

Antibiotic Allergy and Blood Eosinophils Percent Could Be Prognostic Indicators of Glioma

Liming Cao

Harbin Medical University School of Public Health

Zhanghua Lv

Harbin Medical University Third Hospital: Tumor Hospital of Harbin Medical University

Weiliang Wang

Harbin Medical University Third Clinical College: Tumor Hospital of Harbin Medical University

Xue Li

Harbin Medical University School of Public Health

Jing Shi

Harbin Medical University School of Public Health

Hongsheng Liang

First Affiliated Hospital of Harbin Medical University

Yiwei Zhang

Harbin Medical University School of Public Health

Fulan Hu (✉ hufu1525@163.com)

Harbin Medical University School of Public Health <https://orcid.org/0000-0002-2386-1503>

Research article

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Abstract

Background: Antibiotic allergy and blood eosinophil percentage (EOS%) may play an important role in the prognosis of gliomas, but few studies reported the relationship between antibiotic allergy and glioma as well as EOS% and glioma. The aim of our study was to estimate the relationships between antibiotic allergy, blood eosinophil percentage (EOS%) and glioma prognosis and to conduct a nomogram model for glioma patients. Estimating the effect of antibiotic allergy and EOS% on glioma prognosis may conduce to finding low-cost and safe prognostic indicators of glioma.

Methods: We conducted a retrospective cohort study with 656 glioma patients to estimate the associations between antibiotic allergy, EOS% and glioma prognosis by Kaplan-Meier and Cox regression analysis. Stratified analyses were performed according to tumor grade. We constructed a nomogram with age at diagnosis, gender, tumor grade, antibiotic allergy, EOS% to predict the survival probabilities of glioma.

Results: During 12 months follow-up, a total of 227 patients were alive and 318 patients died. Antibiotic allergy and EOS% >1.65 conferred a survival advantage on glioma patients. In the stratified analysis by tumor grade, antibiotic allergy was significantly associated with the prognosis of the prognosis of low-grade gliomas (HR = 0.36, 95%CI: 0.13-0.97) and high-grade gliomas (HR = 0.58, 95%CI: 0.36-0.93) in the univariate Cox regression analysis. However, after adjusting for confounding factors in the multivariate Cox regression analysis, antibiotic allergy was only significantly associated with high-grade gliomas (HR_{adj} = 0.50, 95%CI: 0.30-0.82); the relationship between EOS% and glioma prognosis was restricted to low-grade gliomas (HR_{adj} = 0.50, 95%CI: 0.30-0.82). The C-index of nomogram was 0.74.

Conclusions: Antibiotic allergy was a protective prognosis factor of high-grade gliomas, EOS% >1.65 was a protective prognosis factor of low-grade gliomas. The nomogram with antibiotic allergy and EOS% could effectively predict the survival probability of glioma.

Introduction

Gliomas are the most common malignant brain tumors. The World Health Organization (WHO) classified gliomas into grades I-IV [1]. Grades I/II are categorized as low-grade glioma (LGG) and grades III/IV are high-grade glioma (HGG) [2]. Gliomas were characteristic with poor prognosis, the median survival time of glioblastoma (grade IV) was 16 to 18 months and 2 years survival rate was 14.8% [3]. The prognosis of glioma was affected by various factors including age, histology and chemotherapy [2, 3]. Interestingly, recent research indicated that allergy may play a pivotal role in both the development of and host defense against brain tumors [4].

Allergies represent a type of immunological disorder resulting from an aberrant reaction to certain substance triggered by a decreased immune tolerance[5]. Allergies have been reported to be protective against several cancers, including glioma [3]. Moreover, a history of allergy and atopic conditions may confer better survival on patients with glioma [6]. However, most studies focus on the relationship between allergy and glioma risk, and the majority of reports have found that allergic conditions could decrease glioma risk by as much as 20% to 40% [6-8]. The effect of allergy on the prognosis of glioma needs more exploration and verification.

Allergies represent a broad spectrum of pathologies, with various symptoms and mechanisms depending on the allergen [9]. Previous studies about the association between allergy and glioma mostly concentrate upon food and respiratory allergy[10, 11], and few studies have reported the relationship between drug allergy and glioma, especially antibiotic allergy. Antibiotics are the most common class of drugs that cause individual allergies or intolerances [12] and drug-induced hypersensitivity reactions [13]. Because antibiotic allergy has a well-defined mechanism, it is likely to provide new ideas or evidence for immunotherapy of glioma by studying the relationship between antibiotic allergy and glioma prognosis.

Eosinophil was an established effector cell in allergic disease [14]. The activation state of eosinophil could affect the tumor microenvironment and tumor development [15-19]. Eosinophil has been reported to be associated with the various stages of disease progression and better survival of several tumors including colon, stomach and brain [20]. Furthermore, eosinophil may participate in the inverse association between allergy and glioma [21]. In general, each patient must undergo preoperative antibiotic sensitivity test and routine blood test that includes blood eosinophil percent (EOS%). Therefore, estimating the effect of antibiotic allergy and EOS% on glioma prognosis may conduce to finding low-cost and safe prognostic indicator of glioma.

The purpose of our study was to conduct a retrospective cohort study with 656 glioma patients to estimate the relationship between antibiotic allergy and glioma prognosis, as well as the relationship between blood eosinophil percent and glioma prognosis. Because of the overwhelming effect of tumor grade on survival, we conducted stratified analyses by tumor grade (LGG and HGG). Moreover, we

constructed a nomogram based on antibiotic allergy and EOS% to predict the survival probability of glioma and to evaluate the predictive value of antibiotic allergy and EOS% for glioma patients.

Material And Methods

Study population

We included consecutive patients who underwent surgical resection and were pathologically diagnosed as glioma at the Third Affiliated Hospital of Harbin Medical University from January 2010 to March 2018. Histological diagnoses were made by at least 2 neuropathologists according to the WHO classification guidelines. We excluded glioma patients who had received immunotherapy. This study was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We obtained informed consent from all patients or patient's relatives and approval from the Ethics Committee of Third Affiliated Hospital of Harbin Medical University.

Clinical data collection

Clinical data was collected from the medical records of glioma patients, including the following information: age at diagnosis, gender (male and female), height, weight, smoking (yes and no), drinking (yes and no), Karnofsky Performance Status (KPS) score (≤ 70 and >70), chemotherapy (yes and no); radiotherapy (yes and no); tumor diameter ($<5\text{cm}$ and $\geq 5\text{cm}$); tumor grade (low-grade and high-grade); antibiotics allergy (yes and no), drugs allergic to; first-time preoperative peripheral blood eosinophil percentage (EOS%).

Body mass index (BMI) was calculated as weight (kg)/height (m²). KPS scores were evaluated by clinicians based on clinical performance according to functional status scoring criteria. Tumor grade was defined according to WHO classification standards[22].

Follow-up

Survival data was collected by clinical visit, phone interviews, medical records and inquiring the death monitoring system of Municipal Disease Control Center Death from March 1st, 2018 to March 1st, 2019. Death due to glioma was considered as an outcome event. The primary outcome was overall survival (OS), which was calculated from the first surgery date to the last follow-up visit.

Defined of antibiotic allergy

Antibiotics intracutaneous test was performed on the day before surgery, patients with positive results were defined as antibiotic allergy. Briefly, 2500 units of antibiotic were dissolved in 5 ml 0.9% NaCl. The intracutaneous test was performed on the volar forearm using 0.1 ml of the solution and was read after 20 minutes [23]. Positive results, consisting of a wheal ≥ 1 cm in diameter and flare response, were determined and recorded by at least 2 nurses.

The aim of antibiotic skin test before surgery in our hospital is to determine the intraoperative and postoperative antibiotic prescription. Therefore, some participants were diagnosed as allergic to several antibiotics. According to allergic drugs, patients were divided into four groups: Cephalosporin allergy, Cephalosporin & Penicillin allergy, Penicillin allergy, and Sulfonamide allergy (Additional file 1: Figure S1). More details were presented in Table S1 of Additional file 2.

Statistical analysis

Continuous variables were tested by the independent T-test, presented as mean and standard deviation (SD). Categorical variables were tested by the Chi square test and presented as frequency and percentage. EOS% was dichotomized by using optimal cutoff values determined by the "surv_cutpoint" function of the "survminer" R package, and EOS% was ranked into 2 groups: >1.65 , ≤ 1.65 (Additional file 1: Figure S2). Survival curves were estimated by the Kaplan-Meier method, the statistical differences were evaluated by 2-sided log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated by univariate and multivariate Cox regression analysis.

Nomogram was constructed with tumor grade (low-grade and high-grade), age at diagnosis, gender (male and female), antibiotic allergy (yes and no), EOS% (≤ 1.65 and >1.65) to predict the 2-years, 3-years and 5-years survival probability of glioma patients. The bootstrap method with calibration curves was used for evaluating the performance of the nomogram. The validated function in the "rms" package was used to analyze the bias corrected concordance index (c-index) that evaluated the predictive discrimination of the model. The value range of c-index is 0-1, 1 represents the prediction accuracy rate is 100%.

Statistical analyses were performed using *R* software (version 3.6.2, Institute for Statistics and Mathematics; Vienna, Austria), statistical significance was considered as $p < 0.05$.

Results

Patients characteristics

A total of 656 eligible glioma patients were recruited in our study, with males and females accounting for 55.64% and 44.39% respectively. The age was 46.4 ± 14.6 (mean \pm SD) years. Among the 656 glioma patients, 305 were LGG and 351 were HGG. Totally 84 glioma patients (45 LGG and 39 HGG) were defined as allergic to antibiotics. The characteristics of glioma patients stratified by tumor grade were summarized in Table 1. Age, KPS score, tumor diameter, EOS% were statistically different between LGG and HGG ($p < 0.05$).

Survival time

Follow-up data was available for 545 glioma patients. During 12 months follow-up, a total of 227 patients were alive and 318 patients died, with the missing rate of 16.9%. The overall two-year survival rate was 49.4%, and 5-year survival rate was 36.7%. The two-year survival of LGG was 75.1%, the median survival time was 104 months. The two-year survival of HGG was 28.4%, the median survival time was 14 months.

We respectively conducted survival curves of antibiotic allergy, EOS% in all patients, LGG and HGG, shown as Figure 1. Whether in all patients, LGG or HGG, the survival probabilities of glioma patients with allergic to antibiotics were higher than that of glioma patients without allergic to antibiotics ($p < 0.05$). In addition, the survival probabilities of patients with EOS% > 1.65 were higher than patients with EOS% ≤ 1.65 in all and LGG ($p < 0.05$). However, there was no significant association between EOS% and survival probabilities in HGG ($p > 0.05$).

Antibiotic allergy, EOS% and glioma prognosis

Overall, antibiotic allergy and EOS% were both associated with the prognosis of glioma in the multivariate Cox regression analyses ($HR_{adj} = 0.58$, 95%CI: 0.38-0.89; $HR_{adj} = 0.64$, 95%CI: 0.50-0.81) (Table 2).

In the stratified analyses by tumor grade, antibiotic allergy was significantly associated with the prognosis of LGG in univariate Cox regression analysis ($HR = 0.36$, 95%CI: 0.13-0.97), but there was no statistical significance in multivariate Cox regression analysis ($p > 0.05$) (Table 2). EOS% > 1.65 was significantly associated with the prognosis of LGG in both the univariate ($HR = 0.49$, 95%CI: 0.30-0.80) and multivariate Cox regression analysis ($HR_{adj} = 0.50$, 95%CI: 0.30-0.82) (Table 2).

In addition, there was significant association between antibiotic allergy and HGG prognosis in the univariate ($HR = 0.58$, 95%CI: 0.36-0.93) and multivariate Cox regression analysis ($HR_{adj} = 0.53$, 95%CI: 0.33-0.88) (Table 2). However, there was no significant association between EOS% and HGG prognosis ($p > 0.05$) (Table 2).

Nomogram construction and performance

We constructed a nomogram including tumor grade, age at diagnosis, gender, antibiotic allergy and EOS% to predict the 2-years, 3-years and 5-years survival probability for all glioma patients (Figure 2). The c-index of the nomogram was 0.74, which indicated the nomogram could effectively predict the survival probability of glioma. The calibration curves presented that the 2-years 3-years survival probability predicted by this nomogram was consistent with the actual survival probability, while the 5-years survival probability predicted was less than the actual survival probability (Figure 3).

Discussion

Our study observed that antibiotic allergy and EOS% > 1.65 were associated with better survival of glioma. In the stratified analyses by tumor grade, the relationship between antibiotic allergy and glioma prognosis was restricted to HGG, and the association between EOS% and glioma prognosis was restricted to LGG. To the best of our knowledge, this is the first study identifying that preoperative antibiotic allergy and blood eosinophil percent were effective prognostic indicators of glioma.

Although in recent years, numerous studies have reported the inverse association between allergy and glioma risk [3, 4, 24], few studies revealed the association between allergy and the prognosis of glioma. One study focusing on history of allergy observed that history of

allergy conferred a survival advantage on glioma patients in The Cancer Genome Atlas (TCGA) database [6]. Our consistent results of significant association between antibiotic allergy and glioma prognosis further confirmed the protective effect of allergy on glioma prognosis, especially HGG prognosis. Conversely, another study failed to observe a significant association between penicillin allergy and the prognosis of glioblastoma [23]. The discrepancies may be explained by the different mechanisms of antibiotics. We focused on antibiotics, mainly cephalosporins allergy, which is different from penicillin allergy. Besides, considering the number of samples, our study focused on all high-grade gliomas rather than glioblastoma.

At present, the underlying biological mechanism of the association between antibiotic allergy and favorable glioma prognosis is not entirely clear, the protective effect may be explained by the following: First, allergic patients have a more sensitive and active immune system, enhanced surveillance would protect glioma patients with antibiotic allergy have better prognosis [8]. Second, appropriately targeted allergic reactions are beneficial [25]. Allergic inflammation has been recently rediscovered to protect patients from a wide array of environmental triggers which can induce DNA damage and ultimately lead to cancer development, such as xenobiotics and carcinogens [26]. Third, antibiotic allergy was mediated by IgE [27]. Theoretically, antigen-specific IgE might promote direct tumor killing through antibody-dependent cell-mediated cytotoxicity [28], longer median survival period in glioma were associated with elevated serum IgE level[29] which was similar to the result in a mouse model of ovarian cancer [29, 30]. Finally, excessive use of antibiotics may cause pathogenic bacteria to develop resistance and toxic reactions including neurotoxic reactions [31], whereas glioma patients with antibiotic allergy could avoid excessive use of antibiotics and the resulting damage.

Eosinophils are response cells of allergic conditions, peripheral blood eosinophil percent is one of the indicators in blood routine test and necessary data for surgery patients. Therefore, we further analyzed the relationship between blood EOS% and glioma prognosis to find safe and low-cost prognostic indicators for glioma patients. Our study observed that high EOS% presented better survival of gliomas while the association restricted to LGG. However, a review reported that eosinophil may hold a functional role in the initiation, promotion and progression of the developing glioblastoma. The difference may be due to the cutoff value of EOS% being calculated based on our own data, further studies are required to reveal the relationship between EOS% and high-grade gliomas. Moreover, a preliminary study has shown that eosinophil was associated with tumor grade of glioma[32], and assumed that eosinophil could be a prognostic indicator of glioma, which was verified by our study. As innate immune cells, eosinophils participate in the construction of tumor microenvironment [33]. The experimental models and human population study suggested that the induction of an eosinophil-mediated immune response might be beneficial to counteract tumor development [26]. Furthermore, immunotherapeutic approaches have shown that eosinophilic infiltration of tumor correlates with a positive outcomes of immunotherapy [29]. The effect of eosinophils on the prognosis of glioma may be associated with the function of eosinophils. Eosinophils are able to produce growth factors, cytokines, chemokines, blood coagulants, and cytotoxic mediators that may affect each stage of tumor development [14].

To present our findings more intuitively, we constructed a nomogram that included antibiotic allergy, EOS%, tumor grade, gender and age for glioma patients. The nomogram model could effectively predict the survival probability of glioma. Furthermore, the nomogram revealed that the prognostic value of antibiotic allergy was better than EOS% for glioma patients.

As a prospective study, our study provides convincing evidence about the association between antibiotic allergy, EOS% and the prognosis of glioma, but the limitation of our study should also be considered. First, patients were from the same hospital, which may lead to selection bias. Second, all the patients didn't receive immunotherapy treatment, we could not imply the association between antibiotic allergy, EOS% and immunotherapy treatment effect. Third, the cutoff value of EOS% was calculated based on this data, more studies are needed to evaluate the effectiveness of the cutoff value. Finally, more data is warranted to externally validate our nomogram.

Conclusions

In conclusion, antibiotic allergy was a protective prognosis factor of high-grade gliomas, EOS% >1.65 was a protective prognosis factor of low-grade gliomas. The nomogram with antibiotic allergy and EOS% could effectively predict the survival probability of glioma.

Abbreviations

EOS%: blood eosinophil percentage

WHO: World Health Organization

LGG: low-grade glioma

HGG: high-grade glioma

OS: overall survival

KPS: Karnofsky Performance Status

SD: standard deviation

HR: Hazard ratios

CI: confidence intervals

TCGA: The Cancer Genome Atlas

Declarations

Ethics approval and consent to participate

This study was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We obtained informed consent from all patients or patient's relatives and approval from the Ethics Committee of Third Affiliated Hospital of Harbin Medical University.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FH, LC and ZL participated in the design of the study and drafted the manuscript. LC, WW, XL, JS, HL and YZ collected and analyzed the data of this study. All authors read and approved the final manuscript.

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Tables

Table 1. Characteristics of 656 baseline subjects by Tumor Grade^a.

Factors	Glioma		P value	Total (656)
	LGG (305)	HGG (351)		
Age	41.3±14.4	50.7±13.3	<0.001*	46.4±14.6
BMI	23.96±14.39	23.57±4.23	0.651	23.75±10.3
Gender			0.603	
Male	173(26.37)	192(29.27)		365(55.64)
Female	132(20.12)	159(24.24)		291(44.36)
Smoke			0.893	
No	242(36.89)	277(42.23)		519(79.12)
yes	63(9.60)	74(11.28)		137(20.88)
Drink			0.357	
No	284(43.29)	320(48.78)		604(92.07)
Yes	21(3.20)	31(4.73)		52(7.93)
KPS score			0.007*	
>70	232(35.37)	233(35.52)		465(70.88)
≤70	73(11.13)	118(17.99)		191(29.12)
Chemotherapy			0.508	
No	179(27.29)	197(30.03)		376(57.32)
Yes	126(19.21)	154(23.48)		280(42.68)
Radiotherapy			0.233	
No	157(23.03)	197(20.03)		354(53.96)
Yes	148(22.56)	154(23.48)		302(46.04)
Tumor Diameter			<0.001*	
<5cm	186(28.35)	154(23.48)		340(51.83)
≥5cm	119(18.14)	197(30.03)		316(48.17)
Antibiotic allergy			0.131	
No	260(39.63)	312(47.56)		573(87.20)
Yes	45(6.86)	39(5.95)		84(12.80)
EOS%			0.030*	
≤1.65	354(55.49)	40(6.27)		394(61.76)
>1.65	205(32.13)	39(6.11)		244(38.24)

^a: Abbreviation: BMI, Body Mass Index; KPS, Karnofsky score; EOS%, Eosinophil percentage; LGG, Low-grade glioma; HGG, High-grade glioma. *: $P < 0.05$.

Table 2. Hazard Ratio (95%CI) for glioma prognosis in Cox regression ^a.

Variables	Glioma				LGG				HGG			
	Univariate		Multivariate **		Univariate		Multivariate **		Univariate		Multivariate **	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Antibiotic allergy		0.003		0.013		0.043		0.078		0.02		0.013
No	1.00		1.00		1.00		1.00		1.00		1.00	
Yes	0.53 (0.34-0.81)		0.58 (0.38-0.89)		0.36 (0.13-0.97)		0.40 (0.15-1.11)		0.58 (0.36-0.93)		0.53 (0.33-0.88)	
EOS%		<0.001		<0.001		0.005		0.007		0.163		0.073
≤1.65	1.00		1.00		1.00		1.00		1.00		1.00	
>1.65	0.65 (0.51-0.82)		0.64 (0.50-0.81)		0.49 (0.30-0.80)		0.50 (0.30-0.82)		0.82 (0.63-1.08)		0.77 (0.58-1.03)	

^a: CI: Confidence interval; EOS%: Eosinophil percentage.

** : Adjusted for gender, age, BMI, KPS, drink, smoke, chemotherapy, radiotherapy, tumor diameter.

Figures

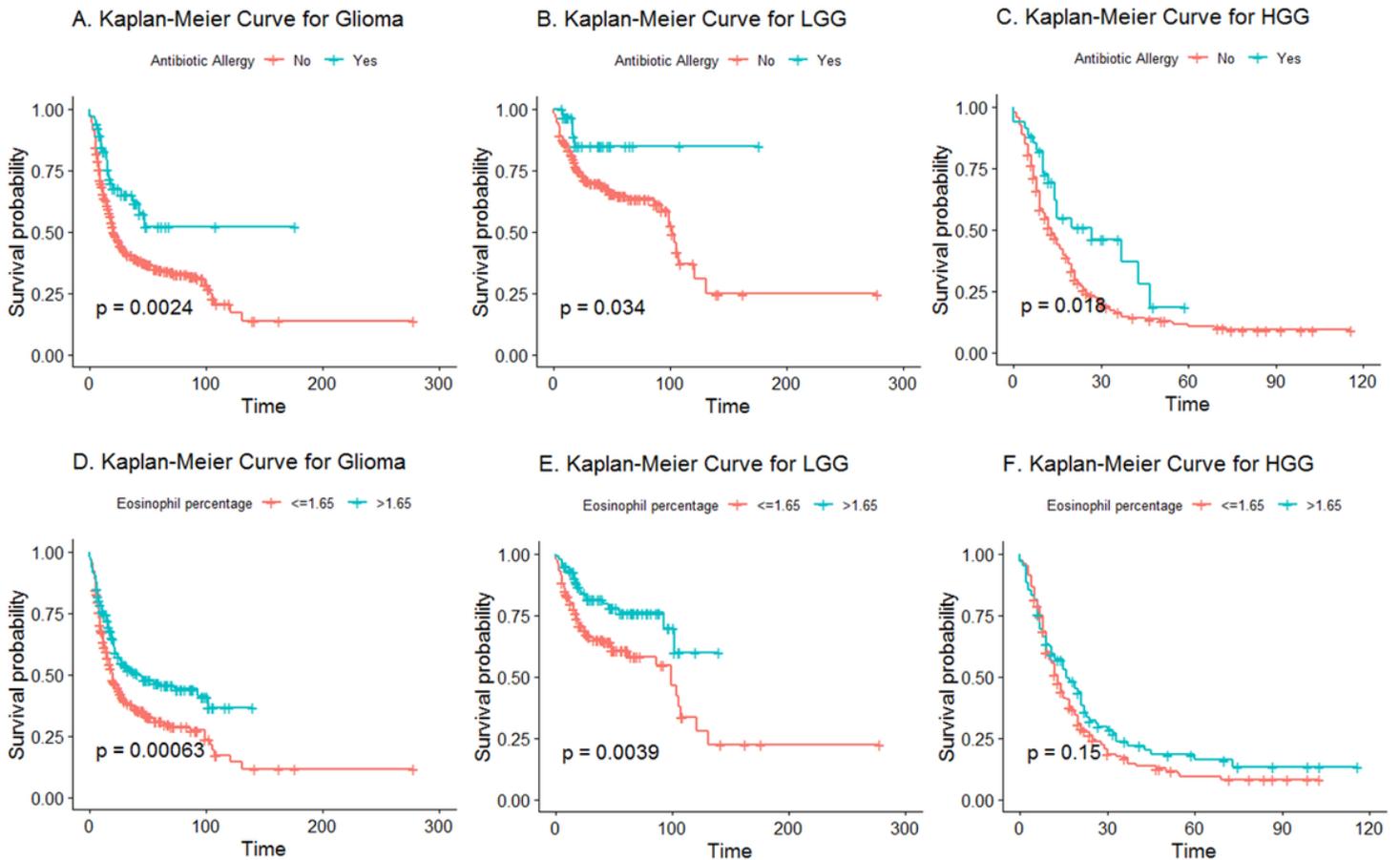


Figure 1

Kaplan-Meier survival analysis. (A) Survival curve of antibiotic allergy for glioma ($p < 0.05$). (B) Survival curve of antibiotic allergy for low-grade glioma ($p < 0.05$). (C) Survival curve of antibiotic allergy for high-grade glioma ($p < 0.05$). (D) Survival curve of Eosinophil percentage (EOS%) for glioma ($p < 0.05$). (E) Survival curve of Eosinophil percentage (EOS%) for low-grade glioma ($p < 0.05$). (F) Survival curve of Eosinophil percentage (EOS%) for high-grade glioma ($p > 0.05$).

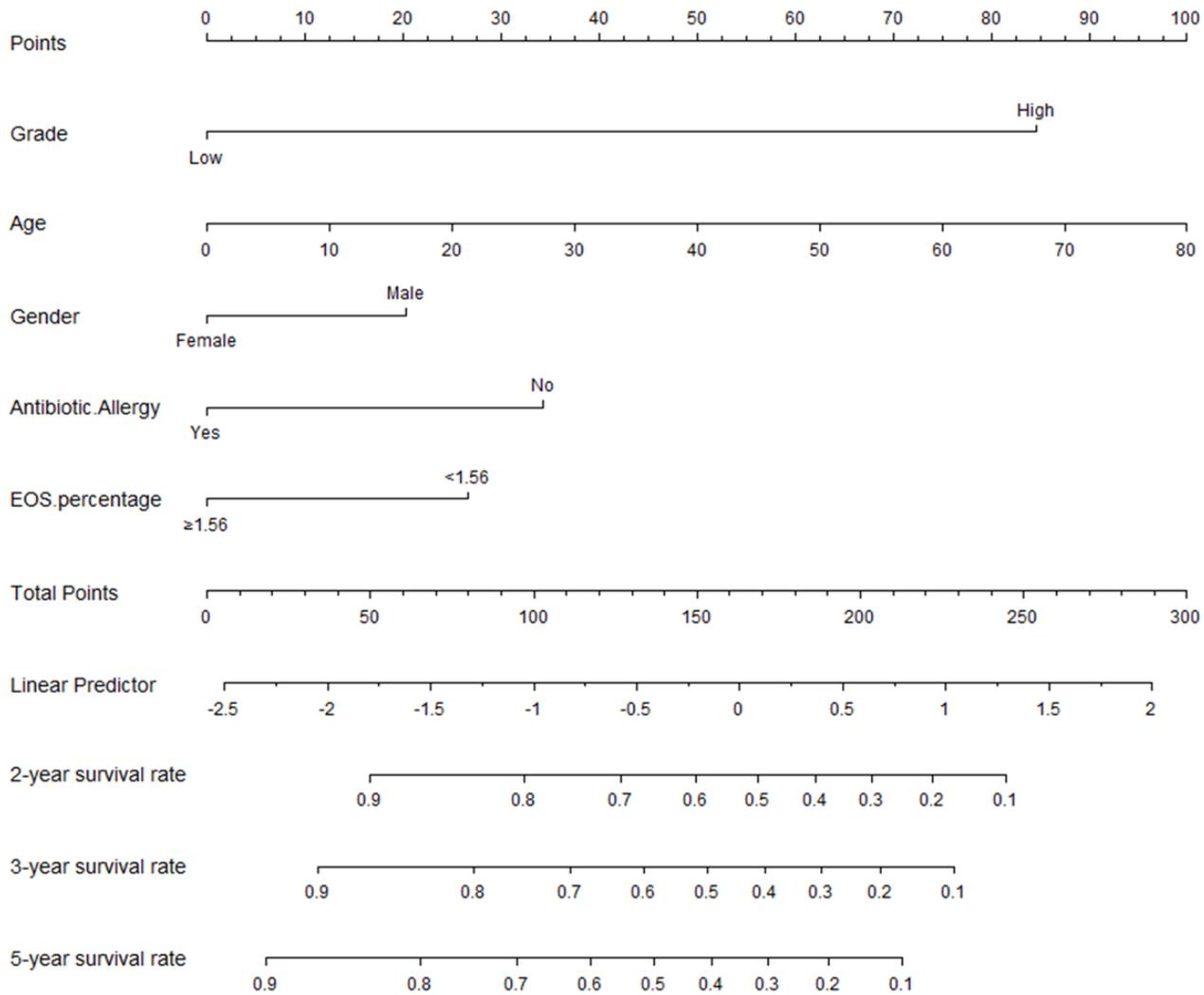


Figure 2

Nomogram predicting 2-year, 3-year, 5-year survival probability of glioma. To use the nomogram, draw a straight line upward from the patient's characteristics of age, gender, tumor grade, antibiotic allergy, EOS%, EOS to the upper points scale, the sums of the scores of all variables. Then, draw another straight line down from the scale of the total points through the 2-year, 3-year, 5-year survival rate. This is the probability of the presence of prognosis in an individual.

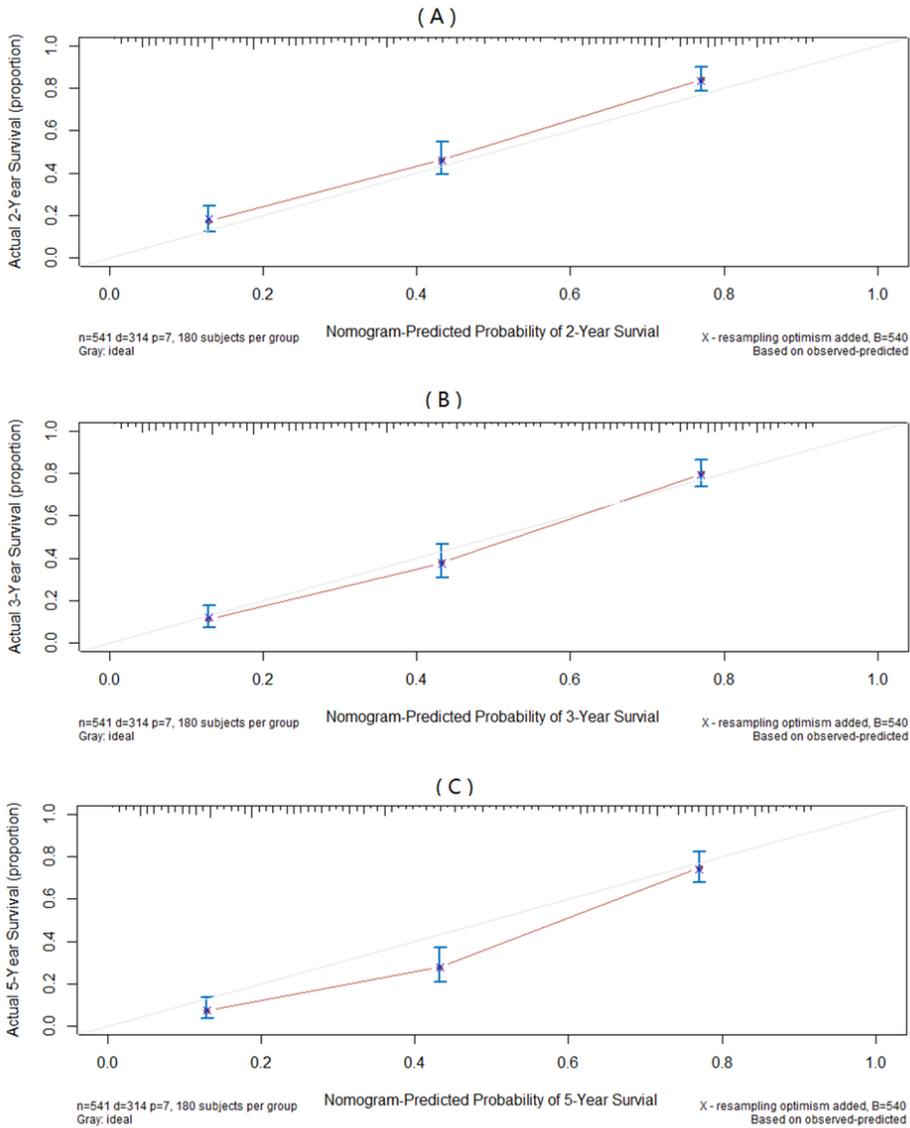


Figure 3

Calibration curves of survival probabilities of glioma. (A) 2-Year calibration curves. (B) 3-Year calibration curves. (C) 5-Year calibration curves.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1.docx](#)
- [Additionalfile2.docx](#)