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Original Article

A Nomogram for Predicting Overall Survival of Patients With Primary Spinal Cord Glioblastoma

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Objective: Primary spinal cord glioblastoma (PSCGBM) is a rare malignancy with a poor prognosis. To date, no prognostic nomogram for this rare disease was established. Hence, we aimed to develop a nomogram to predict overall survival (OS) of PSCGBM.
Methods: Clinical data of patients with PSCGBM was retrospectively collected from the neurosurgery department of Soochow University Affiliated Second Hospital and the Surveillance Epidemiology and End Results database. Information including age, sex, race, tumor extension, extent of resection, adjuvant treatment, marital status, income, year of diagnosis and months from diagnosis to treatment were recorded. Univariate and multivariate Cox regression analyses were used to identify independent prognostic factors for PSCGBM. A nomogram was constructed to predict 1-year, 1.5-year, and 2-year OS of PSCGBM.
Results: A total of 132 patients were included. The 1-year, 1.5-year, and 2-year OS were 45.5%, 29.5%, and 18.9%, respectively. Four variables: age groups, tumor extension, extent of resection, and adjuvant therapy, were identified as independent prognostic factors. The nomogram showed robust discrimination with a C-index value for the prediction of 1-year OS, 1.5-year OS, and 2-year of 0.71 (95% confidence interval [CI], 0.61–0.70), 0.72 (95% CI, 0.62–0.70), and 0.70 (95% CI, 0.61–0.70), respectively. The calibration curves exhibited high consistencies between the predicted and observed survival probability in this cohort.
Conclusion: We have developed and internally validated a nomogram for predicting the survival outcome of PSCGBM for the first time. The nomogram has the potential to assist clinicians in making individualized predictions of survival outcome of PSCGBM.

Keywords: Spinal cord, Glioblastoma, Nomogram, Rare diseases, Prognostic factors

INTRODUCTION

Primary spinal cord glioblastoma (PSCGBM) is a rare disease, accounting for approximately 1.5% of intraspinal tumors.[1] To date, no standard treatment algorithm of PSCGBM was established. In contrast to its intracranial counterpart, PSCGBM was reported to have poorer survival outcome. The median survival time for PSCGBM is just about 9 months.[2-4]

Several factors might contribute to its worse prognosis. Firstly, gross total resection (GTR) of PSCGBM is a great challenge due to dense nerve fiber in spinal cord and no definite margin between normal spinal cord and tumor.[5] As a result, patients with PSCGBM frequently had high postoperative residual tumor burden. Secondly, infertile blood supply of spinal cord might lead to insufficient chemotherapeutic drug permeability. Thirdly, MGMT promoter methylation, which is a prognostic marker for benefit from temozolomide (TMZ), infrequently occurred in spinal cord astrocytoma.[6,7] In conclusion, the cur-

rent investigation is still ongoing to determine the precise efficacy of TMZ in the treatment of PSCGBM.[1,8-10]

In previous studies, sex, ages, adjuvant treatment and surgical treatment were found to be prognostic factors of PSCGBM in Cox proportional hazards model.[11-14] However, Cox model could not be used to predict individual survival outcome and quantify survival probability. In recent years, nomograms are widely used for cancer prognosis.[15-17] As compared with traditional Cox regression model, a nomogram is a simple, visual and personalized scoring system for the prognostic prediction and can be used to predict individual survival probability. To date, no nomogram for predicting survival outcome of PGCGBM is established. Here, we have developed a nomogram for PSCGBM in our study to predict OS based on a large cohort.

MATERIALS AND METHODS

1. Study Population

Data were extracted from Surveillance Epidemiology and End Results (SEER) database (the Incidence-SEER 8Regs Custom Data, Nov 2021 Sub [1975–2019 varying] and Incidence-SEER 17Regs Custom Data, Nov 2021 Sub [2000–2019 varying]). Overlapped data between the 2 subdatabases were identified based on unique patient ID. Only patients who were diagnosed with glioblastoma (ICD-O-3 code: 9940, 9941) and lesions located at the spinal cord or cauda equina (ICD-O-3 code: C72.0 for "spinal cord"; C72.1 for "cauda equina") were included. Additionally, patients who were diagnosed with PSCGBM and underwent surgery at the Department of Neurosurgery, the Second Affiliated Hospital of Soochow University, were also included. Patients meet the following criteria would be excluded: (1) metastasis, instead of primary lesion, which could be identified by sequence number and primary tumors were marked with "one primary only" nor "1st of 2 or more primaries"; (2) no surgery was performed or surgical strategy was unknown; (3) death from other causes or cause was unknown; (4) survival time was not available; (5) diagnostic confirmation was not based on pathological examination. The following data were collected: age groups, sex, race, tumor extension, extent of resection, adjuvant therapy, year of diagnosis, marital status at diagnosis, median household income (MHI) adjusted for inflation to 2019 and months from diagnosis to treatment. Detailed screening flow chart is shown in Fig. 1.

The study was approved by the Institutional Review Board (IRB) of the Second Affiliated Hospital of Soochow University (IRB No. JD-HG-2024-047).

2. Definition of Variables

Age distribution was categorized into 3 groups: 5–17, 18–64, and ≥65 years. Race was divided into white, black, and other/unknown. Tumor invasion was stratified into localized, distant and unknown. Extent of resection was classified as biopsy, partial resection (PR), GTR, and unknown. Adjuvant treatment was divided into none, radiotherapy (RT) only, chemotherapy (CT) only, radiochemotherapy, and unknown. Years of diagnosis were categorized into 3 groups at 20-year intervals. Marital status was stratified into single (never married), married (including common law), and divorced/widowed. MHI inflation adjusted to 2019 was categorized as ≤$50,000, $50,000–$59,999, $60,000–$69,999, ≥$70,000 and unknown. Months from diagnosis to treatment were categorized into 2 groups based on whether patients received immediate treatment within 1 month. Survival outcome was dichotomized into alive and cancer-specific death.

3. Data Analysis and Diagnostic Prediction Model Building

Continuous variables were reported as mean±standard deviation or median±interquartile range (IQR), as appropriate. Categorical data were presented as the frequency (percentage). Two-tailed t-test was used for normally distributed continuous variables and Mann-Whitney U-test for nonnormally distributed continuous variables; chi-square test or Fisher test was used for categorical variables. The Kaplan-Meier method was applied to calculate survival time and rates. The nomograms were built based on the results of multivariable Cox analyses of OS. The final model selection for the nomograms was performed by a backward step-down selection process using the Akaike information criterion. The performance of the nomogram was measured by the C-index. Calibration of the nomogram for 1-, 1.5-, 2-year survival was done by comparing the predicted with the observed survival. In the present study, the nomogram was subjected to 1,000 bootstrap resamples for internal validation. Furthermore, decision curve analysis (DCA) was performed to finalize the ranges of threshold probabilities within which the nomograms were clinically valuable by rmda (risk model decision analysis) package. A significance level of $p < 0.05$ was used to denote statistical significance. All statistical analysis was performed using R software (ver. 4.3.2, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 132 patients with PSCGBM were included (SEER

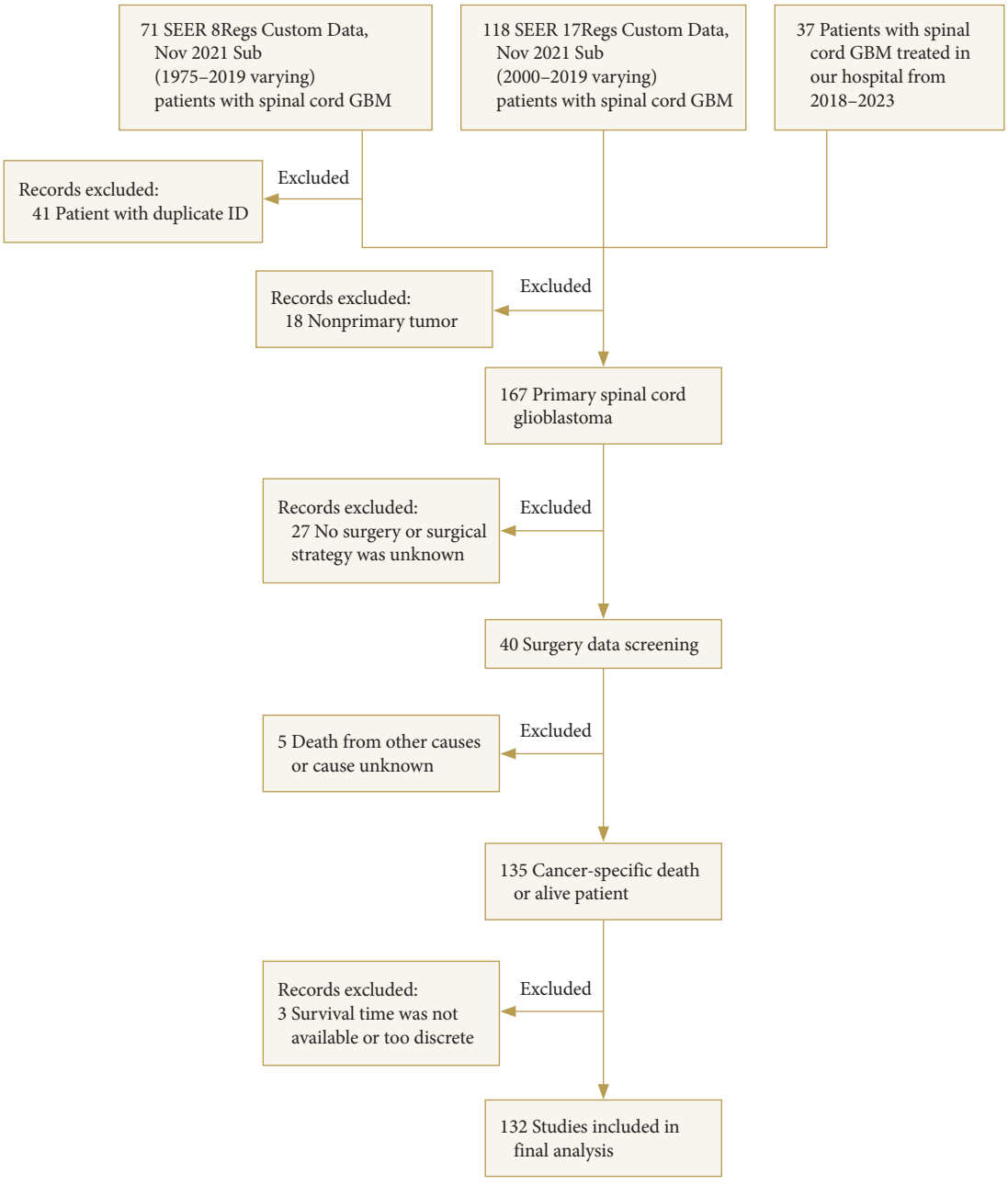

Fig. 1. The final diagnosis flowchart for patient enrollment. SEER, Surveillance Epidemiology and End Results; GBM, glioblastoma.

database: 97 patients; our institute: 35 patients). 61 (46.2%) were female. The median age at diagnosis was 30 years (IQR, 15–46). The majority (78.8%) of lesions were localized, 7.6% of tumors exhibited distant dissemination. 71 (53.8%) and 47 (35.6%) of patients underwent PR and GTR, respectively. As to adjuvant therapy, 18 (13.6%) and 2 (1.5%) of patients received RT only and CT only, respectively, while 88 (66.7%) of patients received radiochemotherapy. The majority (77.3%) received treatment within one month after diagnosis (Table 1).

The median survival time was 11 months (Fig. 2). Kaplan-Meier survival curves by variable categories showed that age groups, extent of resection and adjuvant therapy were associated with survival outcome (Fig. 3A–J).

Multivariate Cox regression analysis demonstrated that age groups (18–64 years: hazard ratio [HR], 0.59; 95% CI, 0.38–0.92; p = 0.021), tumor extension (distant: HR, 2.71; 95% CI, 1.33–5.52; p = 0.006), extent of resection (GTR: HR, 0.36; 95% CI, 0.14–0.93; p = 0.034), adjuvant therapy (radiochemothera-

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Table 1. Demographic and treatment characteristics of patients with primary spinal cord glioblastoma

Variable	Total (n = 132)	Alive (n = 24)	Cancer-specific death (n = 108)	p-value
Age (yr), median (IQR)	30 (15–46)	37.5 (24.0–53.5)	28 (14.8–46.0)	0.102
Age groups (yr)				0.106
0–17	39 (29.5)	3 (12.5)	36 (33.3)	
18–64	83 (62.9)	18 (75.0)	65 (60.2)	
≥ 65	10 (7.6)	3 (12.5)	7 (6.5)	
Sex				0.967
Female	61 (46.2)	11 (45.8)	50 (46.3)	
Male	71 (53.8)	13 (54.2)	58 (53.7)	
Race				0.194
White	75 (56.8)	10 (41.7)	65 (60.2)	
Black	7 (5.3)	1 (4.2)	6 (5.6)	
Other/unknown	50 (37.9)	13 (54.2)	37 (34.3)	
Tumor extension				0.074
Localized	104 (78.8)	23 (95.8)	81 (75.0)	
Distant	10 (7.6)	0 (0)	10 (9.3)	
Unknown	18 (13.6)	1 (4.2)	17 (15.7)	
Extent of resection				0.087
Biopsy	14 (10.6)	0 (0)	14 (13.0)	
Partial resection	71 (53.8)	12 (50.0)	59 (54.6)	
Gross total resection	47 (35.6)	12 (50.0)	35 (32.4)	
Adjuvant therapy				0.936
None	10 (7.6)	2 (8.3)	8 (7.4)	
Radiotherapy only	18 (13.6)	4 (16.7)	14 (13.0)	
Chemotherapy only	2 (1.5)	0 (0)	2 (1.9)	
Radiochemotherapy	88 (66.7)	15 (62.5)	73 (67.6)	
Unknown	14 (10.6)	3 (12.5)	11 (10.2)	
Year of diagnosis				< 0.001*
1975–1994	10 (7.5)	0 (0)	10 (9.3)	
1995–2014	63 (47.7)	4 (16.7)	59 (54.6)	
2014–2023	59 (44.7)	20 (83.3)	39 (36.1)	
Marital status at diagnosis				0.191
Single (never married)	73 (55.3)	10 (41.7)	63 (58.3)	
Married (including common law)	50 (37.9)	13 (54.2)	37 (34.3)	
Divorced/widowed	9 (6.8)	1 (4.2)	8 (7.4)	
MHI inflation adjusted to 2019 (USD)				0.397
< 50,000	40 (30.3)	10 (41.7)	30 (27.8)	
50,000–59,999	21 (15.9)	5 (20.8)	16 (14.8)	
60,000–69,999	27 (20.5)	4 (16.7)	23 (21.3)	
> 70,000	36 (27.3)	5 (20.8)	31 (28.7)	
Unknown	8 (6.1)	0 (0)	8 (9.3)	

(*Continued*)

Table 1. Demographic and treatment characteristics of patients with primary spinal cord glioblastoma (Continued)

Variable	Total (n = 132)	Alive (n = 24)	Cancer-specific death (n = 108)	p-value
Months from diagnosis to treatment				0.003*
Immediate treatment within 1 mo	102 (77.3)	13 (54.2)	89 (82.4)	
No immediate treatment within 1 mo	30 (22.7)	11 (45.8)	19 (17.6)	

Values are presented as number (%) unless otherwise indicated.
IQR, interquartile range; MHI, median household income; USD, United States dollar.
*p < 0.05, the groups exhibited statistically significant differences.

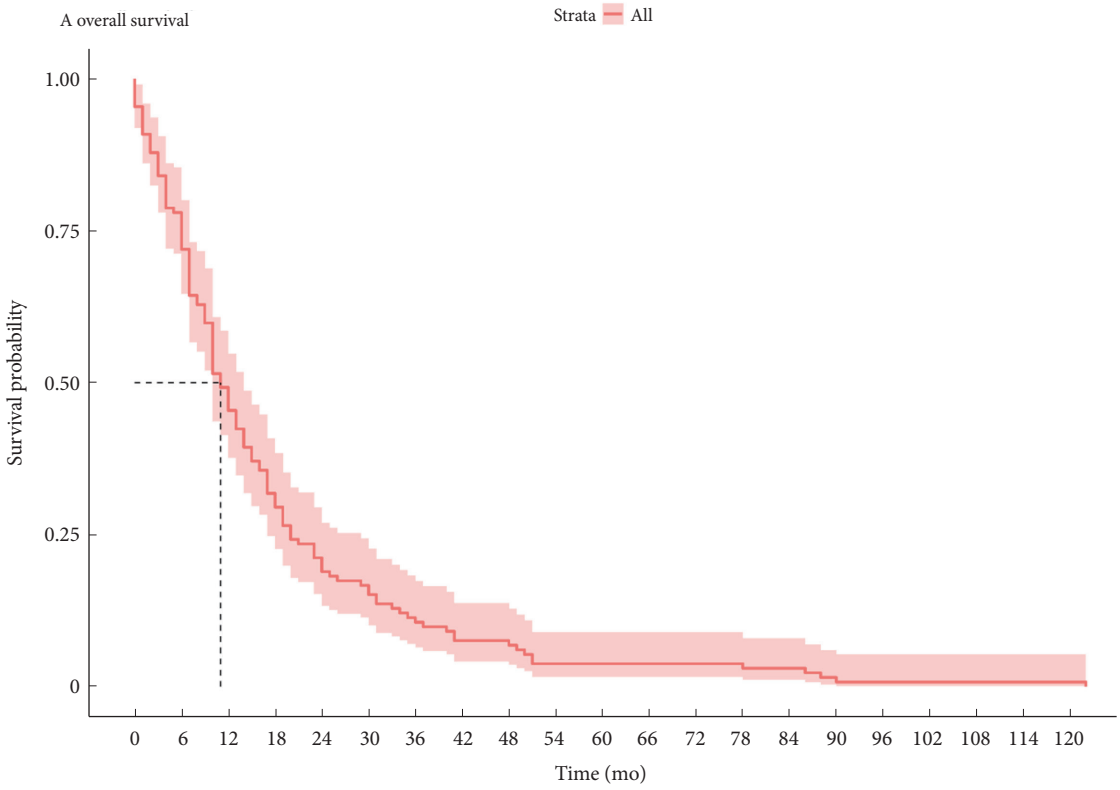

Fig. 2. In primary spinal cord glioblastoma, the median survival time is 11 months. The overall survival rates at 1, 1.5, and 2 years were 45.5%, 29.5%, and 18.9%, respectively.

py: HR, 0.37; 95% CI, 0.16–0.85; p = 0.019; unknown: HR, 0.27; 95% CI, 0.09–0.78; p = 0.016) were independent predictors of OS (Table 2).

Although the median survival time of PSCGBM is relatively short, of note, we observed that 45 patients had a survival time of at least 18 months. Therefore, it will be helpful for clinician to discriminate patients with relative better survival outcome from those with relative poorer survival outcome by using a nomogram. Based on independent predictors of OS identified by multivariable Cox analysis, a nomogram for predicting 1-year OS, 1.5-year OS, and 2-year OS was constructed (Fig. 4). In terms of discrimination of the nomogram model, the C-index value was 0.71 (95% CI, 0.61–0.70), 0.70 (95% CI, 0.61–0.70), and 0.72 (95% CI, 0.62–0.72) for the prediction of 1-year OS, 1.5-year OS, and 2-year OS, respectively and comparable C-index values were confirmed through bootstrapping validation (C-index for the prediction of 1-year OS, 1.5-year OS, and 2-year OS: 0.74, 0.74, 0.75) (Fig. 5A–C). As respect to calibration, the calibration curves of the score system showed high consistencies between the predicted and observed survival probability in this cohort (Fig. 5D–F). Finally, DCA was performed to evaluate the clinical usefulness of the nomogram. When the predicted threshold probability was 80%–100% for 1-year OS, 1.5-year OS, and 2-year OS, application of this mod-

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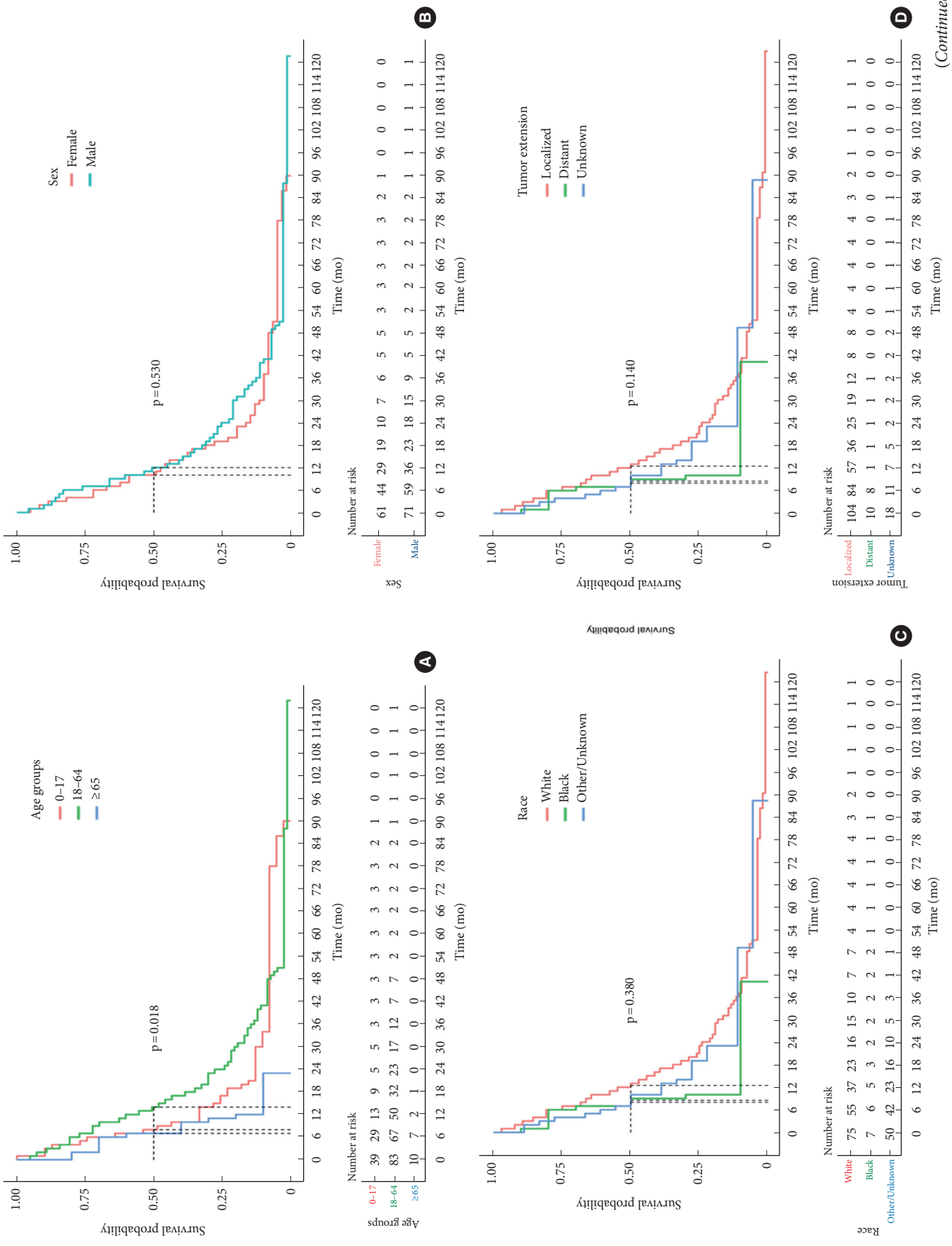

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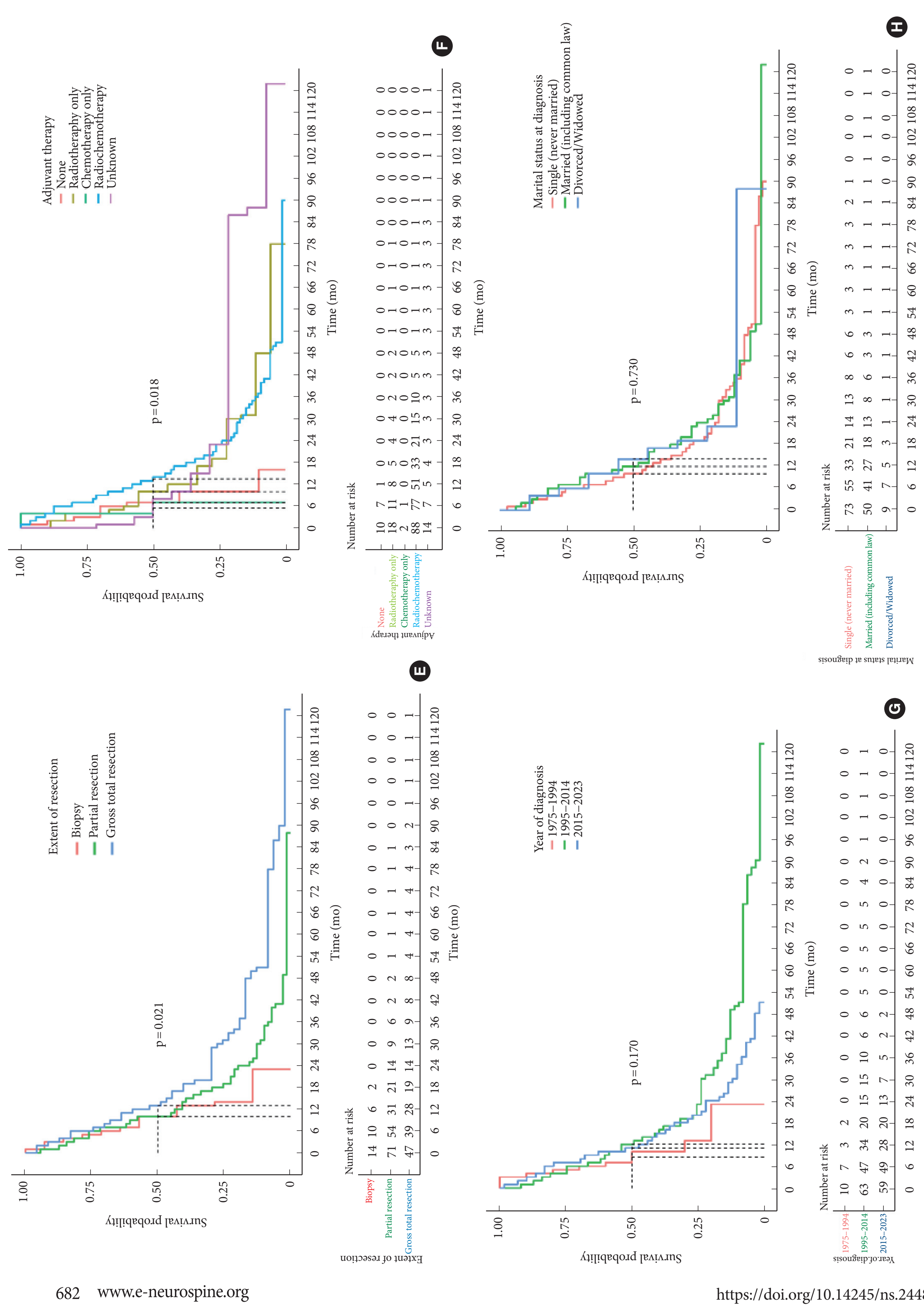
Fig. 3. In the Kaplan-Meier survival curve analysis, we considered variables such as age groups (A), sex (B), race (C), tumor extension (D), extent of resection (E), adjuvant therapy (F), year of diagnosis (G), marital status at diagnosis (H), median household income (MHI) inflation adjusted to 2019 (I), and months from diagnosis to treatment (J). The analysis revealed significant differences only in age groups, adjuvant therapy and extent of resection.



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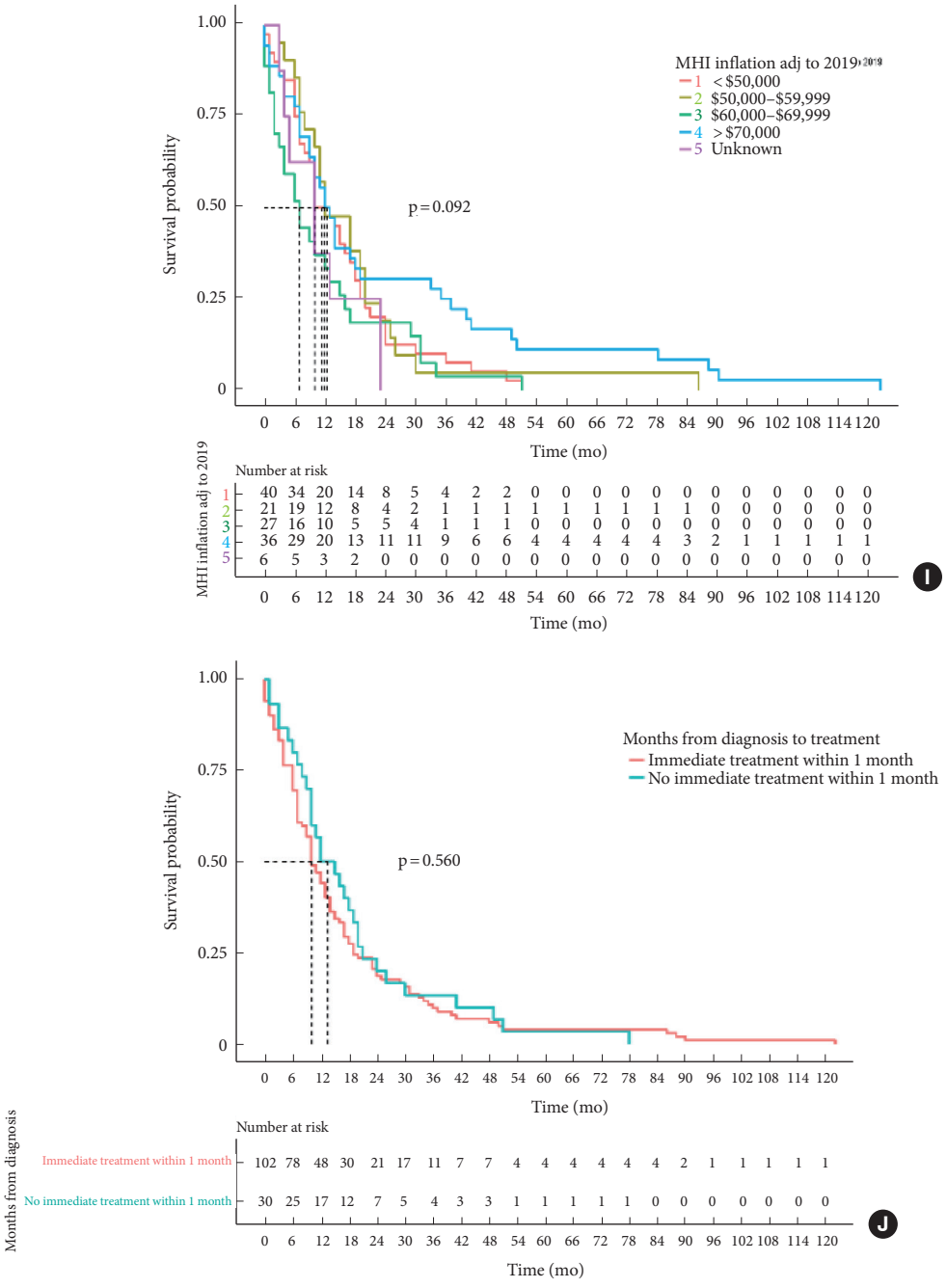

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el to predict survival outcome could add more benefit than the treat-all or treat-none strategy (Fig. 5G–I).

DISCUSSION

PSCGBM accounts for only 1%–5% of central nervous system glioblastomas and 1.5% of all spinal cord tumors.[18] Consistent with the findings of our study, previous studies reported that the disease has a poor prognosis with a median survival time of 12–14 months.[1,19] Due to its rarity, prognostic factors associated with OS of PSCGBM are not well understood. In our study, univariate and multivariate Cox regression analysis indi-

Table 2. Univariate and multivariate Cox analysis of cancer-specific survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age groups (yr)						
0–17	Reference					
18–64	0.64	0.42–0.97	0.034*	0.59	0.38–0.92	0.021*
≥65	1.26	0.55–2.85	0.586	1.21	0.48–3.05	0.690
Sex	0.92	0.63–1.34	0.651			
Race						
White	Reference					
Black	0.70	0.30–1.63	0.410			
Other/unknown	0.96	0.64–1.45	0.855			
Tumor extension						
Localized	Reference					
Distant	2.34	1.20–4.56	0.012*	2.71	1.33–5.52	0.006*
Unknown	1.48	0.88–2.51	0.143	0.76	0.32–1.79	0.532
Extent of resection						
Biopsy	Reference					
Partial resection	0.62	0.35–1.12	0.117	0.70	0.29–1.66	0.417
Gross total resection	0.38	0.20–0.72	0.003*	0.36	0.14–0.93	0.034*
Adjuvant therapy						
None	Reference					
Radiotheraphy only	0.48	0.20–1.17	0.106	0.45	0.17–1.24	0.123
Chemotherapy only	1.85	0.39–8.80	0.438	2.23	0.46–10.81	0.320
Radiochemotherapy	0.43	0.20–0.91	0.027*	0.37	0.16–0.85	0.019*
Unknown	0.39	0.15–1.02	0.054	0.27	0.09–0.78	0.016*
Year of diagnosis						
1975–1994	Reference					
1995–2014	0.57	0.29–1.12	0.104	0.77	0.23–2.63	0.677
2014–2023	0.46	0.23–0.93	0.031*	0.44	0.11–1.69	0.230
Marital status at diagnosis						
Single (never married)	Reference					
Married (including common law)	0.76	0.51–1.15	0.196			
Divorced/widowed	0.89	0.42–1.86	0.748			
MHI inflation adjusted to 2019 (USD)						
<50,000	Reference					
50,000–59,999	0.92	0.05–1.68	0.777			
60,000–69,999	1.53	0.89–2.63	0.128			
>70,000	0.83	0.49–1.39	0.474			
Unknown	1.74	0.79–3.81	0.166			
Months from diagnosis to treatment						
Immediate treatment within 1 mo	Reference					
No immediate treatment within 1 mo	0.63	0.38–1.03	0.067			

HR, hazard ratio; CI, confidence interval; MHI, median household income; USD, United States dollar.
*$p < 0.05$, a statistical difference with the first subgroup within the group.

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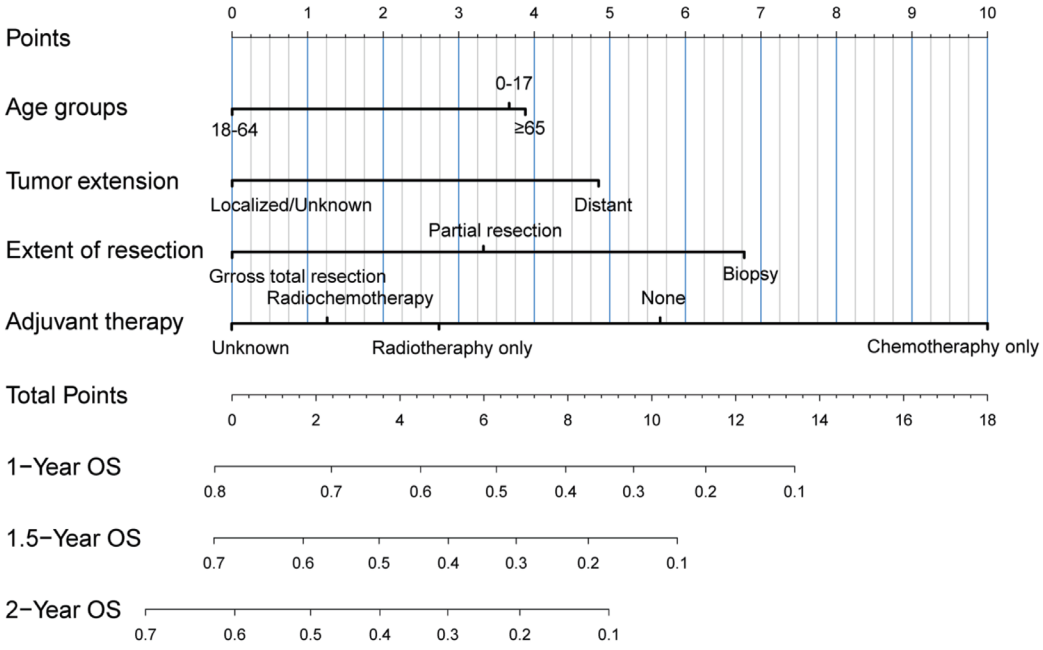

Fig. 4. The nomogram functions as a visual tool, effectively depicting the correlation between each variable and the annual survival rate. The variables in the nomogram design hold different degrees of importance, where a higher cumulative score indicates a lower annual survival rate. OS, overall survival.

cated that age groups, tumor extension, extent of resection and adjuvant therapy were predictors of PSCGBM. Likewise, a multicenter study by Inoue et al.[11] suggested that adolescent and young adult (HR, 3.53; 95% CI, 1.17–10.64), intracranial dissemination (HR, 4.30; 95% CI, 1.29–14.36), and no radiation-therapy (HR, 57.34; 95% CI, 6.73–488.39) were risk factors for mortality of patients with PSCGBM.

In contrast to intracranial GBM, PSCGBM frequently occurred in younger aged population and showed no sex predilection.[3,19,20] The median age in our cohort was 30 years (IQR, 16–45). Consistently, the study by Konar et al.[21] revealed that mean age of PSCGBM was 27 years and 51% of patients were below 18 years of age. However, in their study, age was not identified as an independent predictor of mortality. A retrospective study by Moinuddin et al.[14] included 190 patients with PSCGBM, the mean age was 40.8 ± 22.3 and age was found to be significantly associated with OS ($p = 0.046$).

The majority of PSCGBM primarily occurs in the cervical, thoracic and conus medullaris regions.[22,23] In line with our findings, Moinuddin et al.[14] found that extended lesion was associated with unfavorable survival outcome of PSCGBM. The study conducted by Ardeshiri et al.[24] also revealed that patients with more than 3 segments involved exhibited a higher likelihood of experiencing neurological deterioration in comparison to those with only one segment involved. It was reported that 40%–50% patients with PSCGBM could develop cerebrospinal fluid (CSF) dissemination and CSF dissemination was significantly related to poor OS.[10,11,21] Closer anatomic proximity of spinal tumors to the subarachnoid space compared to their intracranial counterparts might contribute to the high rate of CSF dissemination.

As to extent of resection, the role of surgical resection in PSCGBM is not well understood. The study of Lam et al.[13] indicated no statistically significant effect of the extent of resection on the length of survival among patients with PSCGBM. Even worse, McGirt et al.[3] and Wolff et al.[25] found that radical resection could worsen survival outcome of PSCGBM. Conversely, a large cohort study involving 208 PSCGBMs by Chalif et al.[26] demonstrated that GTR independently conferred a survival benefit to patients with PSCGBM (HR, 0.194; $p < 0.001$). Consistently, Kahn et al.[27] and Corradini et al.[28] also found that GTR could improve survival outcome of PSCGBM. Additionally, cordectomy, which is a more radical type of GTR and viewed as a salvage treatment, is expected to improve long-term survival by restricting or delaying intracranial dissemination of PSCGBM.[3,29-36] In our study, GTR was identified as a protective factor of favorable survival outcome (HR, 0.36; 95% CI, 0.14–0.93; $p = 0.034$). Due to no definite margin between normal spinal cord and PSCGBM, GTR without neurological compromise is a

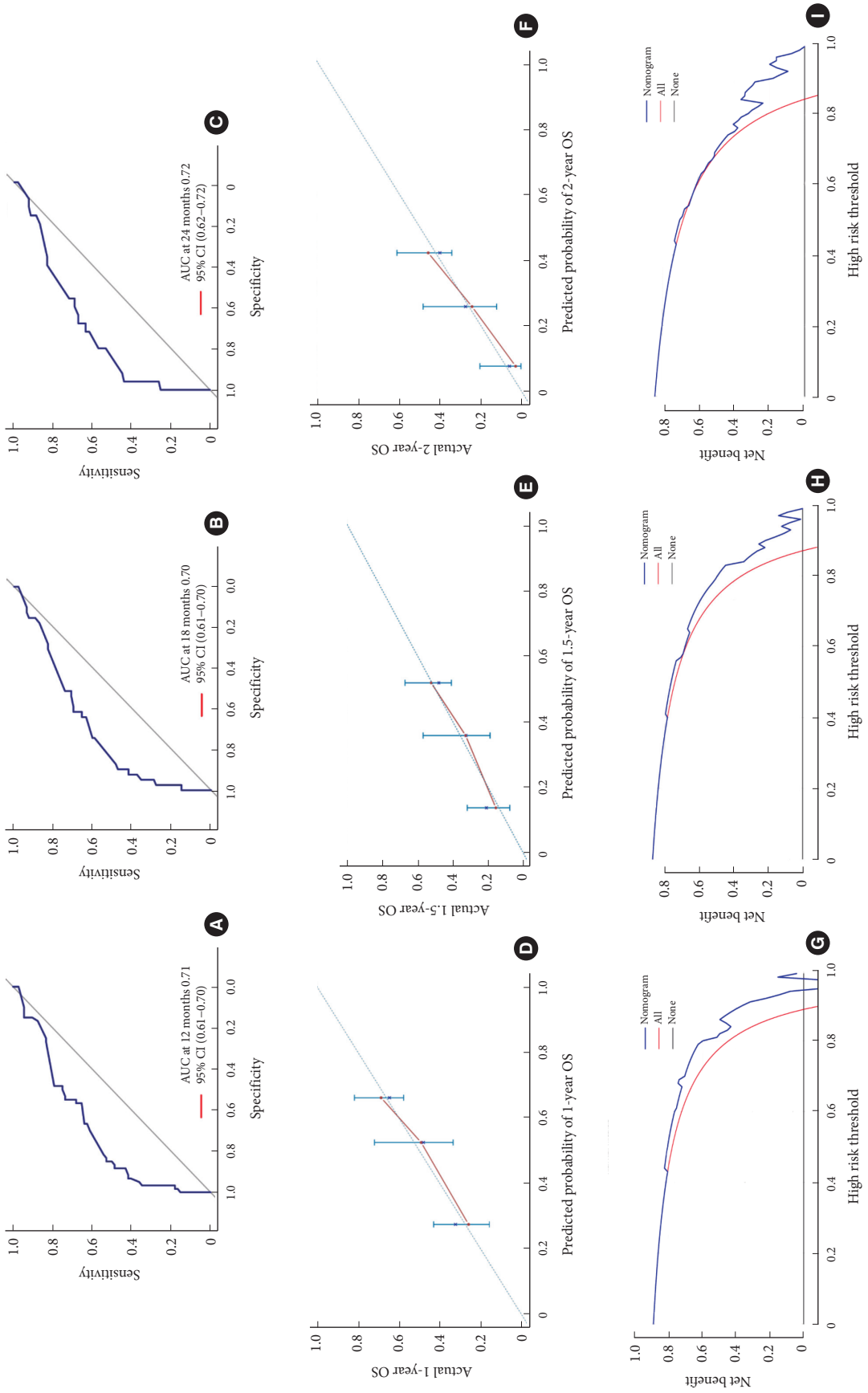

Fig. 5. The area under the curve (AUC) represents the area under the blue curve, providing a method for predicting annual overall survival (OS) accuracy. Specifically, the AUC values for 1 year (A), 1.5 years (B), and 2 years (C) were determined as 0.71, 0.70, and 0.72, respectively. Importantly, an AUC exceeding 0.70 indicates a superior predictive effect. In plots for 1 year (D), 1.5 years (E), and 2 years (F), greater alignment between the red line segment and the blue dashed line signifies higher accuracy in survival prediction by the model. Finally, the decision curve analysis was employed to validate the clinical efficacy of 1- (G), 1.5- (H), and 2-year OS rates (I). CI, confidence interval.

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great challenge. Although GTR can improve patient outcomes, we need to make a balance between the patient's neurological function and survival prognosis. In our view, for patients with intact neurological function (McCormick grade ≤ 3), we do not recommend pursuing complete tumor resection at the risk of functional compromise, while for paraplegic patients (McCormick grade = 5), we recommend GTR or even cordectomy in the case of preoperative informed consent is available and intraoperative frozen pathology indicates high-grade glioma.

The role of radiochemotherapy in PSCGBM is controversial. An aggressive approach involving whole-brain irradiation along with focal spinal irradiation has been suggested, even in the absence of evidence indicating intracranial dissemination.[19] However, Chalif et al.[26] found that radiation was not independently associated with improved survival of PSCGBM, while chemotherapy was significantly related to improved survival in patients with PSCGBM. In the retrospective study of Kaley et al.,[37] it was found that both TMZ and bevacizumab could improve the survival rate. However, the impact of CT on PSCGBM is less pronounced as compared to cerebral GBM.[1] The study by Hernandez-Duran et al.[38] did not show a significant relationship between TMZ and prolonged survival. Although the effect of RT on PSCGBM is not well established, RT was frequently prescribed to PSCGBM following surgical treatment, which repurpose the treatment strategy of intracranial GBM.[17,22] It is worth noting that the study by Inoue et al.[11] demonstrated that RT was associated with prolonged survival time of PSCGBM, but chemotherapy did not. In our study, only radiochemotherapy showed protective effect in patients with PSCGBM, while radiation only or chemotherapy only did not confer survival benefit. Likewise, the study by Cheng et al.[1] revealed that radiation plus TMZ could prolong survival time as compared to TMZ only or none ($p = 0.002$). Additionally, immunotherapy showed favorable efficacy in hematological malignant tumor.[39] In recent years, immunotherapy was tested in brain glioblastoma and shown promise in intracranial gliomas with some research suggesting benefit for spinal cord gliomas.[40] The application of immunotherapy, such as immune checkpoint inhibitors or chimeric antigen receptor T-cell therapy, to PSCGBM stands for future direction of research.[41]

In our study, a nomogram was constructed to predict individual survival outcome of PSCGBM. In recent years, nomograms were widely used to predict survival outcome of other tumors, such as gastric cancer,[42] non–small-cell lung cancer,[43] hepatocellular Carcinoma[44] and proved to be an excellent tool of predicting individual survival outcome in recent years. As to generalizability, the development of our nomogram was based on a large public dataset and patients treated in our institute, which contained different populations. In addition, the nomogram showed good discrimination and calibration. Therefore, our nomogram has good generalizability. Although several Cox proportional hazards models of PSCGBM were developed and some survival predictors were found,[11-14] the advantage of nomogram over traditional Cox hazard-proportional model is that nomogram could be used to predict individual survival outcome of PSCGBM and quantify the survival probability of an individual with PSCGBM. Therefore, this tool could be used to guide clinical decision-making based on quantized survival outcome and to discriminate patients with relatively better survival outcome and patients with relatively poorer survival outcome. Moreover, this tool could be applied to facilitate preoperative clinician-patient communication.

However, several limitations should be noted. Firstly, preoperative neurological findings and spinal lesion levels were not recorded in SEER database, which might influence the interpretation of our findings. Secondly, the dosage of RT and chemotherapeutic drug was not indicated in SEER database. Thirdly, *H3 K27M* mutation, a diagnostic and prognostic marker of diffuse midline glioma, H3 K27-altered, World Health Organization (WHO) grade 4, frequently occurred in primary spinal cord astrocytoma, but was not recorded in SEER database.[45] PSCGBM with *H3 K27M* mutation will be assigned an integrated diagnosis of diffuse midline glioma, H3 K27-altered, WHO grade 4. Therefore, integrated analysis without selecting out these cases with H3 K27M might confound our final result. Finally, due to the rarity of PSCGBM, no extra samples are available for an external validation. A multicenter study with large sample size is warranted to validate our findings.

CONCLUSION

A robust population-based survival-predicting model for PSCGBM is established and internationally validated. This nomogram offers clinicians a simple-to-use method for assessing mortality risk in patients with PSCGBM.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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