Research Square

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Nomograms individually predict the overall survival and cancer-specific survival of adult patients with hemispheres lower-grade gliomas: A SEER-Based Study

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Abstract

(1) Background: The 2016 WHO classification of Tumors of the Central Nervous System brought an escalating research interest in lower-grade gliomas (LGGs). This study aims to establish individualized prognostic nomograms to predict the overall survival (OS) and cancer-specific survival (CSS) of patients with LGGs;

(2) Methods: We searched the Surveillance, Epidemiology, and End Results (SEER) database for adult patients diagnosed with LGGs from 1998 to 2016. The patient data set selected from SEER was randomly divided into training and validation data sets at a ratio of 7:3. The significant prognostic factors were identified by using multivariate regression models in the training dataset. Then OS and CSS nomograms were developed and internally validated;

(3) Results: After the inclusion and exclusion criteria set, a total of 12,630 patients were enrolled in our research. The prognosticators for OS contained age, sex, race, marital status, surgery, radiotherapy, chemotherapy, tumor size/site, laterality, WHO grade, while only chemotherapy among the 11 indicators mentioned above was not related to CSS. The c-indexes of OS and CSS of the validation cohort were 0.749 and 0.761, respectively. The calibration curve plots showed that the predicted probability of 3-, 5-, and 8-years survival rates corresponded well with the actual observed OS and CSS rates;

(4) Conclusion: The present study using the SEER database constructed and internally validated prognostic nomograms to predict the OS and CSS of patients with LGGs. The nomograms showed perfect predictive abilities and may be useful clinical tools for decision aids and better supporting patient counselling.

Simple Summary

At present, histology alone is often insufficient to present an accurate prognostic prediction for lower-grade gliomas (WHO grade II and II gliomas), and there is no other more powerful tool for the prediction of prognosis. Therefore, this study aims to develop individualized prognostic nomograms to predict overall and cancer-specific survival in adult patients with low-er-grade hemispheric gliomas. Finally, our research using the SEER database constructed and internally validated prognostic nomograms to predict patients' overall and cancer-specific survival with lower-grade gliomas. The nomograms showed perfect predictive abilities and may be useful clinical tools for decision aids and better supporting patient counselling.

1. Introduction

Glioblastoma (WHO IV) accounts for approximately 55% of intracranial glioma, and the rest 45% contains several different histologies including WHO grade II (diffuse) and grade III (anaplastic) astrocytoma as well as WHO grade II and III oligodendroglioma[1]. The concept of ‘lower-grade gliomas (LGGs)’ was used to designate WHO II-III astrocytomas and oligodendrogliomas instead of 'low-grade gliomas', 'high-grade

glioma' or glioblastoma[2]. According to the 2016 WHO classification of Tumors of the Central Nervous System, LGGs shared a common set of molecular markers to histology[3]. Based on 1p19q codeletion and IDH mutation, LGGs can be divided into three different molecular categories as follows: (1) IDH-mutant, 1p/19q codeleted; (2) IDH-mutant, 1p/19q noncodeleted; and (3)

IDH-wildtype[4,5]. Histology alone is often insufficient to present accurate prognostic prediction for LGGs[2]. Current treatment for LGGs involves surgical resection and adjuvant therapies. Maximal safe resection was introduced as the first-line treatments of the LGGs and surgical intervention has been shown to prolong survival in several retrospective research[6,7]. Adjuvant therapeutic approaches could further delay tumour progression and im-prove survival.

Nomograms have been established for various cancers and are considered reliable tools for individualized survival and risk prediction[8-12]. Given the small sample sizes of retrospective studies on low-grade and high-grade glioma, a large population-based study on LGGs is needed. Therefore, we want to analyze the clinical outcomes of supratentorial LGGs to predict prognosis in adult patients, using a dataset from the Surveillance, Epidemiology and End Results (SEER) database, and eventually developed prognostic nomograms to predict overall survival and cancer-specific survival of LGGs.

2. Materials And Methods

Patient Cohort

We analyzed a cohort of 124,487 patients diagnosed with gliomas and registered with the SEER database (Nov 2018 Sub (1975-2016 varying)), in which all enrolled cases came from the United States, available publicly for anyone who used SEER*Stat 8.38. Of all patients, we identified 54,003 diagnosed with supratentorial gliomas during the 1998–2016 period. However, given a wide variety of glioma histology, subjects for the research were limited to 14,836 patients diagnosed with the histologic types as follows: oligoastrocytoma (9382/3), anaplastic oligoastrocytoma (9382/3), diffuse astrocytoma (9400/3), pleomorphic xanthoastrocytoma (9424/3), anaplastic astrocytoma (9401/3), oligodendroglioma (9450/3), anaplastic oligodendroglioma (9451/3). Patients with unknown follow-up time and those with non-primary tumours were excluded. Only adult patients (18 or more than 18 years old) were enrolled in this study, remaining a final total of 12,630 patients for analysis. Access to the SEER database needed no patient informed consent, and the Ethics Committee of the First Affiliated Hospital of Jinan University approved this study.

Clinicopathological Covariables

We extracted information from the SEER database for the clinicopathological variables as follows: age at diagnosis, year of diagnosis, sex, marital status at diagnosis, race/ethnicity, primary site, ICD-O-3 Hist/behavior, lateral-ity, tumour size, radiation sequence with surgery, chemotherapy recode (yes, no/unk), SEER cause-specific death classification, vital status recodes, survival months. Surgery was classified as gross total resection (code 30) or subtotal resection (code 21), receiving surgery (code 20,

22, 40, 55, 90, 99), and no surgery (code 00, 10). Radiation treatment strategies were grouped as "radiation after surgery", "no radiation and/or cancer-directed surgery", and others (any other radiotherapy strategies). "Not done/unknown" for chemotherapy means no evidence was found in the medical data records. The optimal cutoff values of age at diagnosis, year at diagnosis, and tumour size were obtained using X-tile (Version 3.6.1).

Statistical Analysis and the Development of Nomograms

All 12,630 patients were randomly assigned to the training and validation cohorts at a ratio of 7:3, and the R function "set. seed" would ensure that outcome events were random between the two cohorts. We used a stepwise regression analysis to select significant variables from the training cohort for inclusion in the nomograms. The nomograms estimated the 3-/5-/8-years overall survival (OS) and cancer-specific survival (CSS) probabilities. Nomograms prediction abilities were internally validated by the concordance index (C-index) and area under the time-dependent receiver operating characteristic curves (time-dependent AUCs), which was calculated by the bootstrapping method (n=500). Calibration curves were plotted to evaluate internally calibrating ability. AUC values and C-index can range from 0.5 to 1, with 0.5 considered poor prediction and 1.0 representing utter prediction, while greater than 0.7 suggest a reasonable estimation. We also measured the clinical usefulness of the nomograms through decision curve analysis (DCA).

OS and CSS were the primary endpoints of interest in our study calculated from diagnosis to death of all causes or cancer-specific causes. Significant covariates included in the nomogram followed Harrell's guideline that the number of covariates should be less than 10% of the number of events. Statistical differences of all variables between the training and validation cohorts were analyzed through the Chi-square test. Survival differences be-tween the training and validation cohorts were evaluated by using the Log-Rank test. We tested for multicollinearity of the covariates in the nomogram using the variance inflation factor (VIF). Variables with tolerance < 0.4 and VIF>2.5 were eliminated from the analysis. A P-value of less than 0.05 ($p < 0.05$) was considered significant. All analyses were performed using Rstudio (https://rstudio.com/) based on R statistical programming language version 4.0.3 for Windows (https://www.r-project.org/).

3. Results

Patient Baseline Characteristics

Using the SEER database released in November 2018, we identified a total of 12,630 eligible adult individuals for the study. The median age at diagnosis of the cohort was 45 years old (range 19-97, interquartile range (IQR), 34–58 years). Baseline patient demographics and grade II/III tumour characteristics are shown in Table 1. The majority of patients were male (56.52%), diagnosed after 2002 (78.05%), of White ethnicity (87.17%), and married (58.76%). These tumours were mainly located in the Frontal lobes (56.34%), and to some extent on the right side (38.70%), smaller than 50mm (39.62%), and diagnosed histologically as WHO II tumours (48.87%). The extent of resection was known in 2970 cases;

1653 (13.09%) patients underwent gross total; subtotal resection was achieved in 1317 (10.43%). Chemotherapy and radiotherapy after surgery were given to 44.64% and 44.32% of patients, respectively.

Survival Analysis and Variable Screening

The median duration of follow-up was 39 months (IRO, 12-93months). Overall, 6256 (49.53%) and 5565 (44.06%) patients died during follow-up for all-cause and cancer-specific causes, respectively. Figure 1 summarized the multivariate COX regression survival analysis for OS and CSS. Through the Cox stepwise regression, 11 clinical indicators are screened out for OS and ten clinical indicators for CSS. The model variables' VIF values were all close to 1 (Table 1), indicating that low multicollinearity existed between screened variables. Figure 3 shows the optimal cutoff value for age at diagnosis, year at diagnosis, and tumour size confirmed by using X-tile software.

Nomograms for prediction of OS and CSS

Figure 2 illustrates the predictive nomograms constructed for the 3-, 5-, and 8-year OS and CSS rates based on the selected significant parameters in the training cohort. Both OS and CSS nomograms indicated that age was the most potent prognosis factor, followed by radiotherapy and surgery. Each parameter is given a score from 0 to 100 on the points scale of each nomogram. Anyone can easily calculate the probability of individual survival by adding the scores for each enrolled variable.

Nomogram Validation

The C-indexes of the prediction nomogram for OS and CSS were 0.762 and 0.761 in the training dataset, while the values were 0.749 and 0.761 in the validation dataset. AUC models of the 3-, 5-and 8-year OS and CSS rate regarding the prediction ability of the data set were used (Figure 4). For the data set of the OS model, the AUCs of the nomogram predicting the 3-, 5-and 8-year overall survival rates were 0.822, 0.789, and 0.760 in the training dataset, respectively, while the values were 0.814, 0.782, and 0.753 in the validation dataset, respectively. The 3-, 5-, and 8-year AUC values of the nomogram for CSS were 0.826, 0.790, 0.758 in the training dataset; 0.826, 0.790, 0.751 in the validation cohort. Typical Calibration curves were plotted to validate the accuracy between the predicted survival rates and the actual survival rate (Figure 5 A-D). Furthermore, DCA demonstrated that the predictive nomograms' utility could generate superior net benefits (Figure 5 E-F).

4. Discussion

With the increasingly popularization of the concept of precision medicine, the accurate prediction of patients’ prognosis is becoming much more critical[13,14]. Many previous studies have shown the accurate predictive ability of nomograms for predicting overall survival in patients with low-grade endometrial stromal sarcoma[10], adrenocortical carcinoma[15], hepatoblastoma[16], and many other system cancers. So far, only a few sporadic studies have investigated the straightforward application of nomograms in glioma based on the SEER database[17-20]. WHO grade II/III glioma is a relatively rare

tumour, with no individualized prognostic predictive tool to manage follow-up and aid accurate prognostic assessment. Based on this, we developed two nomograms for predicting OS and CSS, respectively. Eleven and ten variables were screened through stepwise regression and incorporated into the OS and CSS nomograms, respectively. The nomograms were validated to have accurate predictive ability, with high C-indexes. Besides, the area under the ROC curve (AUC) is used to demonstrate the nomograms' excellent predictive ability. The calibration curve plots also showed that the predicted probability of 3-, 5-, and 8-year survival rates corresponded well with the actual observed OS and CSS rates concerning both the training & validation datasets.

The concept of lower-grade glioma (LGG, WHO Grades II and III) was proposed after the update to classify the central nervous system tumors by WHO in 2016[3]. Compared to glioblastoma, LGGs were known to have a better prognosis and more prolonged survival and shared some similar molecular alterations[21,22], clinical and pathological features [21], or even treatment modalities[22,23]. Therefore, LGGs could not be clustered in the group of low-grade gliomas or high-grade glioma simply, and both the research of Zhao et al[17] and the study of Yang et al[20] were not well applicable for LGGs. Furthermore, the OS and CSS nomograms in the current research fit well with our observation of survival for LGGs, and the inclusion of each covariable in the models may improve the accuracy of prognosis prediction.

According to our nomograms, age at diagnosis was confirmed as the most critical outcome predictor for LGGs. Previous research divided the low-grade glioma patients more simply into two groups according to age and found the younger one (age $\leq$ 39y) exhibiting a relatively good prognosis[17]. The young adult may share analogous biology, epidemiology, and outcomes with the adolescent and be different from older age groups regarding central nervous system tumors[24-26]. The present study had the same founding and further suggested that the age score in both scales of nomograms increased with age. The efficient precise subgrouping of age would optimize the prediction models and improve its predictive ability.

A safe maximal excision of the glioma without neurological functioning deficiency was the main therapeutic strategy as strong evidence has demonstrated that more extensive resections can prolong patients' survival time [6,27,28]. Both the OS and CSS nomograms in the study showed that surgery was a strong individual predictive factor for LGGs and gross total resection (GTR) is recommended under permissive conditions. When GTR was challenging to achieve, patients still can benefit from subtotal surgical resection compared to no surgery performed. MCCreate suggested that with increasing the extent of resection, pediatric high-grade gliomas' survival time was gradually prolonged[29]. Radiotherapy is another essential modality in LGGs during cancer treatment as a curative modality[30]. In contrast, postoperative radiotherapies (PORTs) were not recommended for LGGs by both OS and CSS nomograms in the study as it was associated with shorter survival duration. PORTs are often used for low-grade gliomas and provides improved progression-free survival but does not extend overall survival[31]. A large phase III randomized study, EORTC 22845, which revealed similar conclusions challenged the role of immediate PORTs, but it appears worthwhile to attempt PORTs for young patients who present with minimal symptoms[32]. Additionally, chemotherapy plays a key role in patients' treatment and prognosis

with glioma[33]. PCV (procarbazine, CCNU or lomustine, and vincristine) and temozolomide chemotherapy were initially proved to have a useful role in LGGs by multiple pieces of research [34-37]. Likewise, chemotherapies in our study were factors with protective properties and associated with a more favorable OS. Although chemotherapy did not significantly improve CSS, more patients have more significant benefit from it indeed. Surgery, radiotherapy, and chemotherapy are a continuous process as surgery could help obtain molecular profiling and assist clinicians with a guideline to provide more appropriate therapeutic regimens for individualized precision therapy in LGGs.

The WHO grade is the critical prognostic factor for LGGs, and numerous studies have provided evidence that grade II gliomas had a significantly better prognosis than grade III[38-40]. Both OS and CSS nomograms gave high-er scores to patients with grade III gliomas that were more likely to have death. Also, according to our nomograms, the magnitude of poor prognosis was associated with increased tumour size. Pignatti[41] defined high-risk patients with low-grade glioma as the largest diameter of the tumour ≥ 6 cm, and Gorlia[42] suggested that the numerical value was accurate to 5cm. Then the value was rapidly lowered to 2.6cm in patients with high-grade gliomas[43]. Taken together, it is more reasonable than the value was determined to be 4.9cm by our research and the value would make the parameter more suitable to serve as a prognostic and/or predictive factor for LGGs. In the previous study, researchers analyzed the prognosis in different tumour locations. The analyses showed that the tumour's frontal location had a significant positive prognostic value for both PFS and OS in low-grade gliomas[44], while only the temporal lobe was significant for OS in both low and high-grade gliomas[42]. Frontal location was found to be protective factor LGGs in both OS and CSS nomograms and we can only speculate on that different tumour locations were associated with IDHmut status which in turn affects the disease[45,46]. Information on tumour laterality was not systematically analyzed so far, and only a small number of studies showed that tumour crossing the midline was associated with poorer overall survival[41,42]. We reported that survival of unilateral tumours is better than bilateral and other LGGs.

OS and CSS nomograms support may contribute to a better prognosis among married and female patients with LGGs. Additionally, the previous study of glioma incidence and survival across a long period demonstrates substantial variation by race or ethnicity[47]. Indeed, blacks have a higher risk than whites[48,49], which is coherent with the findings of our study. However, only a few reports of the association between yellows and disease are available in the literature[50,51]. The effect of the level of yellows on the survival of LGGs was similar according to survival models. Notably, yellows were one of the most protective of the factor in OS and CSS models. However, racial differences in cancer susceptibility and survival matter more than the skin colour [52]. Different cultural, socioeconomic, language, diet, and cultural identity all of those had important implications[53]. Further, we suspect that it may be a more intuitive and specific presentation of genetic variants that influence human disease risk.

Our analysis developed more objective and scientific nomograms that incorporated a vast number of candidate variables about patients' characteristics, tumour characteristics, and treatment history. By performing DCA, we consider that both OS and CSS nomograms could present net benefit for LGGs. Using nomograms to identify some specific groups of patients with a more homogeneous prognosis,

clinicians can evaluate a diverse range of prognostic factors with more objectiveness and precision LGGs so that the interpretation of clinical outcomes and treatment strategies become clearer. Moreover, OS nomograms might be more feasible in routine clinical practice, because it may provide clinicians with a guideline to develop more appropriate therapeutic regimens for individualized precision therapies in LGGs.

There were several non-negligible limitations in this study. In particular, the lack of specific information concerning the use of chemotherapy and radiotherapy which have been consistently reported as an essential treatment for gliomas[54-56], hindered optimization of the treatment protocol to optimize clinical outcomes further. Another limitation is that our nomograms were constructed using only a series of clinicopathological factors. Indeed, some certain additional variables (e.g., biological markers or genes) were defined to provide potential prognostic information for LGGs; however, these key variables were not included in the nomogram because they are not currently available the SEER database.

5. Conclusions

In conclusion, the present study using the SEER database constructed and internally validated prognostic nomograms to predict the OS and CSS of patients with LGGs. The nomograms showed perfect predictive abilities and may be useful clinical tools for decision aids and better supporting patient counselling.

Abbreviations

CSS, cancer-specific survival; LGGs, lower-grade gliomas; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results

Declarations

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Conflicts of Interest: The authors declare that no conflict of interest exists.

Availability of data and material: All data needed to assess the conclusions in the paper are present in the paper.

Code availability: Not applicable.

Ethics approval: "Not applicable." For the study based on the SEER database, an opening database freely accessible to the public.

Consent to participate: Not applicable.

Consent for publication: Publication consent was obtained from all authors.

Author Contributions: Methodology, C.W.; software, C.W.; validation, L.C., L.J. and W.W.; formal analysis, C.W.; resources, C.W., L.C; writing—original draft preparation, C.W.; writing—review and editing, W.X., L.J.; supervision, W.X., L.J.; project administration, W.X. All authors have read and agreed to the published version of the manuscript.

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Table

Table 1

Baseline patient demographics and WHO grade II/III tumors characteristics

Characteristics	Categories	Total (%)	Training (%)	Validation (%)	VIF
Age	19y-39y	4625(36.62%)	3286(37.17%)	1339(35.34%)	1.067
	40y-55y	4263(33.75%)	2922(33.05%)	1341(35.39%)	
	56y-73y	2815(22.29%)	1998(22.60%)	817(21.56%)	
	74y-97y	927(7.34%)	635(7.18%)	292(7.71%)	
Year	Before 2002	2772(21.95%)	1928(21.81%)	844(22.28%)	1.802
	After 2002	9858(78.05%)	6913(78.19%)	2945(77.72%)	
Sex	Male	7139(56.52%)	4952(56.01%)	2187(57.72%)	1.008
	Female	5491(43.48%)	3889(43.99%)	1602(42.28%)	
Race	White	11009(87.17%)	7697(87.06%)	3312(87.41%)	1.007
	Black	681(5.39%)	478(5.41%)	203(5.36%)	
	Yellow	297(2.35%)	217(2.45%)	80(2.11%)	
	Other	643(5.09%)	449(5.08%)	194(5.12%)	
Marital status	Married	7422(58.76%)	5196(58.77%)	2226(58.75%)	1.015
	Single	3136(24.83%)	2193(24.80%)	943(24.89%)	
	DSW	1566(12.40%)	1098(12.42%)	468(12.35%)	
	Other	506(4.01%)	354(4.00%)	152(4.01%)	
Grade	II	6172(48.87%)	4300(48.64%)	1872(49.41%)	1.075
	III	4618(36.56%)	3246(36.72%)	1372(36.21%)	
	Undefined	1840(14.57%)	1295(14.65%)	545(14.38%)	
Site	Frontal	7116(56.34%)	5006(56.62%)	2110(55.69%)	1.028
	Temporal	3334(26.40%)	2317(26.21%)	1017(26.84%)	
	Parietal	1876(14.85%)	1305(14.76%)	571(15.07%)	
	Occipital	304(2.41%)	213(2.41%)	91(2.40%)	
Size(mm)	≤ 49	5004(39.62%)	3514(39.75%)	1490(39.32%)	1.031
	≥50	3541(28.04%)	2476(28.01%)	1065(28.11%)	

VIF, variance inflation factor; DSW, divorced/separated/widowed; GTR, gross total resection; STR, subtotal resection.

Characteristics	Categories	Total (%)	Training (%)	Validation (%)	VIF
	Other	4085(32.34%)	2851(32.25%)	1234(32.57%)	
Laterality	Right	4888(38.70%)	3443(38.94%)	1445(38.14%)	1.736
	Left	4670(36.98%)	3259(36.86%)	1411(37.24%)	
	Other	3072(24.32%)	2139(24.19%)	933(24.62%)	
Surgery	GTR	1653(13.09%)	1161(13.13%)	492(12.98%)	1.244
	STR	1317(10.43%)	928(10.50%)	389(10.27%)	
	Receiving surgery	7015(55.54%)	4895(55.37%)	2120(55.95%)	
	No surgery	2645(20.94%)	1857(21.00%)	788(20.80%)	
Radiotherapy	No/Unknown	6927(54.85%)	4863(55.01%)	2064(54.47%)	1.419
	After Surgery	5598(44.32%)	3900(44.11%)	1698(44.81%)	
	Other	105(0.83%)	78(0.88%)	27(0.71%)	
Chemotherapy	Yes	5638(44.64%)	3958(44.77%)	1680(44.34%)	1.312
	No/Unknown	6992(55.36%)	4883(55.23%)	2109(55.66%)	
Months			39(12-58.3)	40(12-58.93)	

VIF, variance inflation factor; DSW, divorced/separated/widowed; GTR, gross total resection; STR, subtotal resection.

Figures

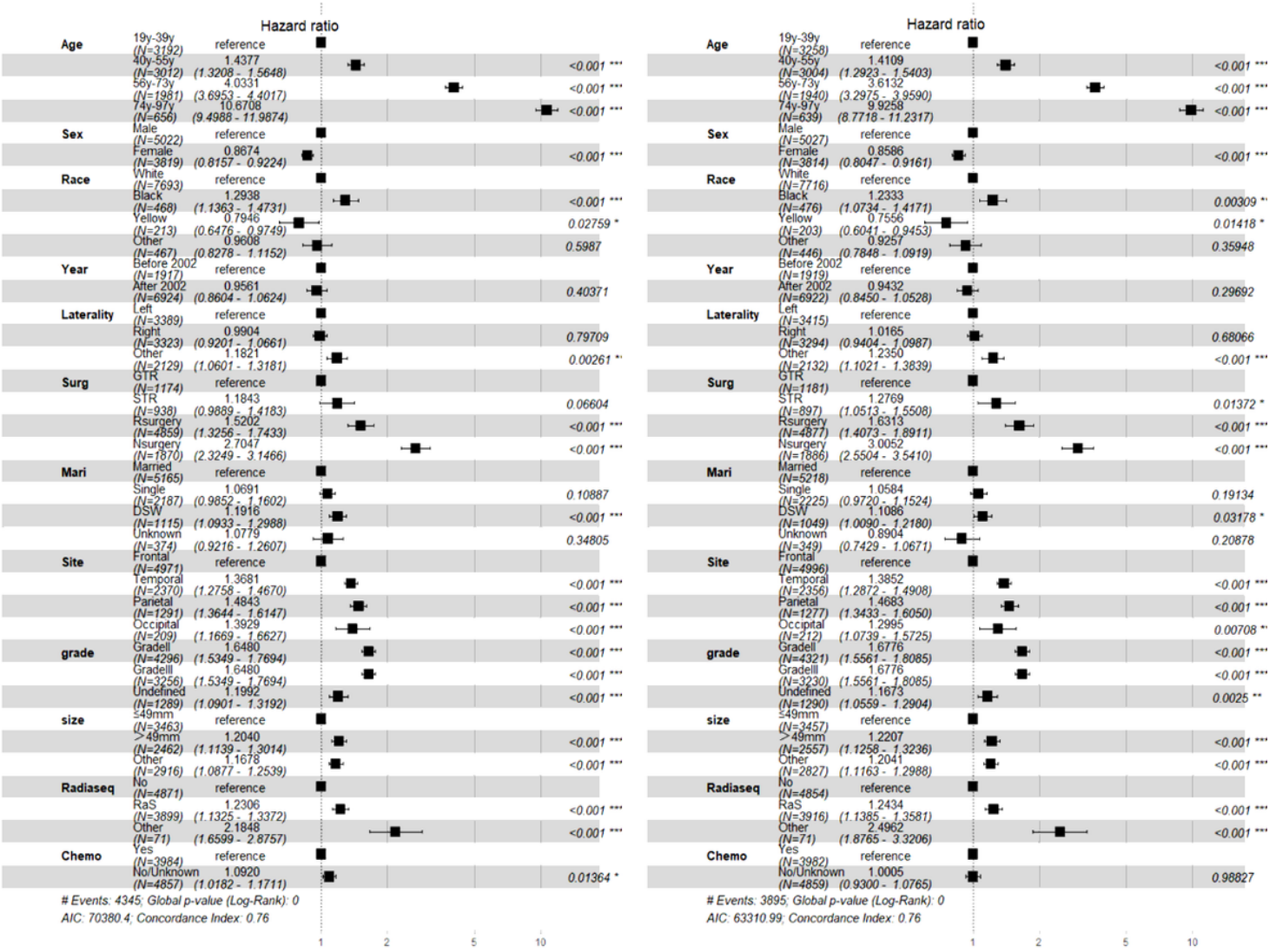

Figure 1

Multivariate analysis of factors of overall survival (Left) and cancer-specific survival (Right) of patients with lower-grade gliomas.

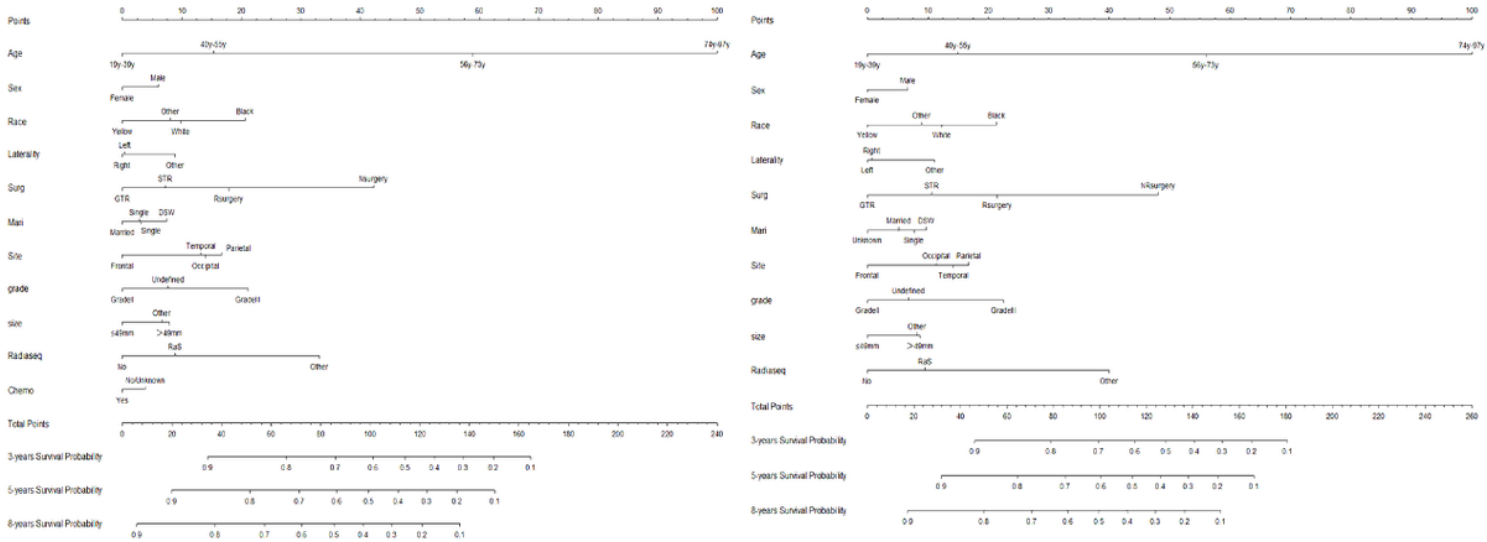

Figure 2

Nomograms predicting the 3-, 5- and 8-years overall survival (Left) and cancer-specific survival (Right) rates of patients with lower-grade gliomas. The identified points of each variable correspond to the score on the scale. The total score projected on the bottom scales corresponds to probabilities of 3-, 5- and 8-years survival.

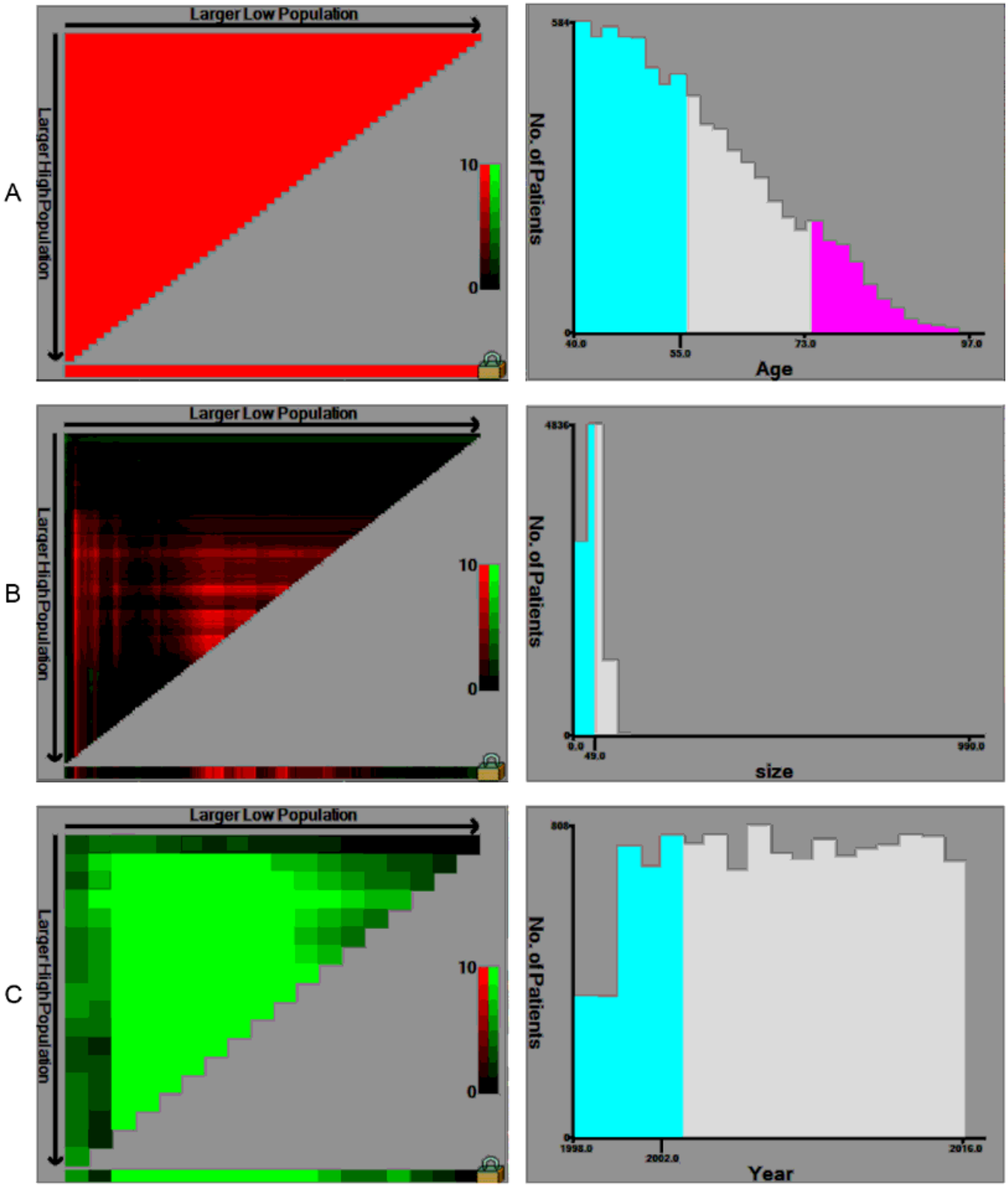

Figure 3

X-tile was used to generate cut points for age at diagnosis (A), tumor size (B), and year at diagnosis (C).

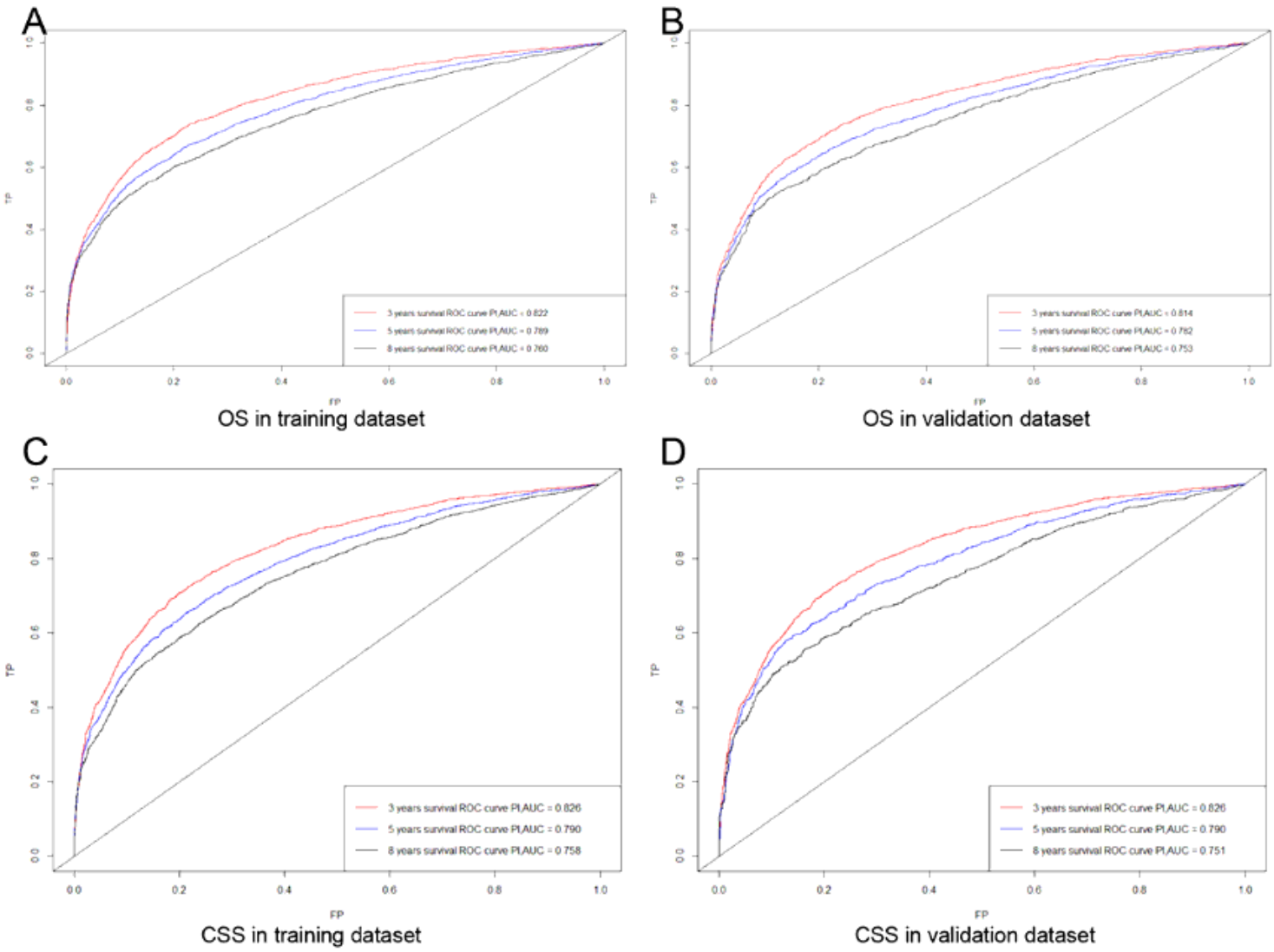

Figure 4

The area under the curves (AUCs) of the overall survival (OS) and cancer-specific survival (CSS) nomograms. AUCs of the nomograms to predict overall survival at 3 years, 5 years, and 8 years using LGGs training set (A) and validation set (B) as well CSS at 3 years, 5 years, and 8 years using LGGs training set (C) and validation set (D).

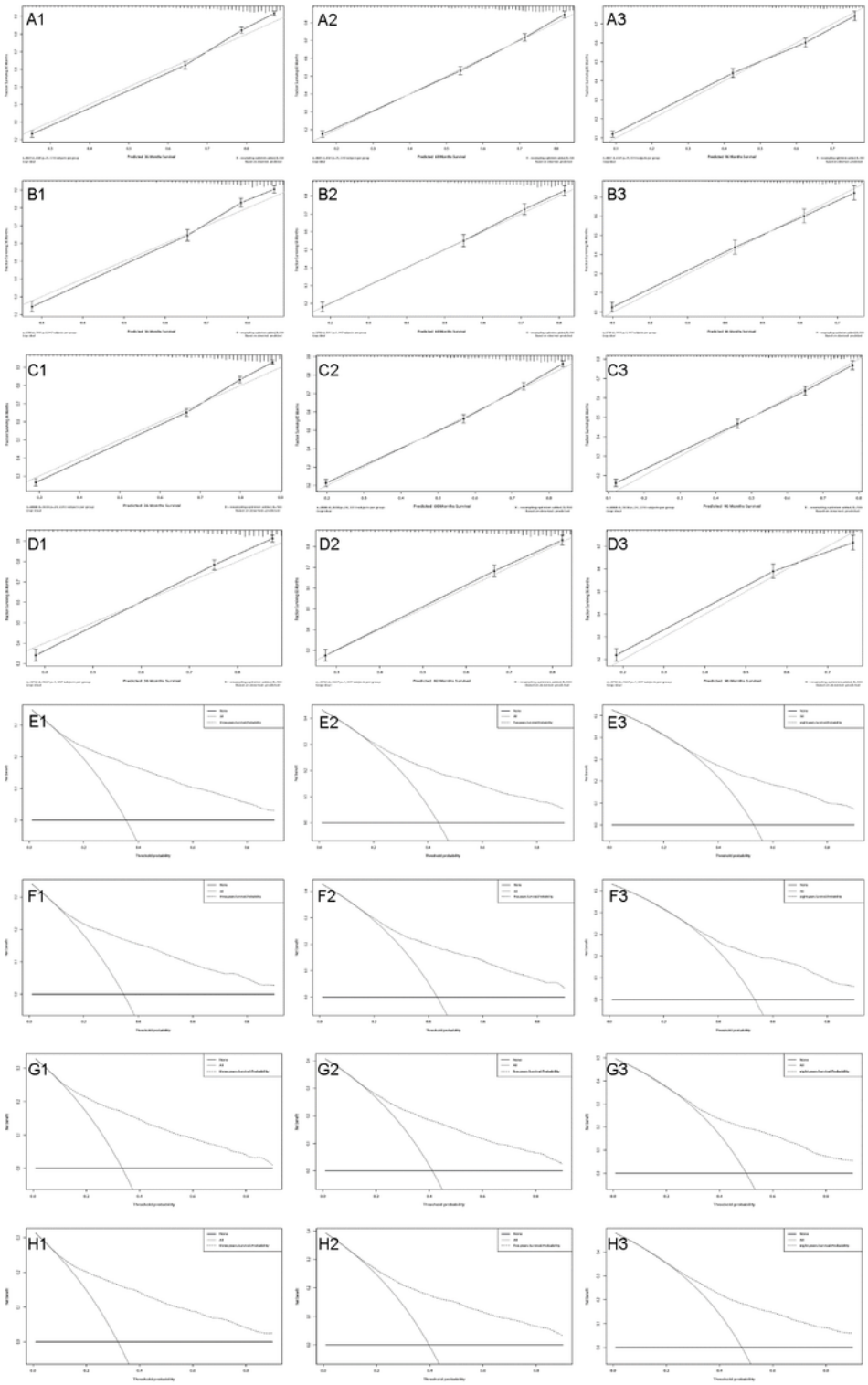

Figure 5

The calibration plots and decision curve analysis (DCA) curves. The first four columns were the calibration plots and the x-axis represents the nomogram's predicted survival rate, whereas the y axis represents the actual observed survival rate. The first and second column shows the calibration of the overall survival (OS) nomogram of three-year (A1), five-year (A2) and eight-year (A3) survival rate using the training set; three-year (B1), five-year (B2) and eight-year (B3) survival rate using the validation set.

The third and fourth column shows the calibration of the cancer-specific survival nomogram of three-year (C1), five-year (C2) and eight-year (C3) survival rate using the training set; three-year (D1), five-year (D2) and eight-year (D3) survival rate using the validation set. DCA for evaluating the clinical benefit of OS models was applied to nomogram by quantifying net benefits at three year (E1), five year (E2), and eight year (E3) using training dataset as well at three year (F1), five year (F2) and eight year (F3) using the validation set. The seventh and eighth columns shows DCA for CSS models at three year (G1), five year (G2) and eight year (G3) using training dataset as well at three year (H1), five year (H2) and eight year (H3) using the validation set.