A prognostic model of newly diagnosed glioblastoma based on clinical characteristics

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Research

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Abstract

Background

Using isocitrate dehydrogenase (IDH) mutations to classify survival outcomes of patients with glioblastoma multiforme was recommended based on novel histopathological classification of brain tumors. Considering this novel classification, it is unclear whether the extent of tumor resection (EOR) is still important. The aim of this study was to investigate prognostic value of clinical factors (age, sex, EOR, status of IDH mutations, and adjuvant therapy) in patients with newly diagnosed glioblastoma.

Methods

In total, 269 patients were retrospectively enrolled and randomly divided into training (n = 179) and validation (n = 90) cohorts. Clinical information and survival outcomes were acquired from inpatient records and follow-ups. After adjusting for risk coefficients, the independent prognostic factors were selected in a multivariable analysis to generate a model to evaluate survival outcomes. Additionally, a receiver operating characteristic curve was used to assess accuracy for predicting survival outcomes at 12, 15, 18, and 24 months.

Results

Total resection of the contrast-enhanced region, age ≤ 60 years, received chemotherapy, and IDH mutations were favorable independent factors for overall survival. Area under the curve (AUC) for prediction of survival in the training cohort was 0.815, 0.851, 0.849, and 0.836 at 12, 15, 18, and 24 months, respectively. In the validation cohort, the AUC for prediction of survival was 0.780, 0.807, 0.836, and 0.849 at 12, 15, 18, and 24 months, respectively.

Conclusion

Total resection of the contrast-enhanced region is still crucial and recommended for patients with glioblastoma. Our prognostic model was able to predict survival outcomes, especially for long-term survival prediction.

Background

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor[1] and constitutes 80% of all primary malignancies in the central nervous system.[2] The median overall survival (OS) is only 14.6 months for primary GBMs after surgery, radiation therapy, and chemotherapy.[3] The generation of prognostic models to identify favorable and harmful factors was crucial to improve prognosis prediction of patients with GBM. Based on the findings from previous studies, factors such as the extent of tumor

resection (EOR),[4] Karnofsky Performance Scale (KPS) at diagnosis,[5] molecular biomarkers,[6, 7] adjuvant treatment,[5, 8–10] and age[11] were associated with the prognosis of patients with GBM.

The accepted optimal treatment for GBM was surgical resection with radiation therapy and chemotherapy.[12, 13] As the initial treatment for GBM, tumor resection has played a crucial role in improving survival outcomes among patients with GBMs using a multivariable Cox regression analysis.[14, 15] A previous study recommended a predictive system with a continuous variable for EOR that enabled the prediction of the survival time for patients individually. This system was a large contribution to the prediction of survival outcomes. However, the previous system did not include information regarding IDH mutations. Based on the recommendations outlined in the 2016 World Health Organization classification of tumors of the central nervous system, it was recommend that the isocitrate dehydrogenase (IDH) mutation status be used to predict survival outcomes of patients.[16] Moreover, in high-grade glioma, gross total resection only affected the OS of patients with IDH1/2 mutations without 1p/19q co-deletion.[17] It remains unclear whether totally removing the region of T1 contrast-enhanced of GBM improves the OS of patients with wild type IDH.[18] Therefore, a novel evaluative system including information regarding EOR and the IDH mutation status is necessary to assist in predicting prognosis and guiding individualized adjuvant therapy.

The aims of this study were: 1) to identify the independent clinical variables that were significant predictors of OS in patients with newly diagnosed GBM; 2) to generate a scoring system to quickly evaluate the prognostic risks of patients with GBM; 3) to investigate whether total resection of the enhanced region on T1-images was beneficial for patients with wild type IDH.

Materials And Methods

This study was approved by the local institutional review board.

Study design and patients

We conducted a retrospective study of patients who underwent initial surgical resection from March 29, 2005 to April 26, 2018 at ** Hospital and had histologically confirmed GBM. All patients aged 18 to 75 years were eligible for inclusion (n = 444). Patients were excluded for the following reasons: IDH mutation status not available (n = 109); had GBM with an oligo component (n = 43); incomplete clinical variables, postoperative treatment, and follow-up information during the study period (n = 23). Thus, in total, 269 patients were enrolled and randomly classified into training (n = 179) and validation (n = 90) cohorts (Fig. sup-1).

Data variables and outcomes

The clinical variables derived from inpatient records, included age, sex, IDH mutation status, and records regarding radiation therapy and chemotherapy. Age was dichotomized as > 60 and ≤ 60 years. Additionally, the IDH mutation status which was tested at the Molecular Pathology Testing Center of **

Neurosurgical Institute was classified as mutation and wild type. Moreover, total resection was defined as the gadolinium-enhanced region totally removed based on the preoperative and postoperative T1-weighted contrast-enhanced MRI. If the contrast-enhanced region were not totally removed, the EOR would be defined as non-total resection. The preoperative KPS score was dichotomized as > 80 and ≤ 80, corresponding to those with and without neurological impairment.

Time to death was derived based on the information in the follow-up records. The OS was calculated as the time interval between the date of tumor resection and the date of death or date that the patient was last investigated; the final follow-up date was February 23, 2020.

Statistical analysis

Statistical analysis was performed using SPSS (19.0 version, IBM) and GraphPad Prism 7 (GraphPad Software Inc, San Diego, USA). Student t-tests were used to assess the difference in means for continuous variables while chi-squared tests were used to assess the differences in categorical variables.

A Cox proportional hazards model was used to investigate the univariate and multivariate predictors of survival. After identifying the significant ($p < 0.05$) independent predictors of OS in the multivariate analysis, these predictors were selected to generate a model to derive a risk score for each patient based on the beta value. In this risk system, the score of each item was calculated using the following formula:

Item score = variable value × beta value

Subsequently, the final score for each patient was equal to the sum of the score for each item.

The receiver operating characteristic curve (ROC) was used to analyze the survival outcomes at 12, 15, 18, and 24 months and to determine the cut off value for the risk score at each survival time point. Based on the cut-off value, all patients were classified into high or low risk groups.

The Kaplan-Meier method was used to illustrate the survival curves. Survival curves for the various subgroups were compared between the low-risk and high-risk groups in both the training and validation cohorts.

Results

Clinical characteristics

Table 1 summarizes the clinical characteristics of the 269 included patients; 161 (59.9%) were men and the median age was 51 years (range of age = 19 ~ 79 years). Of these, 196 (62.8%) were younger than 60 years old. The preoperative KPS score was at least 80 in 248 (92.2%) patients. The median follow-up time was 510 days (range, 34-4303). Until the final follow-up date, 224 (83.3%) patients died and the remaining 45 (16.7%) patients were still alive. Moreover, 108 (40.1%) patients underwent total resection and 37 (13.8%) patients had an IDH mutation. Additionally, 239 (88.8%) and 207 (77.0%) patients

underwent radiation therapy and chemotherapy, respectively. There were no differences in the clinical characteristics between the training and validation cohorts.

Table 1
Demographic and clinical characteristics of patient with primary GBM

Demographic and Clinical Characteristics	Training group (n = 179)	Validation group (n = 90)	P value
Gender	106	55	0.79
Male	73	35	
Female			
Age (y) *	51.06 ± 0.93	50.38 ± 1.23	0.67
≥ 60y	130	66	0.99
< 60y	49	24	
Handness	179	0	-
Right	90	0	
Left			
Chemotherapy	138	69	0.99
Yes	41	21	
No			
Radiotherapy	160	79	0.69
Yes	19	11	
No			
Extent of tumor resection	71	37	0.90
Total resection	108	53	
Non-total resection			
IDH status	156	77	0.71
IDH mutation	23	13	
IDH wildtype			

* Values are means ± standard error mean deviations.

The Mann-Whitney U test was used to compare preoperative Karnofsky performance status (KPS) between training and validation groups.

Chi-square tests were used to compare gender, and IDH status between training and validation groups.

Demographic and Clinical Characteristics	Training group (n = 179)	Validation group (n = 90)	P value
Preoperative KPS score	6	2	
100			
90	97	45	0.41
80	61	37	
70	15	6	
* Values are means ± standard error mean deviations.			
The Mann-Whitney U test was used to compare preoperative Karnofsky performance status (KPS) between training and validation groups.			
Chi-square tests were used to compare gender, and IDH status between training and validation groups.			

Prognostic factors for overall survival in the training cohort

The median OS of all patients in training cohort was 522 days (17.4 months) and the mean OS was 738 days (24.6 months). The univariate Cox regression analysis showed that age > 60 years (hazard ratio [HR], 1.687; 95% confident intervention [CI], 1.177–2.417; $p = 0.004$) negatively affected OS. Total resection (HR, 0.285; 95% CI, 0.199–0.408; $p < 0.0001$), chemotherapy (HR, 0.411; 95% CI, 0.281–0.602; $p = 0.001$), and the presence of an IDH mutation (HR, 0.351; 95% CI, 0.201–0.614; $p < 0.0001$) were favorable prognostic factors (Table 2). Having received radiation therapy (HR, 0.669; 95% CI, 0.397–1.126; $p = 0.131$) and the preoperative KPS score > 80 (HR, 0.748; 95% CI, 0.540–1.035; $p = 0.080$) did not have a significant impact on OS.

Table 2
Univariate and multivariate analysis of OS in patients with primary GBM of training group

	B value	Univariate analysis		Multivariate analysis	
		HR (95.0% CI)	p value	HR (95.0% CI)	p value
Age (> 60y)	0.762	1.687 (1.177 to 2.417)	0.004	2.143 (1.465 to 3.135)	< 0.0001
Extent of resection (total resection)	-1.294	0.285 (0.199 to 0.408)	< 0.0001	0.274 (0.188 to 0.401)	< 0.0001
Radiotherapy		0.669 (0.397 to 1.126)	0.131	-	-
Chemotherapy	-0.666	0.411 (0.281 to 0.602)	< 0.0001	0.514 (0.348 to 0.758)	0.001
Preoperative KPS score (> 80)		0.748 (0.540 to 1.035)	0.080	-	-
IDH status of GBM (mutation)	-0.686	0.351 (0.201 to 0.614)	< 0.0001	0.503 (0.283 to 0.897)	0.012
※ KPS = Karnofsky Performance Status					

Additionally, the multivariate Cox regression analysis determined that total resection (HR, 0.274; 95% CI, 0.188–0.401; beta value = -1.294; $p < 0.0001$), chemotherapy (HR, 0.514; 95% CI, 0.348–0.758; beta value = -0.666; $p = 0.001$), and the presence of an IDH mutation (HR, 0.503; 95% CI, 0.283–0.897; beta value = -0.686; $p = 0.012$) were independent favorable prognostic factors for OS. Age > 60 years was an independent negative factor for OS (HR, 2.143; 95% CI, 1.465–3.135; beta value = 0.762; $p < 0.0001$).

ROC analysis of the training and validation cohorts at each time point

Based on the results of multivariate Cox analysis, age, EOR, chemotherapy, and the IDH mutation status were selected to build a model (Table 3). In the training cohort, the results of the ROC analysis are shown in Fig. 1a and Table Sup-1. The AUC was 0.815, 0.851, 0.849, and 0.836 at 12, 15, 18, and 24 months, respectively. The cutoff value for the risk score was − 0.942 in all four ROC analyses.

Table 3
The items of risk score system

Items	Basement score		0 - Beta value
	0	1	
Age	> 60	≤ 60	-0.762
Extent of tumor resection	Non-total resection	Total resection	1.294
Chemotherapy	Unreceived	Received	0.666
IDH mutation status	Wildtype	Mutation	0.686

In the validation cohort, the results of ROC analysis are shown in Fig. 1b and Table Sup-2. The AUC was 0.780, 0.807, 0.836, and 0.849 at 12, 15, 18, and 24 months, respectively. The cutoff value for the risk score was still equal to -0.942 in all four ROC analyses.

Survival curve for the high and low risk groups

Based on the cutoff values for the risk score, the patients were divided into low (risk score ≤ -0.942) and high (risk score > -0.942) risk groups. The median OS for patients in the low risk group was significantly longer than that for the patients in the high risk group in the both the training and validation cohorts, and among all patients, respectively (training cohort, low-risk vs high-risk = 938 vs 333 days, $p < 0.0001$; validation cohort, low-risk vs high-risk = 1122 vs 378 days, $p < 0.0001$; all patients, low-risk vs high-risk = 1105 vs 363 days, $p < 0.0001$, Fig. 2).

ROC analysis of the risk score system and other category methods

We compared the predictive effort by using the risk score system and independently using EOR, IDH mutation status, and age with the ROC analysis at 12, 15, 18, and 24 months after tumor resection. We found that the AUCs of the risk score system were larger than any other independent factors. (Fig. 3).

Prognostic factors for overall survival times among patients with wild type IDH

The results of the univariate analysis for patients with wild type IDH showed that total resection (HR, 0.279; 95% CI, 0.203–0.383; $p < 0.0001$), chemotherapy (HR, 0.442; 95% CI, 0.321–0.608; $p < 0.0001$), and having received radiation therapy (HR, 0.585; 95% CI, 0.381–0.897; $p = 0.014$) positively affected OS. Age > 60 years (HR, 1.386; 95% CI, 1.029–1.867; $p = 0.032$) negatively affected OS. After multivariate analysis, total resection (HR, 0.269; 95% CI, 0.195–0.372; beta value = -1.313; $p < 0.0001$), received chemotherapy (HR, 0.458; 95% CI, 0.331–0.634; beta value = -0.781; $p < 0.0001$), and age > 60 years (HR, 0.1.775; 95% CI, 1.310–2.406; beta value = 0.574; $p < 0.0001$) remained independent factors for OS.

Furthermore, the prognostic factors for OS in patients with IDH mutation were shown in supplemental part 1.

Discussion

The current recommended treatment for patients with newly diagnosed GBM is resection followed by adjuvant chemoradiotherapy. Based on the new histopathological criteria for glioma, the presence of IDH mutations was highlighted as important to the distinct prognosis of patients with GBM. However, it remains unknown whether total resection is beneficial for patients with wild type IDH GBM. The current study generated a risk scoring system that included information regarding clinical characteristics and IDH mutation status to evaluate the risk factors associated with the prognosis of GBM patients and to predict the survival outcomes at 12, 15, 18, and 24 months. It was determined that total resection, age < 60 years, received chemotherapy, and IDH mutation were independent factors associated with improved OS. Moreover, this study confirmed that totally removing the region of contrast-enhancement of GBM was beneficial for prolonging the OS of those with wild type IDH.

Total resection of the contrast-enhancement region of tumor has been proven the most beneficial factor for improving OS in patients newly diagnosed GBM patients.[1, 4, 19, 20] Removing more than 78% of contrast-enhancement of GBM has also been shown to be valuable for OS.[4] Moreover, Sawaya et al. recommended that more than 53.21% of the surrounding region of the T2-FLAIR abnormality beyond the 100% contrast-enhancement resection should be removed since that was able to bring more benefit for prolonging OS than only removing the region of contrast-enhancement.[15] Our findings were consistent with previous studies. In our risk scoring system, the impact coefficient of total resection was nearly twice that of other variables. Our findings re-verified that total resection was essential for improving OS of patients with GBM. Furthermore, referring to the literature review recently published, whether patients with GBM and wild type IDH have benefits associated with totally resection still unknown.[18] Our results confirmed that total resection would not only significantly prolong OS of patients with GBM and IDH mutations but also would prolong OS in patients with IDH wild type (supplemental part 2).

Radiation therapy plus chemotherapy is helpful for prolonging OS of patients with newly diagnosed GBM. [10, 11] Although the period of enrolled patients was too long to implement uniform treatment strategies for chemotherapy, having received chemotherapy was an independent favorable factor for OS. Hence, our findings suggest that chemotherapy was necessary for patients with newly diagnosed GBM. Additionally, our results showed that having received radiation therapy was not a significant beneficial prognostic factor for OS. However, our findings did not suggest that radiation therapy was unnecessary for the treatment of newly diagnosed GBM. As various previous studies have shown, [21–23] radiation therapy was undoubtedly beneficial for the OS of patients with GBM. In our study, almost all patients (nearly 90%) received radiation therapy. Hence, there was no significant difference in OS between the patients with and without radiation therapy. Hence, the variable of receiving radiation therapy was not selected to generate our risk system because all patients were recommended to receive radiation therapy after GBM resection at present.

Although the mutation rate in primary GBM was much lower than that in secondary GBM, IDH mutations were reported to have a strong positive correlation with OS in GBM.[24, 25] Our previous study showed that the IDH mutation status was able to predict the OS of patients with secondary GBM by using microRNA signature. In the current study, the IDH mutation status could be applied to classify the survival outcomes of newly diagnosed GBM patients. Using the criteria regarding histological tumors in neural central system (WHO 2016), it was recommended that molecular characteristics (IDH mutation, 1p/19q co-deletion) be used to diagnose different kinds of glioma.[3, 16] However, to our knowledge,[1, 6, 12, 26] our risk system was the first evaluative system, generated based on clinical characteristics, information regarding adjuvant treatment, and the IDH mutation status, to classify the survival outcomes of patients with GBM. Our findings remedied the lack of inclusion of molecular information in the evaluative systems that were previously recommended.

Our findings revealed that age > 60 years was significantly associated with decreased survival; similar findings have been shown in previous studies.[27–30] As has been previously demonstrated, elderly people may have a decreased ability to withstand neurological insults caused by the tumor, surgery, and/or adjuvant therapy.[27] In our study, there was no significant difference in the number of younger (≤ 60 years) and elderly (> 60 years) patients with total resection and chemotherapy. Consequently, we inferred that the reason that elderly age was still a negative prognostic factor because elderly people have fewer chances to undergo secondary surgical treatment or adjuvant therapy.[30] Moreover, we found a significant decline in the preoperative KPS score among elderly patients when compared with younger patients ($p < 0.0001$). This finding was consistent with those from previous studies, in which lower KPS scores were negatively associated with OS.[27, 31] These findings are likely explained by the fact that elderly patients may harbor tumors with different molecular profiles and resistance genes that confer more aggressive behaviors.[32]

The main advantage of our evaluative system was its stability; both the training and validation cohorts used the same cut-off values to classify survival outcomes. Moreover, the evaluative system was generated based on clinical characteristics and the IDH mutation status; these variables were processed in a binary manner. Our findings indicated that patients would possibly be able to live longer if they were younger than 60 years, received total resection and chemotherapy, and had an IDH mutation. Hence, our system will be efficient and accurate in assisting clinical neurosurgeons or oncologists to predict survival outcomes of patients. Additionally, we found that the AUC for survival prediction at 18 and 24 months was higher than that at 12 and 15 months in both the training and validation groups. This indicates that our system will be more advantageous for a long-term versus short-term survival prediction.

Although our system had some advantages for survival prediction, it was not externally validated to assess its robustness. In the future, multicenter trials will be performed to validate our risk system.

Conclusions

For patients with newly diagnosed GBM, being younger than 60 years of age, total resection of the contrast-enhanced region, having received chemotherapy, and IDH mutations were independent factors associated with a favorable OS. Our prognostic system based on these factors enables to help to guide treatment strategy of GBM because this system was stable and able to predict the survival outcomes, in particular the long-term survival.

Abbreviations

IDH = isocitrate dehydrogenase, EOR = extent of tumor resection, AUC = Area under the curve, GBM = glioblastoma multiforme, OS = overall survival, KPS = Karnofsky Performance Scale, ROC = receiver operating characteristic curve, HR = hazard ratio, CI = confident intervention.

Declarations

1. Ethics approval and consent to participate

This study had been approved by IRB of Beijing Tiantan Hospital.

2. Consent for publication

All authors agreed that this manuscript was publicized with open access.

3. Availability of data and materials

Anonymized data will be made available on request.

4. Competing interests

There are no conflicts of interest to declare.

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6. Authors' contribution

Study concept and design: Fang SY and Fan X.

7. Acknowledgments:

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Figures

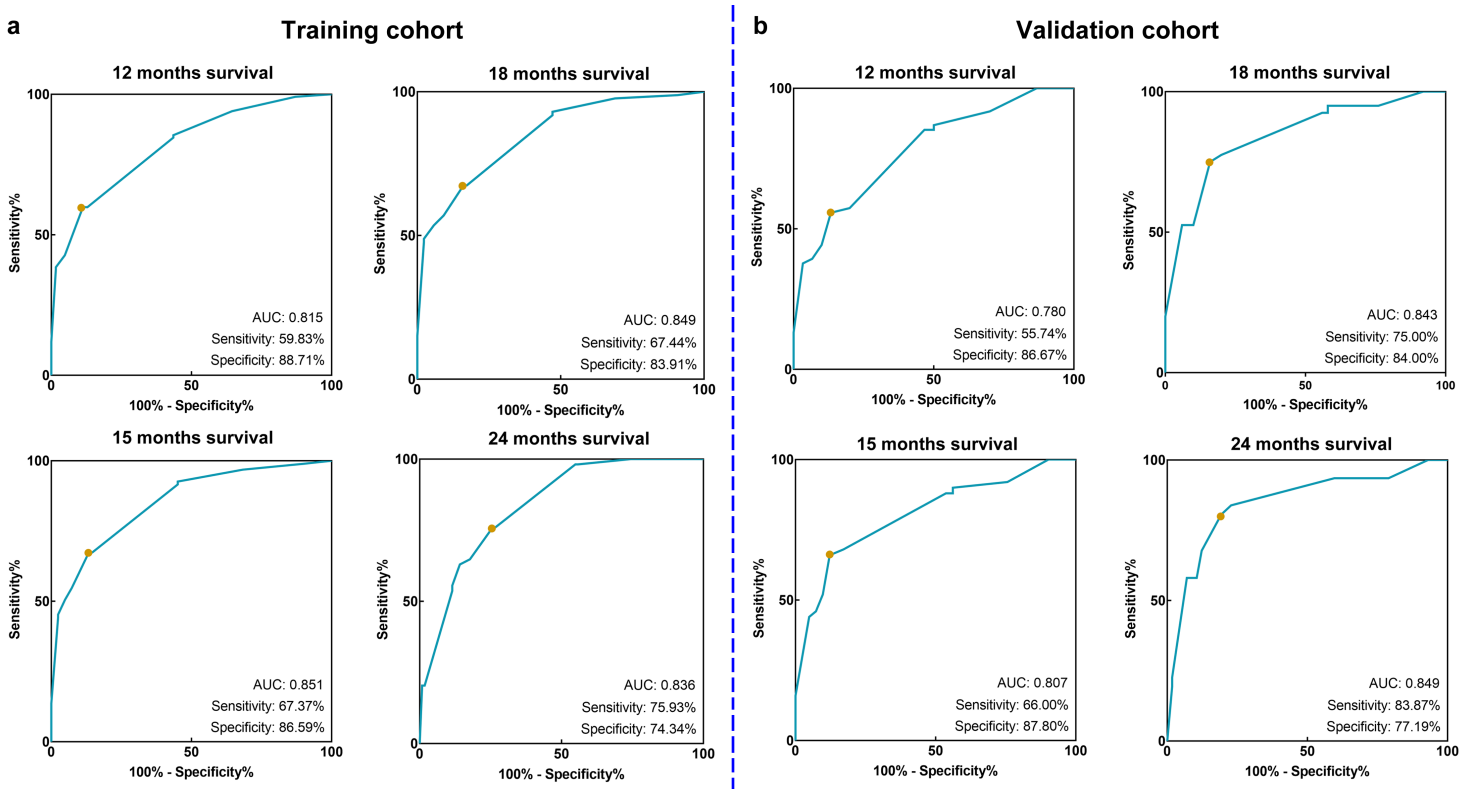

Figure 1

The results of receiver operating characteristic (ROC) curve analysis of the survival outcomes at 12 months, 15 months, 18 months, and 24 months. A) The result of training cohort. B) The result of

validation cohort.

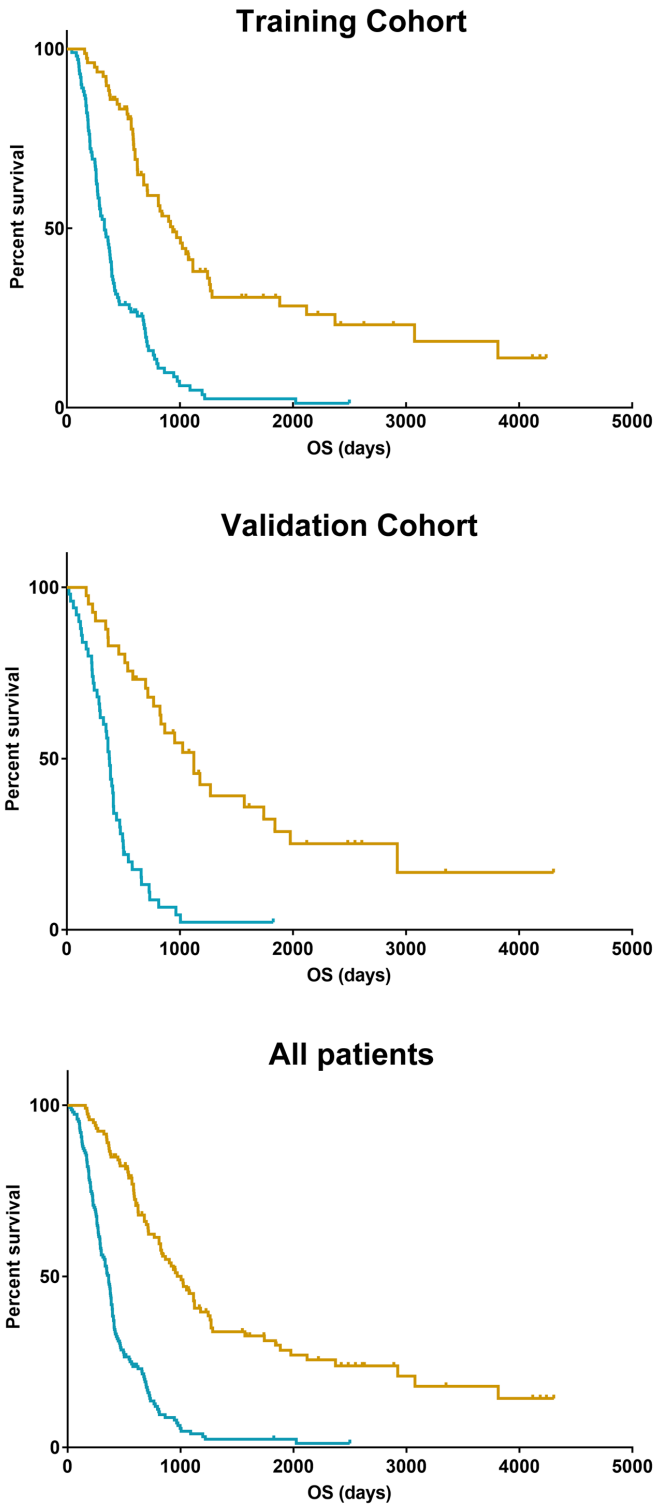

Figure 2

The results of Kaplan-Meier analysis for the overall survival times in the training and validation cohorts and in all patients. The cut-off value to distinct low-risk and high-risk was equal to -0.942.

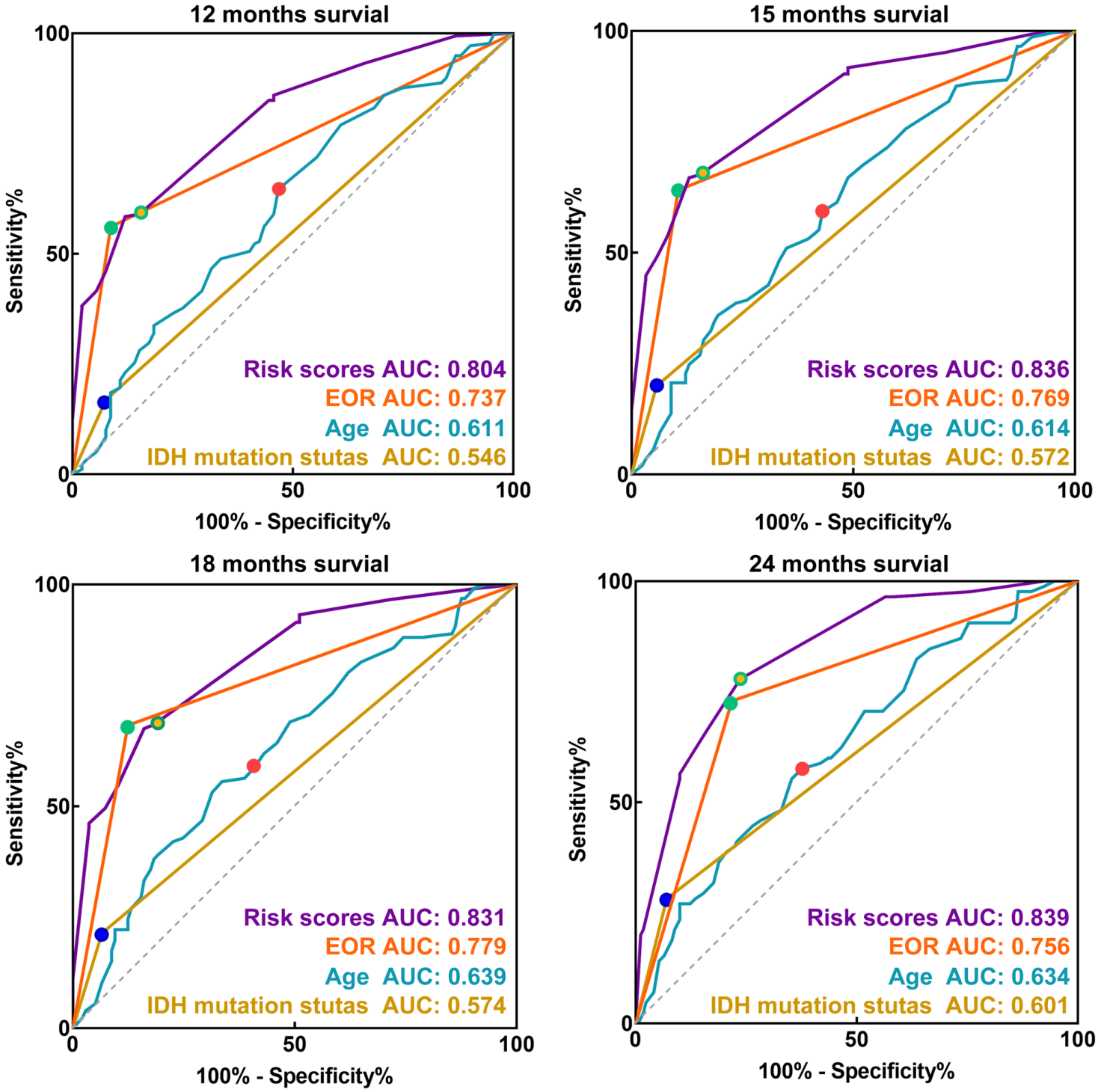

Figure 3

The areas of under curve at different checkpoints with different evaluative methods. The purple line: using risk score system to predict. The orange line: using extent of tumor resection (EOR) to predict. The light blue line: using age to predict. The golden line: using status of IDH mutation to predict.

Supplementary Files

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

- SupplementalMaterials.docx