performing binary logistic regression, the odds ratio is 4.326, which is judged by changing the age group. The sensitivity of WHO grade IV was 64.4%, the specificity was 79.1%, and the total judgment rate was 74.0% ( $p < 0.001$ ).

### **Analysis of the pathological subtypes of glioma across four age groups**

In the 0-15 age group, the proportion of pilocytic astrocytoma in the histological distribution was 16.9%, however, glioblastoma showed the largest proportion among the 15-48, 48-64 and  $\geq 64$  year age group with 22.9%, 46.2% and 66.3%, respectively (Fig. 3C, 3D, 3E, and 3F). Pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ependymoma, anaplastic ependymoma, choroid plexus papilloma, atypical choroid plexus papilloma and ganglioglioma are predisposed to patients aged 0-15 years. Diffuse astrocytoma; diffuse midline glioma, H3K27M-mutant; oligodendroglioma; oligoastrocytoma and myxopapillary ependymoma commonly occur in 15-48 year-old patients. Anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma are more likely to occur in 48-64 year-old patients. Glioblastoma and anaplastic ganglioglioma are more likely to occur in  $\geq 64$  year-old patients ( $p \leq 0.001$ ).

### **Analysis of glioma cell differentiation direction, size, and anatomic location across four age groups**

Patients  $\geq 64$  years old were predisposed to gliomas of astrocyte origin. Patients aged 15-47 years old were predisposed to gliomas of oligodendrocyte origin and hybrid cell sources. Patients aged 0-14 years old were predisposed to gliomas of ependymal cell and other cell differentiation directions (Table 2,  $p = 0.002$ ). The proportion of tumors with sizes of 0-4 cm decreased with age; however, the proportion of tumors with sizes ranging from 4 to 6 cm was larger in older groups (Table 2,  $p = 0.018$ ).

In the 0-14 year-old group, the common locations of gliomas were the cerebellum and ventricle, accounting for 18.6% and 23.3%, respectively (Table 3). However, in the 15-47 and 48-64 year-old groups, the frontal lobe accounted for the largest proportion (Table 3,  $p = 0.000$ ). In the  $\geq 64$  year-old group, the proportion of tumors in the frontal lobe and temporal lobe was higher than that in the other locations (Table 3, 32.7% and 40.8%, respectively).

### **Analysis of molecular marker expression in four age groups**

Glial fibrillary acidic protein (GFAP) expression in all age groups accounted for more than 90.0%. The expression rate of GFAP was the highest in patients aged 15-47 years (99.7%,  $p = 0.004$ ) (Table 2). The proportion of epithelial membrane antigen (EMA) in patients aged 0-15 years was maximal (29.2%,  $p = 0.023$ ) (Table 2). The expression rate of neuronal nuclei (NeuN) was the highest in patients aged 48-63 years (46.0%,  $p = 0.005$ ). Epidermal growth factor receptor (EGFR) expression represented a maximum of 94.7% in patients aged 48-63 years ( $p = 0.000$ ) (Table 2). The proportion of IDH1 mutants was higher in the 15-47 and 48-63 year age groups than in the other two age groups, with the highest proportion being 48.6% in the 15-47 year age group ( $p = 0.000$ ) (Table 2). With increasing age, the proportion of patients with proliferation marker protein Ki-67  $> 10\%$  increased ( $p \leq 0.001$ ) (Table 2), and the proportion of patients with progesterone receptor (PR) expression increased ( $p = 0.017$ ) (Table 2). The proportion of CD3 in patients aged 48-64 years was maximal (42.9%,  $p = 0.005$ ) (Table 2). The proportion of H3K27M wild type in patients aged  $\geq 64$  years was the highest (33.3%,  $p = 0.025$ ) (Table 2). The proportion of thymidylate synthase (TS) expression was significantly higher in patients aged 48-63 and  $\geq 64$  years (74.3% and 80.0%, respectively,  $p = 0.038$ ) (Table 2). Collectively, the pathological markers used for the diagnosis of glioma showed great heterogeneity across the four age groups (Fig. S4A, S4B, S4C, and S4D). More detailed information is recorded in Table 2.

## Discussion

Clinical and biological data clearly indicate that malignant gliomas differ significantly in potential biology between adults and children [13]. A number of studies have showed that the tumor-prone locations, histopathology, prognosis and some molecular markers are different in glioma patients of different ages [30, 31]. Growing research has shown that the molecular characteristics of GBM in elderly patients are worse than those in young patients [13]. Childhood GBM displayed (on average) considerably fewer DNA copy number changes than histologically similar adult tumor [19–22]. In addition, the prognosis of glioma is particularly severe in older adults [32, 33]. The clinical practice patterns show that with increasing age, the application of surgical resection, radiotherapy and chemotherapy decreases [34–36]. Nevertheless, some elderly patients with glioblastoma can benefit from these therapies [34]. These elderly patients will receive aggressive treatment with radiation or chemotherapy. When considering treatment options for children with gliomas, neurosurgeons will try to avoid the deleterious effects of radiotherapy on the developing brains of children. Minimal dysfunction resulting from glioma and treatment should be achieved as much as possible with the expectation of children living to adulthood [37]. Moreover, age is regarded as an important factor related to the prognosis of glioma patients. Therefore, for patients diagnosed with glioma, age should be taken into consideration to perform personalized treatment for better outcome. However, the criterion for appropriately dividing age groups of glioma patients remains an unresolved clinical problem.

A large number of studies used different age groupings, and these studies led us to differential conclusions about the prognosis value of age in glioma patients [23, 24, 38]. These contradictory conclusions could be partly explained by the difference in age classification criteria between different studies. In one study, a multivariate Cox regression model with different cutoff points was used to analyze the effect of age on OS, but, only three age groups were compared, and a univariate analysis was performed using prognostic factors as a classification criterion [22]. OS is a good indicator for valuating patient outcomes, but confounding factors such as tumor size, tumor location, surgical resection extent, and patient compliance, might impair the accuracy of the relationship between age and OS.

To avoid the disturbance of confounding factors as much as possible, our study used the WHO grade of glioma as a dependent variable to assess the prognosis of glioma patients. According to the WHO grade of glioma, using statistical methods, such as logical regression and AIC modeling, the classification criteria for specific diagnostic age groups based on the patient age were 0–14 years old (pediatric group) and 15–47 years old (youth group), 48–63 years old (middle-aged group) and  $\geq 64$  years old (elderly group). However, the 2017 CBTRUS Statistical Report indicate that annual average age-adjusted incidence rates for primary brain and other CNS tumors (2010–2014) and a selection of common cancers (2010–2014) in the US are presented by children(0–14 years old), adolescents and young adults(15–39 years old), and older adults( $\geq 40$  years old) [3].

Based on this age group classification, we further analyzed the characteristics of WHO grade, tumor size, tumor histology, and anatomical location among the four age groups. We found that the proportion of

WHO grade IV gliomas increased significantly as patients became older. In addition, in the older age group, more patients suffered from a heavy tumor burden (tumor size > 4 cm). Many studies have demonstrated that patients with a higher grade of glioma have a worse outcome [7]. Moreover, a larger tumor burden might cause a higher risk of functional deficits, including motor dysfunction, impaired communication ability or decline in neurocognitive function [2]. Therefore, the prognosis of patients with gliomas can initially be evaluated according to age. Regarding the histology of glioma, pilocytic astrocytoma is the most common in children, while glioblastoma accounts for the largest proportion of adult groups. In CBTRUS statistical reports, the incidence of all brain and other central nervous system tumors was the highest among those over the age of 85 years (85.39 per 100000 population) and the lowest among children and adolescents aged 0–19 years (5.76 per 100000 population). The incidence of pilocytic astrocytoma was higher in the young age group, but decreased with the increase of age. The incidence of glioma in the 0–19 year age group decreased with the increase of age, especially for gliomas. After the pilocytic astrocytoma reached the peak at the age of 0–9 years, the incidence of pilocytic astrocytoma decreased at the age of 10–14 years and 15–19 years [3]. The predilection sites of glioma also differ with age. For patients in the 0–14 years age group, most gliomas are found in the ventricle, while the most common tumor location is the frontal lobe in the 15–47, 48–63 and  $\geq 64$  years age groups. As tumor size becomes larger in the older age group, gliomas infiltrate more regions of the CNS, among which frontal and temporal lobes are the most easily involved area in the elderly age group.

Glioma, especially glioblastoma, is a highly heterogeneous malignancy. In addition to the marked heterogeneity of gender, tumor size, tumor histopathology, and anatomical location in glioma patients, the heterogeneity of the molecular characteristics of tumors is becoming increasingly important and is reported in several studies. According to the 2016 WHO classification, glioma is first classified according to histological features, and then more subtypes are classified according to molecular characteristics. There are a variety of indicators that are widely used in clinical practice (such as GFAP, EMA, MGMT, p53, NeuN, Oligo2, EGFR, VEGF, IDH1, Ki-67, 1p/19q), and these indicators are highly correlated with the prognosis of the patients [39–41]. However, heterogeneity within the tumor also has a significant impact on the prognosis of the patients. Age-dependent occurrence and the effects of different biological markers have been reported in breast cancer, gastric cancer, and thyroid cancer [42]. For example, the association between age and tumor grade, Ki-67 markers, apoptosis index, EGFR expression and erbB-2 expression has been reported in breast cancer [43]. A study indicated that the prognostic effects of p53, 1p, and CDKN2A/p16 alterations are dependent on patient age [44]. Increasing translational studies have significantly advanced the understanding of glioma pathogenesis and have identified a number of prognostic factors. Higher tumor grade, older age [38], and increased expression of molecular biomarkers such as p53 [45], MGMT [46, 47], PR [48–50], IDH1-wildtype [51–56], H3K27M mutation of pediatric HGG [57, 58], and Ki-67 [59, 60], were related to poorer prognoses. Analysis of the pathological molecular markers across four age groups showed that the proportion of patients with larger than 10% area of Ki-67 expression or positive PR expression increased with age. Other molecular markers (GFAP, EMA, NeuN, EGFR, IDH1, CD3, and H3K27M) also showed great heterogeneity among the four age groups.

Gender, age, anatomic location of tumor, size of tumor and molecular markers are simple and objective parameters that can be collected easily in clinical practice or in multicentric studies on patients with glioma. Our research can provide clinicians with a simple method to evaluate the prognosis of glioma patients and help to promote the personalized management of glioma patients. In addition, for some clinical trials that need to divide participants of glioma into different groups, this age group classification based on WHO grade will be more objective. However, this study was limited by the sample size, and these data were retrospective. Hospital-based retrospective studies may lead to certain selection biases. Another limitation of this study was that we did not include patients with postoperative recurrence. Further validation of our results will require multicenter prospective studies with larger sample sizes.

## Conclusions

Our research indicated that the classification criteria based on the age for glioma patients were 0–14 years old (pediatric group), 15–47 years old (youth group), 48–63 years old (middle-aged group) and  $\geq 64$  years old (elderly group). Our cohort indicates that pilocytic astrocytoma accounts for the largest proportion in the 0–14 year age group, while glioblastoma accounts for the largest proportion in the other three age groups. Besides, the proportion of tumors of 4–6 cm in size or with Ki-67 > 10% increases with WHO grade. This age group classification will help to improve the diagnosis and personalized treatment of glioma patients.

## Declarations

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### Availability of data and materials

All data generated and analysed during this study are included in this article.

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Contributions

Conception and design of the work: GLH, STQ, ZYL, and RWY.

Acquisition, analysis and interpretation of data: ZYL, RWY, YWL, GZY, ZYL, JLG, KSL, ZZ, JXP, STQ, and GLH.

Drafting of the manuscript: ZYL, RWY and GLH.

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All authors approved the final version of this manuscript.

The authors disclose no conflicts of interest.

Ethics declarations

Ethics approval and consent to participate

A written consent was obtained from a patient or legal guardian on behalf of the participants under the age of 16.

The Institutional Review Board of Nanfang Hospital affiliated to Southern Medical University approved the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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The authors disclose no conflicts of interest.

## **DATA AVAILABILITY STATEMENT**

The data of this study are available from the corresponding authors upon reasonable request.

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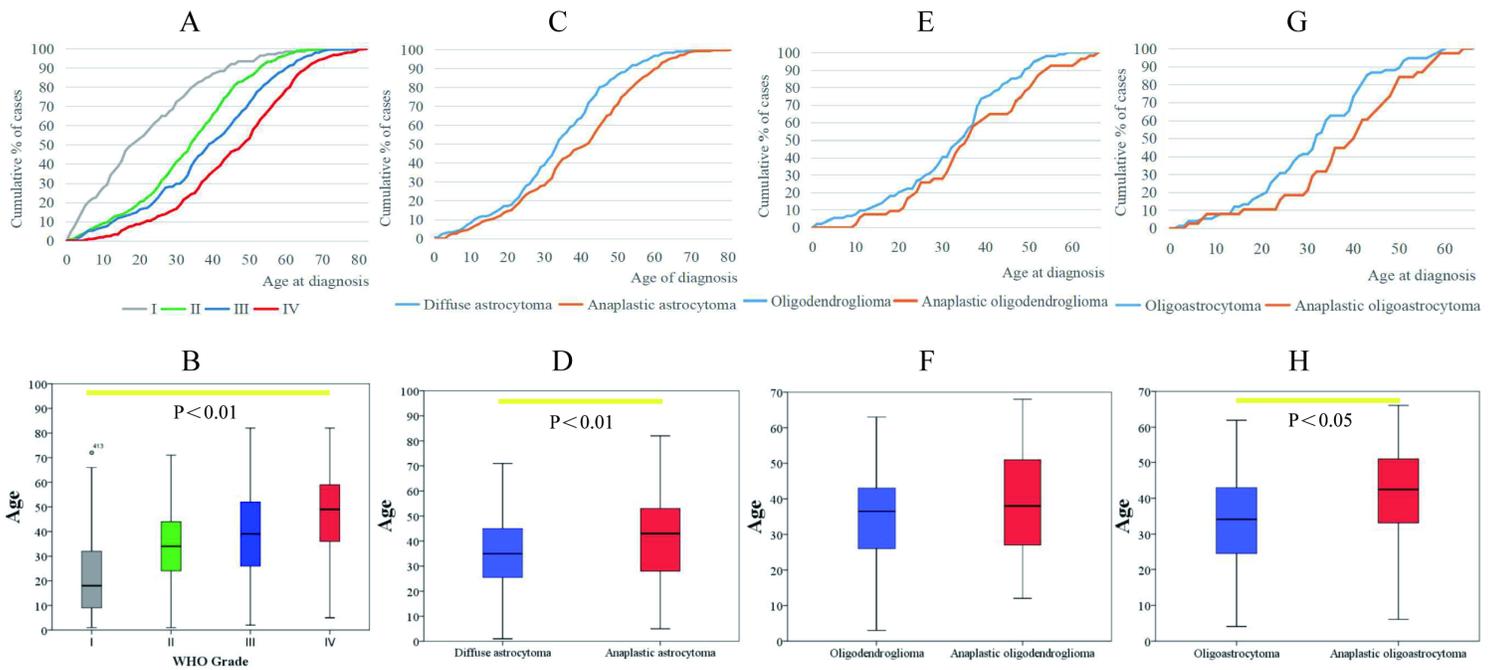
## Abbreviations

(information not available); AIC (Akaike information criterion); CNS (central nervous system); WHO (World Health Organization); LGG (low-grade gliomas); HGG (high-grade gliomas); GBM (glioblastoma); OS (overall survival); CCR (central cancer registry); CBTRUS (Central Brain Tumor Registry of the United States); FISH (fluorescence in situ hybridization); SD (standard deviation); IDH1 (isocitrate dehydrogenase 1); IDH-wt (IDH-wildtype); GFAP (Glial fibrillary acidic protein); PR (progesterone receptor); TS (thymidylate synthase);

## Tables

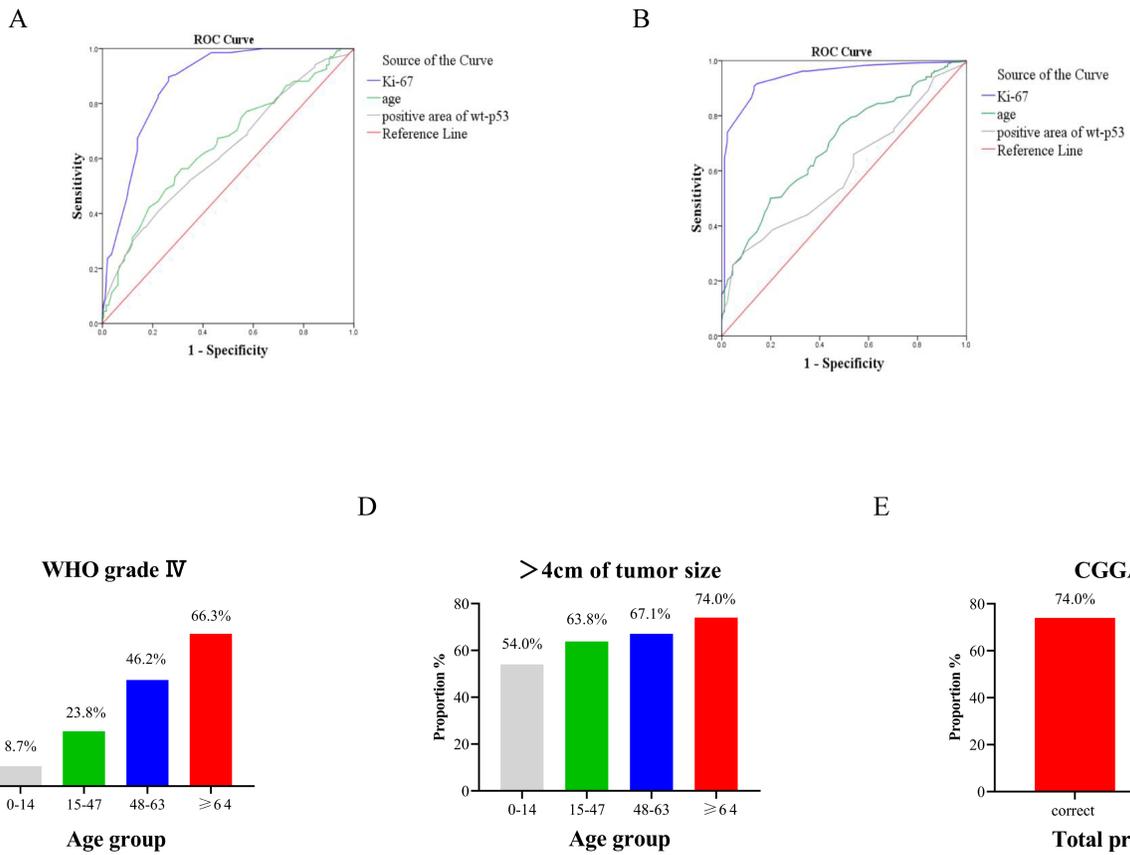
Due to technical limitations, tables are only available as a download in the supplemental files section.

## Figures



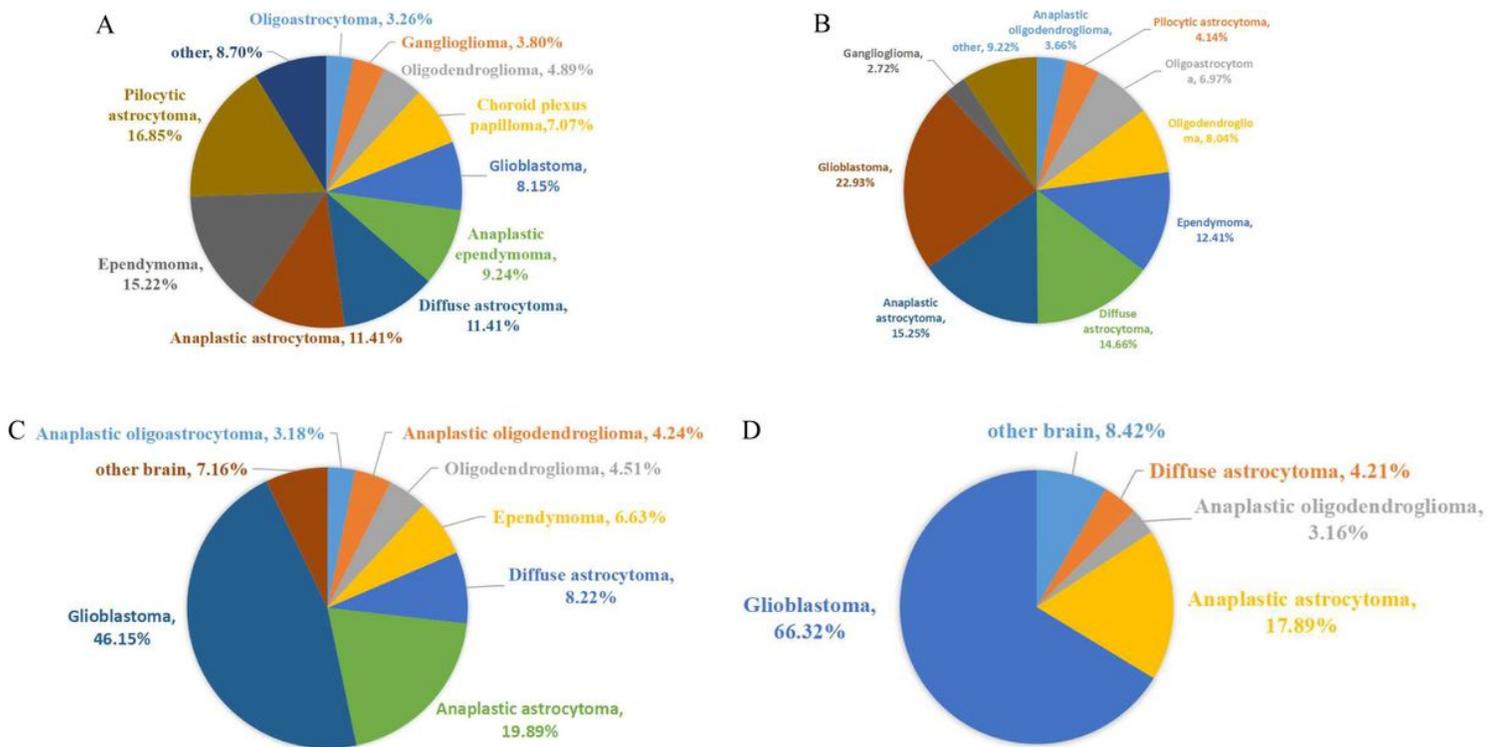
**Figure 1**

Cumulative age distribution and T test of the average age at diagnosis of different types of glioma. A: Cumulative age distribution of WHO I-IV grade glioma, the mean age of glioma patients increases with the WHO grade (WHO I: 21.9 years, WHO II: 33.6 years, WHO III: 38.9 years and WHO IV: 46.3 years, respectively). B: The average age at diagnosis of WHO I-IV grade glioma. C: anaplastic astrocytoma and diffuse astrocytoma, there is likely for an earlier manifestation in diffuse astrocytoma. D: the average age at diagnosis of anaplastic astrocytoma and diffuse astrocytoma. E: Oligodendroglioma and anaplastic oligodendroglioma, most of oligodendroglioma and anaplastic oligodendroglioma arise in adults, with peak incidence in patients aged 30-50 years. F: the average age at diagnosis of oligodendroglioma and anaplastic oligodendroglioma. G: Oligoastrocytoma and anaplastic oligoastrocytoma, the median ages of patients with oligoastrocytoma are 34.0 years. The median age of patients with anaplastic oligoastrocytoma is 42.5 years. H: The average age at diagnosis of oligoastrocytoma and anaplastic oligoastrocytoma.



**Figure 2**

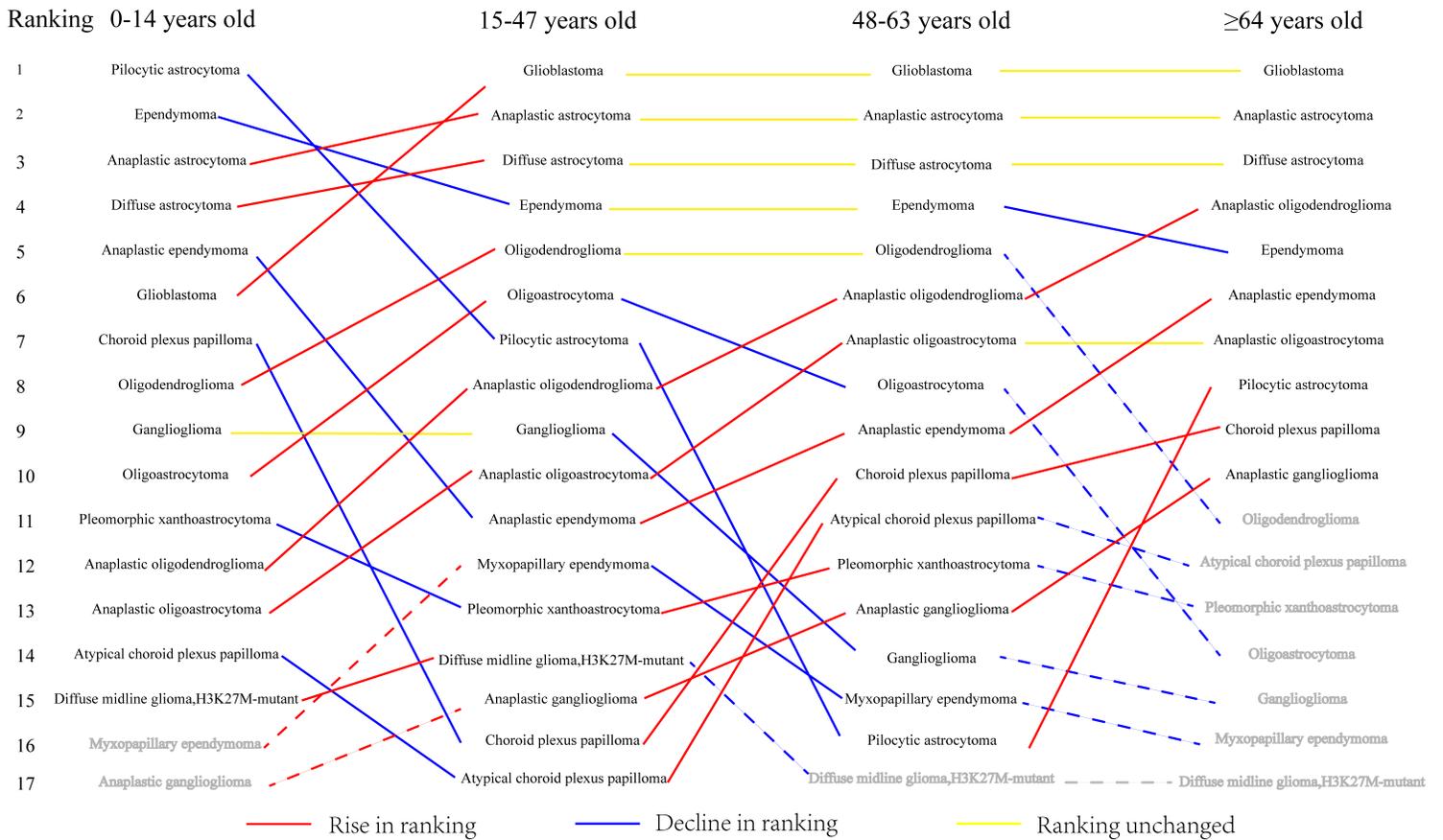
ROC curve of the sensitivity and specificity for diagnosing WHO grade IV glioma (A) and high grade glioma (B). Age, ki-67 and positive area of wt-p53 have great value for the diagnosis of WHO grade IV glioma and high-grade glioma. The proportion of WHO grade IV glioma(C) and >4cm of tumor size(D) increases with age. According to the discriminant classification of whether the pathological diagnosis of the patients was WHO grade IV or not, the prediction probability was taken as the discriminant dividing point, and the total judgment rate was 74.0%(E).



**Figure 3**

Histological distribution by Age groups. A: Histological distribution by 0-14 years old group. B: Histological distribution by 15-47 years old group. C: Histological distribution by 48-63 years old group, and D: Histological distribution by  $\geq 64$  years old group. In the 0-15 age group, the proportion of pilocytic astrocytoma in the histological distribution was 16.9%, however, glioblastoma accounted for the largest proportion of the age group 15-48 years old, 48-64 years old and  $\geq 64$  years old, with 22.9%, 46.2% and 66.3% respectively.

## Composition changes of pathological subtypes across four age groups



**Figure 4**

Composition changes of pathological subtypes across four age groups.

## Supplementary Files

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