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Multi-center real-world data-driven web calculator for predicting outcomes in IDH-mutant gliomas: Integrating molecular subtypes and treatment modalities

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Abstract

Background. Isocitrate dehydrogenase (IDH)-mutant gliomas generally have a better prognosis than IDH-wild-type glioblastomas, and the extent of resection significantly impacts prognosis. However, there is a lack of integrated tools for predicting outcomes based on molecular subtypes and treatment modalities. This study aimed to identify factors influencing gross total resection (GTR) rates and to develop a clinical prognostic tool for IDH-mutant gliomas.

Methods. We analyzed 650 patients with IDH-mutant gliomas from 3 Chinese medical centers (Shanghai, Hong Kong, and Zhengzhou). Data included age, sex, extent of resection, radiotherapy status, tumor grade, histology, and molecular markers (1p19q, TERT promoter, BRAF, EGFR, 10q). Patients were categorized based on GTR status, and a nomogram predicting 3-, 5-, and 10-year overall survival (OS) was developed using Cox proportional hazards regression and validated with time-dependent ROC and calibration plot analyses.

Results. Non-GTR was associated with diffuse astrocytoma (73.0% vs. 53.5%), 1p19q non-codeletion (67.9% vs. 48.7%), and wildtypeTERT promoter (63.6% vs. 52.4%). The nomogram, incorporating age, TERT promoter status, extent of resection, grade, and radiotherapy status, demonstrated strong discriminatory ability (AUC > 0.75) and good calibration. Decision curve analysis indicated that it outperformed WHO grade-based classification in identifying high-risk patients. An online calculator was developed for clinical use (http://www.szflab.site/nomogram/).

Conclusion. We developed and validated a nomogram and online tool that integrates molecular and clinical factors for predicting outcomes in IDH-mutant gliomas, enhancing clinical decision-making.

Key Points

- Surgical resection extent significantly impacts postoperative radiotherapy benefits.
- Integrated nomogram developed for IDH-mutant glioma prognosis.
- Online calculator enhances clinical application of prognostic model.

Importance of the Study

This study addresses a critical gap in the management of IDH-mutant gliomas by developing a comprehensive prognostic tool that integrates molecular and clinical factors. Unlike previous models, our nomogram incorporates the extent of resection, a crucial prognostic factor often overlooked. By accurately predicting individual patient outcomes, this tool enhances clinical decision-making and facilitates personalized treatment strategies. The accompanying online calculator makes the nomogram readily accessible to clinicians worldwide, potentially improving patient care on a global scale. Future prospective studies can validate and refine this tool, paving the way for more precise and effective glioma management.

Gliomas, the most common primary brain tumors, present significant challenges owing to their diverse prognoses and treatment complexities.[1,2] Recent advances in molecular biology have identified the isocitrate dehydrogenase (IDH) mutation as a key marker for glioma classification.[3,4] While IDH-mutant gliomas generally have better outcomes than their wild-type counterparts, substantial survival variations persist within this group, highlighting the need for further investigation into prognostic factors.

The extent of resection (EOR) is a crucial factor for glioma prognosis. Complete tumor removal leads to better survival rates in IDH-mutant gliomas than partial resection.[5,6] However, achieving total resection is not always possible because of factors such as the tumor location and size. Therefore, identifying the factors that influence EOR, along with appropriate follow-up treatments, is essential for developing personalized treatment plans.

Several prognostic models have been developed for patients with IDH-mutant gliomas, each aiming to predict clinical outcomes based on various molecular and clinical parameters.[7–9] However, many of these models have significant limitations. For instance, some are based on small sample sizes, which may restrict their generalizability across diverse patient populations. Others fail to integrate the multifaceted nature of treatment modalities and molecular subtypes,[10] leading to a less comprehensive understanding of prognosis. Given the complexity of gliomas, there is a growing need for predictive tools that incorporate multiple prognostic factors. Real-world data from multiple centers can offer more generalizable and reliable results than traditional clinical trials.[9,11] Nomograms have proven valuable in predicting the outcomes of various cancers by translating complex statistical models into user-friendly visual tools.[12,13] In glioma research, developing a nomogram that combines the molecular and clinical characteristics could significantly support personalized treatment decisions.

In this study, we aimed to create and validate a comprehensive web tool to predict the outcomes of IDH-mutant gliomas. By incorporating multiple factors, including EOR and molecular features, we aimed to provide a more accurate and holistic predictive tool for clinicians. Our approach is innovative in 3 key aspects: (1) using multicenter real-world data, (2) considering a wide range of molecular and clinical factors, and (3) developing an accessible online tool for clinical use.

Our research involved the use of discovery and validation cohorts, employing statistical analyses to identify significant prognostic factors and assess the model's predictive performance. We anticipate that this nomogram will enhance the prognosis prediction accuracy for IDH-mutant glioma patients, thereby informing tailored treatment strategies and improving patient outcomes.

Methods

Patient Cohorts

This study builds on our previous research,[14] drawing data from 650 adult patients (18 years and older) diagnosed with IDH-mutant gliomas. We retrospectively collected these cases from 3 independent institutions: Prince of Wales Hospital at the Chinese University of Hong Kong, Huashan Hospital of Fudan University in Shanghai, and The First Affiliated Hospital of Zhengzhou University. All gliomas were classified according to the World Health Organization 2021 criteria.[3]

Data collected included age, sex, extent of resection, radiotherapy status, tumor grade, histology, and molecular markers (1p19q, TERT promoter, BRAF, EGFR, 10q). Cases that lacked sufficient clinical information or survival data were excluded from the study. Histological sections were centrally reviewed by 2 experienced neuropathologists to ensure consistency in diagnosis. The cases were retrospectively collected without selection bias from these institutions, ensuring a representative sample of gliomas diagnosed and treated during this period.

Our study evaluated the 1p19q co-deletion status, which differentiates IDH-mutant astrocytomas from IDH-mutant 1p19q codeleted oligodendrogliomas and is crucial for accurate prognosis and classification. In addition to assessing the 1p/19q status, our neuropathologists employed a comprehensive approach that included (1) Histopathological examination: Detailed microscopic examination of tumor tissue samples to identify histological features characteristic of different IDH-mutant glioma subtypes. (2) Immunohistochemistry (IHC): Utilization of specific antibodies to detect the presence of proteins that are markers for various glioma types. This included markers such as IDH1R132H, ATRX, and p53, which help in differentiating between IDH-mutant glioma subtypes.

Molecular Profiling Analysis

The selection of specific molecular markers in our study was based on their known prognostic value in gliomas. For

instance, the inclusion of TERT promoter status stems from our long-term interest and our previous research indicating its significant prognostic impact on adult gliomas.[15–17] For all IDH-mutant astrocytomas, we specifically assessed the deletion of CDKN2A/B. According to the 2021 WHO classification of central nervous system tumors, the presence of necrosis or homozygous deletion of CDKN2A/B is diagnosed as CNS WHO grade 4. If a homozygous deletion of CDKN2A/B is detected, the tumor is automatically graded as CNS WHO grade 4, irrespective of histological features. We conducted comprehensive molecular analyses on the samples, including the detection of CDKN2A/B deletions, using fluorescence in situ hybridization for accurate detection. We integrated these molecular findings, including CDKN2A/B status, with histopathological assessments, especially in cases where histological features might indicate a lower grade (such as CNS WHO grade 2) but require upgrading to CNS WHO grade 4 due to CDKN2A/B deletion.

EGFR amplification and 10q deletion were also examined as much as tissues would allow because of our previous findings[18] of their prognostic value and their documentation in the literature.[19–21] BRAF V600E mutations were evaluated whenever tissue was available due to our interest in BRAF and the potential for targeted therapy of IDH wildtype gliomas.[22] The methodology used for the single-gene tests was consistent across the 3 institutions as detailed in our previous study.[14] Briefly, tissue sections obtained through either macrodissection or direct scraping from slides were placed into a Tris-HCl buffer (pH 8.5) containing proteinase K. The mixture was incubated overnight at 56°C, followed by heating at 98°C for 10 min. The resulting crude lysate was then combined with primers and KAPA Robust HotStart ReadyMix or KAPA HiFi HotStart ReadyMix (both from Sigma, St. Louis, MO, USA) for PCR amplification. The PCR products were visualized on an electrophoresis gel, purified with a spin column-based PCR product purification kit and sequenced using the BigDye Terminator Cycle Sequencing Kit v1.1 (Life Technologies, Carlsbad, CA, USA). The PCR primers can be found in Supplementary Table 1.

Clinical Information

Demographics and survival data were obtained from the hospital information systems of the 3 hospitals. The protocol for treating adult IDH-mutant gliomas of Grades 2–4 in all 3 hospitals was maximal safe resection initially. To accurately assess the GTR status of each case, all postoperative imaging was indeed reviewed by our radiology team. This process involved the following steps: (1) Postoperative imaging protocol: Standard postoperative MRI scans were obtained for each patient, typically within 48 h after surgery. These scans included T1-weighted, T2-weighted, FLAIR, and contrast-enhanced T1-weighted sequences to provide a comprehensive view of the surgical cavity and any residual tumor. (2) Radiological imaging review: A team of 3 experienced neuroradiologists from Huashan hospital meticulously reviewed the postoperative MRI scans from 3 centers. The radiologists were blinded to the clinical outcomes to ensure an unbiased assessment of the GTR status. (3) Assessment Criteria: The criteria for determining GTR status included the absence of any visible enhancing tumor on contrast-enhanced T1-weighted MRI sequences. Any residual enhancement within the resection cavity was noted, even if minimal, and such cases were classified as non-GTR. Information about radiotherapy treatment was obtained from patient records, as some but not all patients received adjuvant radiotherapy due to individual clinical situations, and this information was gathered from the hospital information systems. Overall survival (OS) was obtained either from the hospital information systems or by phone calls, consistent with our previous studies. OS was defined as the period between the operation and death or the last follow-up.

This study received ethical approval from the relevant committees at all participating institutions: the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee, the Ethics Committee of Huashan Hospital in Shanghai, and the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. All aspects of this study were conducted in strict accordance with the principles outlined in the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were conducted using R software (v 4.2.0). Our primary focus was on OS, measured from the time of diagnosis to death from any cause. Chi-square tests were used to examine the relationships between the total resection status and various clinical and molecular parameters.

To visualize and compare survival distributions between groups, we created Kaplan–Meier (KM) survival curves[23] and applied log-rank tests. For a more comprehensive analysis, we used Cox proportional hazard regression models to evaluate the influence of molecular features and treatment factors on OS. Our model incorporated key covariates based on clinical relevance and statistical significance, including age at diagnosis, TERTp status, pathological grade, extent of resection, and radiotherapy status. Patients with incomplete or unavailable information were excluded from this analysis.

Using the "rms" package[24] in R, we developed a nomogram to predict 3-, 5-, and 10-year OS probabilities for IDH-mutant glioma patients. This predictive tool was based on multivariate Cox proportional hazards regression analysis. We used the Shanghai cohort to develop the model and independently validated it using Hong Kong and Zhengzhou cohorts.

To assess the nomogram's predictive accuracy, we utilized time-dependent area under the receiver operating characteristic curve (time-dependent ROC) analysis,[25] as described in Gittleman et al.'s research.[7] Calibration plots were also created to visually examine the alignment between the nomogram-predicted probabilities and the actual 3- and 5-year survival rates. In addition, we conducted a decision curve analysis (DCA)[26,27] to evaluate the clinical utility of our nomogram compared to using the WHO grade alone.

Throughout our analysis, we considered *P*-values less than .05 as statistically significant, and all tests were 2-sided.

Web-based Tool Development

To enhance the practical application of our research, we developed an interactive web-based tool that calculated survival probabilities based on our nomogram. This tool, built using the R and Shiny framework,[28] incorporates key patient characteristics and treatment factors, including age, TERTp status, pathological grade, extent of resection, and radiotherapy status. We designed this user-friendly interface to allow clinicians to quickly input patient data and obtain personalized survival probability estimates. This tool is freely accessible online at http://www.szflab.site/nomogram/ or Nomogram_SZFlab (shinyapps.io).

Results

Patient and Disease Characteristics

Our study workflow, outlined in Figure 1a, retrospectively analyzed medical data from 650 IDH-mutant glioma patients from 3 Chinese medical centers. We aimed to examine baseline patient information, the impact of gross total resection (GTR) on postoperative radiotherapy efficacy, factors associated with GTR, and develop a prognostic model incorporating molecular features and therapeutic interventions.

The patient cohort comprised 59.4% males and 40.6% females, with a median age of 41 years at diagnosis and median survival time of 3.87 years. At follow-up, 33.2% of the patients died. Histologically, 58.9% of the patients were diagnosed with IDH-mutant astrocytomas and 41.1% were diagnosed with IDH-mutant oligodendrogliomas. Pathological grading showed 66.2% as grade 2, 24.3% as grade 3, and grade 4 (9.5%). Surgically, 28.5% underwent biopsy or non-GTR, while 71.5% received GTR (Supplementary Table 2).

Molecular analysis revealed that 41.5% of IDH-mutant gliomas had 1p/19q co-deletion, and 42.5% showed TERT promoter mutations. Due to the recent implementation of additional genetic testing, data on BRAF, EGFR, and 10q mutations are limited. However, available data indicated low frequencies of BRAF (0.6%) and EGFR (2.5%)

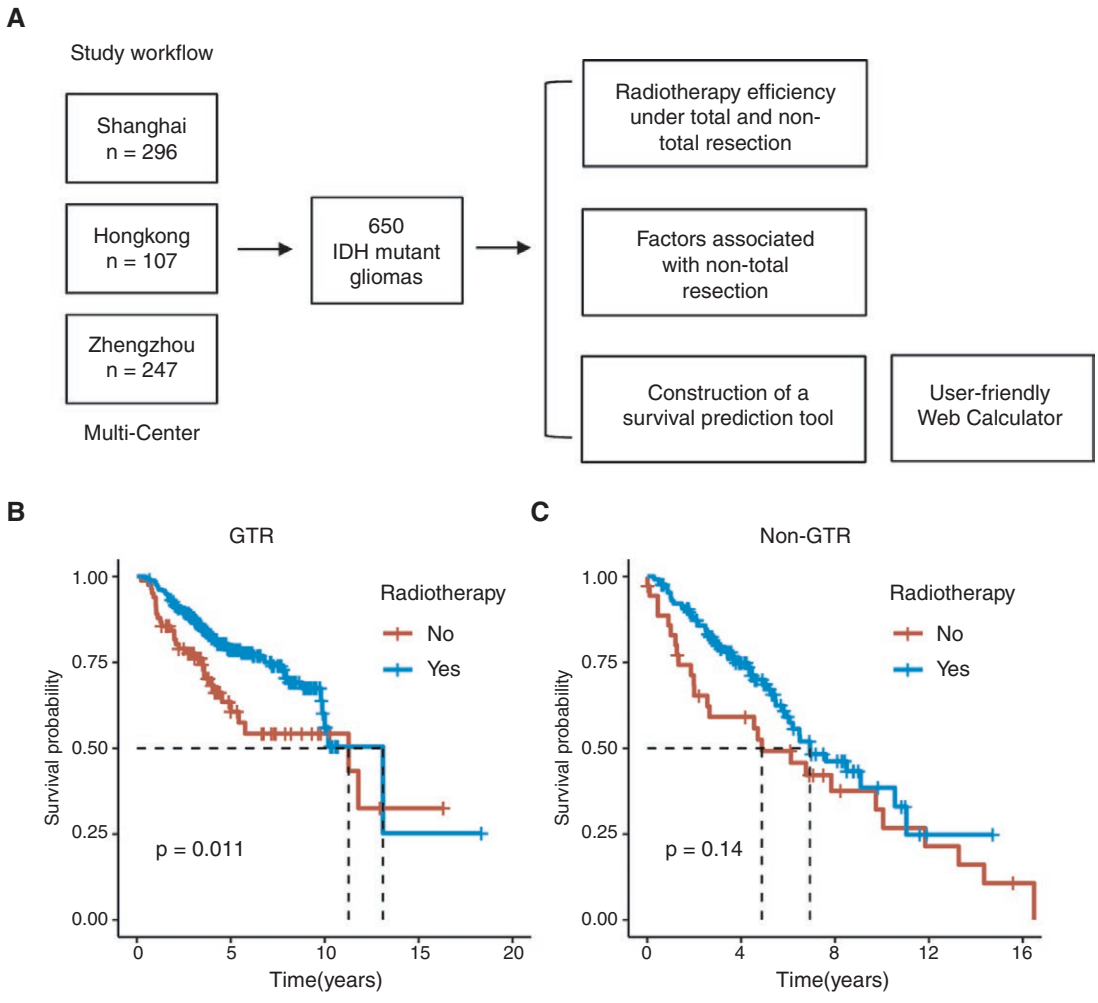

Figure 1. (a) Study workflow for the retrospective analysis of 650 IDH-mutant glioma patients from 3 medical centers. Kaplan-Meier survival curves comparing the efficacy of postoperative radiotherapy in (b) non-GTR and (c) GTR groups of IDH-mutant glioma patients.

mutations in IDH-mutant gliomas, consistent with previous findings.[29,30]

We further investigated the effect of GTR on the efficacy of postoperative RT. Patients were divided into non-GTR and GTR groups and survival analyses were conducted based on radiotherapy receipt. The results showed that the benefit of radiotherapy was significantly lower in the non-GTR group than in the GTR group (Figure 1a, b), underscoring the importance of maximal safe resection combined with postoperative radiotherapy for glioma treatment.

Factors Associated with Gross Total Resection

Given the significant impact of GTR on subsequent treatment efficacy, we aimed to identify the factors associated with achieving GTR in IDH-mutant gliomas. While previous research has demonstrated a strong correlation between IDH mutations and GTR in astrocytomas,[31] few studies have specifically examined factors influencing GTR in IDH-mutant gliomas.

We conducted a comparative analysis of the clinical and molecular characteristics of the GTR and non-GTR groups (Table 1). Our findings revealed distinct patterns among patients who underwent biopsy or subtotal resection: 73% had astrocytomas, 67.9% had 1p19q non-codeletion, and 63.6% had wildtype TERT promoter. These results suggest that molecular features may play a crucial role in determining GTR rates among patients with IDH-mutant gliomas. This insight provides valuable information for surgical planning and may help predict the likelihood of achieving GTR in these patients.

Development and Validation of the Nomogram

Our analysis revealed that 1p19q status, TERT promoter status, and histological types were significantly associated with GTR in IDH-mutant gliomas. We integrated these factors with known clinical prognostic indicators into a Cox hazard model to identify the risk factors after covariate adjustment (Table 2, Italic values indicate factors affected OS after uni- and multi- variable Cox regression analyses). Univariate and multivariate Cox regression analyses showed that patient age, TERT promoter status, resection extent, pathological grade, and postoperative radiotherapy were statistically significant predictors of OS. Notably, the histological subtype was not retained in the multivariate analysis, suggesting that molecular features may have greater prognostic value than histological diagnosis.

To create a comprehensive prognostic prediction tool, we further narrowed down our focus to 559 patients from the original 650, selecting those with complete information on age, TERT promoter status, resection extent, pathological grade, and postoperative radiotherapy. Among these, the Shanghai cohort ($n = 247$) served as the discovery cohort, while Hong Kong ($n = 83$) and Zhengzhou ($n = 229$) cohorts were used as validation cohorts to test the reliability of the prediction model (Figure 2a). The final nomogram is shown in Figure 2b.

We assessed the nomogram's performance using a time-dependent ROC analysis. In the discovery cohort, the nomogram achieved impressive prediction accuracies of 0.9 and 0.84 for 3-year and 5-year survival, respectively (Figure 2c). Similar high accuracies were observed in the validation cohorts (Hong Kong: 3-year, 0.88; 5-year, 0.87; Zhengzhou, 3-year: 0.78, 5-year: 0.77) (Figure 2d), demonstrating a robust discriminative ability across different patient populations. Calibration plots in both the discovery and validation cohorts showed strong concordance between the predicted and observed survival probabilities (Figure 2e, f), further supporting the reliability of the nomogram.

To evaluate the clinical utility of our nomogram, we compared its performance with that of the WHO grading system using decision curve analysis (DCA).[27] DCA curves revealed that our nomogram provided superior prediction of 5-year OS, offering greater net benefit across almost all threshold probabilities in both the discovery and validation cohorts. Moreover, the nomogram outperformed the strategies of treating all patients or none of them (Figure 3a).

In summary, our nomogram demonstrates excellent discrimination and calibration capabilities, potentially offering a more accurate and clinically valuable tool for predicting outcomes in IDH-mutant glioma patients than traditional grading systems. This integrated approach, which combines molecular features and therapeutic interventions, may enhance prognostic accuracy and inform treatment decisions for this patient population.

Online Web Calculator

To enhance the clinical applicability of our prognostic model, we developed an online calculator based on a nomogram. This user-friendly tool is available at http://www.szflab.site/nomogram/ (Figure 4). Our approach was inspired by the research of Gittleman et al. (https://gcioffi.shinyapps.io/Nomogram_For_IDH_Wildtype_GBM_H_Gittleman/).[8]

The calculator incorporates 5 key parameters: (1) patient age (range: 18-80 years), (2) TERT promoter status (wildtype or mutant), (3) extent of resection (Total or Non-total Resection), (4) pathological grade (grade 2, 3, or 4), and (5) radiotherapy status (Yes or No). Users can input relevant clinical information for a specific patient, and the calculator will generate a total nomogram score with predicted 3-, 5-, and 10-year survival probabilities.

This tool offers several advantages (Figure 4):

1. Quick and convenient prediction of survival probabilities under various treatment scenarios
2. Identification of patients likely to respond favorably to conventional treatment approaches
3. Guidance for timely adjustment of treatment strategies for patients predicted to have poor prognoses

By integrating molecular features, clinical factors, and treatment modalities, our online calculator provides a comprehensive and individualized approach for the prognostic assessment of patients with IDH-mutant glioma (Figure 4). This tool may have the potential to support more informed decision-making in clinical practice.

Discussion

This study aimed to develop and validate an individualized prognostic tool for patients with IDH-mutant gliomas,

Table 1. Comparison of Clinical and Molecular Features Between GTR and Non-GTR Groups in IDH-mutant Glioma Patients

		Non-GTR / Biopsy	GTR	*P* value
	N=	185	465	
Age (median [IQR])		41.00 [35.00, 49.00]	41.00 [35.00, 49.00]	.804
Gender (%)	Female	77 (41.6)	187 (40.2)	.81
	Male	108 (58.4)	278 (59.8)	
OS.status (%)	Dead	95 (51.4)	121 (26.0)	**<.001**
	Alive	90 (48.6)	344 (74.0)	
OS (years) (median [IQR])		3.83 [2.10, 6.00]	4.01 [2.81, 6.28]	**.047**
Histology (%)	Diffuse astrocytoma, IDH-mutant	135 (73.0)	248 (53.3)	**<.001**
	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	50 (27.0)	217 (46.7)	
Grade2021 (%)	2	116 (62.7)	314 (67.5)	.44
	3	48 (25.9)	110 (23.7)	
	4	21 (11.4)	41 (8.8)	
1p/19q (%)	Codel	51 (32.1)	219 (51.3)	**<.001**
	Non-codel	108 (67.9)	208 (48.7)	
TERTp (%)	Mutant	64 (36.4)	212 (47.6)	**.014**
	Wildtype	112 (63.6)	233 (52.4)	
BRAF (%)	Mutant	3 (4.1)	1 (1.4)	.642
	Wildtype	71 (95.9)	70 (98.6)	
EGFR (%)	Amplification	5 (5.0)	11 (7.6)	.574
	Non-amplification	96 (95.0)	134 (92.4)	
10q (%)	Deletion	7 (46.7)	11 (42.3)	1
	Intact	8 (53.3)	15 (57.7)	

Table 2. Univariate and Multivariate Cox Regression Analyses of Factors Associated with Overall Survival in IDH-mutant Glioma Patients

		stats	HR (univariable)	HR (multivariable)
Age	Mean ± SD	43.1 ± 10.2	1.02 (1.01–1.04, *P* < .001)	***1.03 (1.02–1.05, P < .001)***
1p19q status	Codel	232 (44.8%)		
	Non-codel	286 (55.2%)	2.92 (2.05–4.16, *P* < .001)	0.84 (0.11–6.32, *P* = .865)
TERTp status	Mutant	263 (50.8%)		
	Wildtype	255 (49.2%)	2.74 (1.98–3.80, *P* < .001)	***1.99 (1.31–3.05, P = .001)***
Surgical Resection	Non-total resection	134 (25.9%)		
	Total resection	384 (74.1%)	0.57 (0.42–0.76, *P* < .001)	***0.69 (0.50–0.96, P = .028)***
Grade2021	2	370 (71.4%)		
	3	136 (26.3%)	3.08 (2.22–4.27, *P* < .001)	***3.02 (2.10–4.34, P < .001)***
	4	12 (2.3%)	11.07 (6.95–17.64, *P* < .001)	***10.48 (5.17–21.25, P < .001)***
Radiotherapy	No	101 (19.5%)		
	Yes	417 (80.5%)	0.59 (0.43–0.81, *P* = .001)	***0.62 (0.43–0.90, P = .012)***
Histology	Astrocytoma	289 (55.8%)		
	Oligodendroglioma	229 (44.2%)	0.31 (0.22–0.44, *P* < .001)	0.44 (0.06–3.29, *P* = .426)

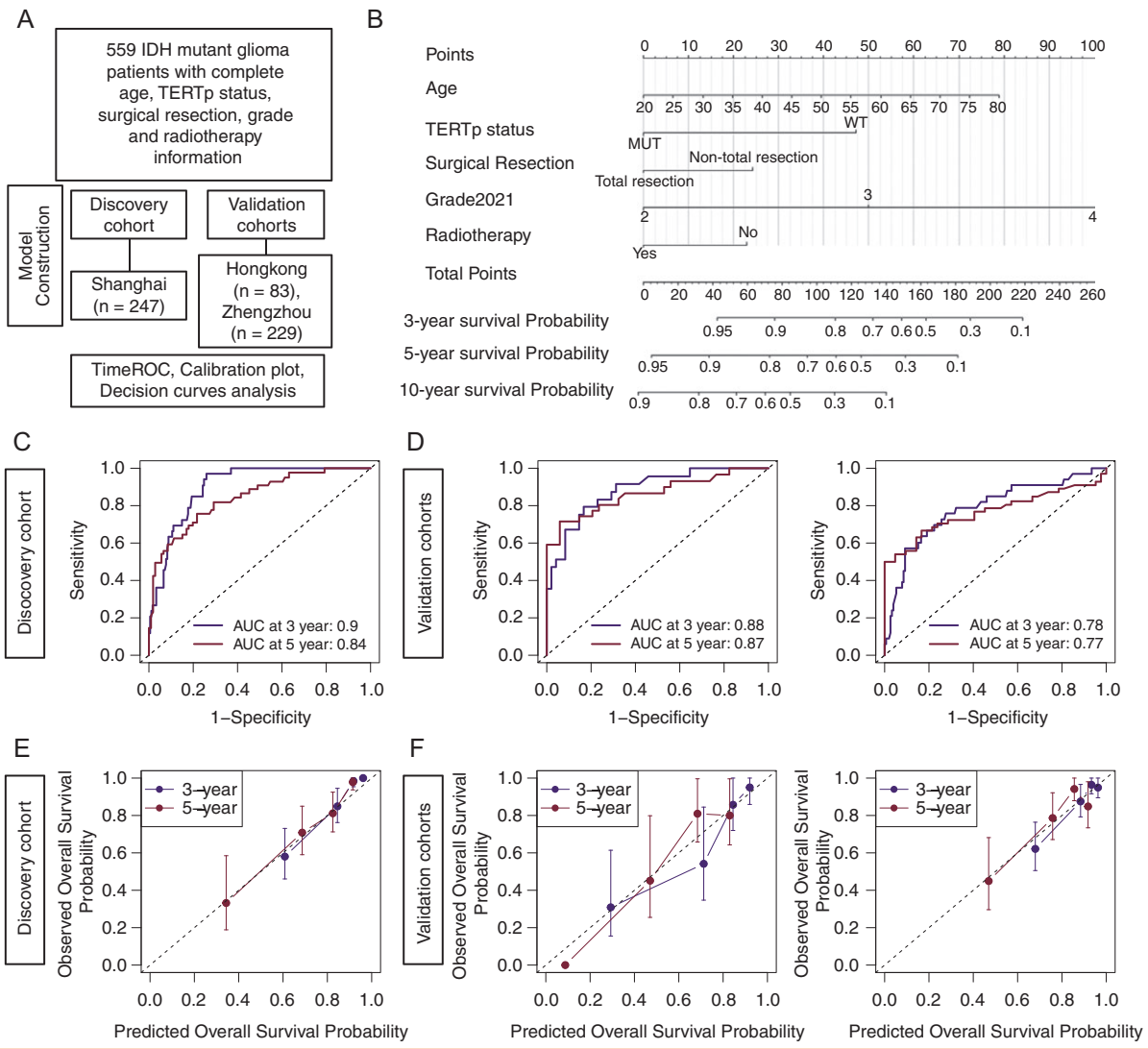

Figure 2. Development and validation of the prognostic nomogram for IDH-mutant gliomas. (a) Schematic representation of the model construction and validation process. (b) Nomogram predicting 3-year, 5-year, and 10-year overall survival in IDH-mutant glioma patients. (c) Time-dependent ROC curves for 3-year and 5-year survival prediction in the discovery cohort. (d) Time-dependent ROC curves for 3-year and 5-year survival prediction in the Hong Kong and Zhengzhou validation cohorts. (e) Calibration curves for 3-year and 5-year survival predictions in the discovery cohort. (f) Calibration curves for 3-year and 5-year survival predictions in the validation cohorts.

a subtype characterized by more favorable outcomes than their wild-type counterparts. Given the extended survival often observed in this patient population, accurate long-term prognostication is crucial for informed clinical decision making.[32,33]

A key finding of our investigation was the differential effect of postoperative radiotherapy based on the extent of surgical resection. Our analysis revealed a significant disparity in radiotherapy benefits between patients who underwent GTR and those who underwent subtotal resection (non-GTR). Specifically, the survival advantage conferred by radiotherapy markedly diminished in the non-GTR cohort. This observation underscores the critical importance of maximal safe resection of IDH-mutant gliomas and provides a compelling rationale for tailoring postoperative management strategies. It also raises intriguing questions for future research, such as whether more aggressive multimodal approaches might be warranted for non-GTR patients and whether the potential long-term sequelae of radiotherapy in GTR patients are outweighed by its survival benefits.

The impact of molecular markers on the EOR in gliomas is an emerging and complex field of study. In recent years, the discovery of molecular features such as IDH1/IDH2 mutations and 1p/19q codeletion has transformed our understanding and classification of gliomas.[34,35] Our study also provides novel insights into factors that influence GTR in IDH-mutant gliomas. Our analysis revealed significant differences in clinical and molecular characteristics between the GTR and non-GTR groups. Notably, among patients

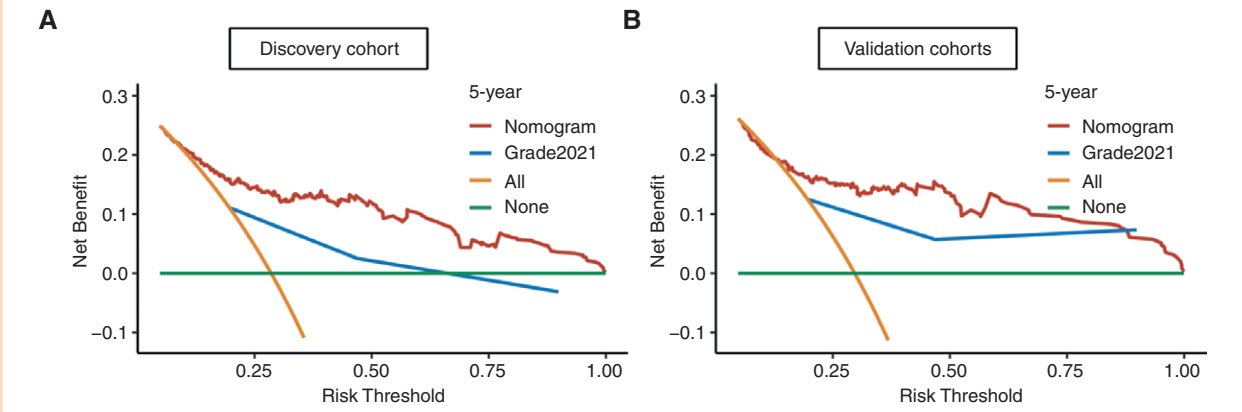

Figure 3. Decision curve analysis (DCA) comparing the clinical benefit of the nomogram to WHO tumor grading for predicting 5-year overall survival in (a) discovery and (b) validation cohorts.

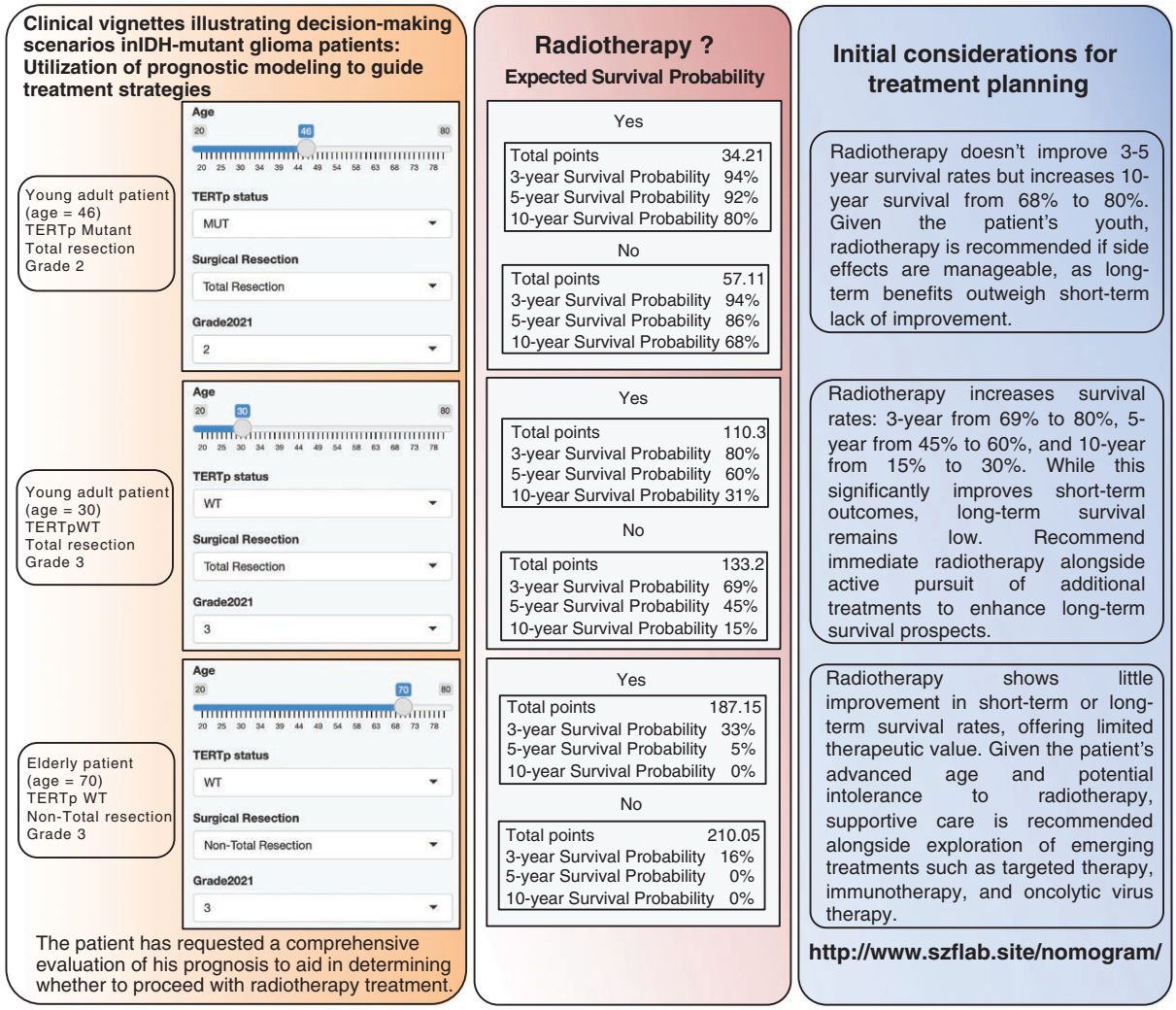

Figure 4. Examples of Clinical Scenarios and the Prognostic Utility of the Online Nomogram-Based Calculator. The web-based tool, accessible at http://www.szflab.site/nomogram/, provides personalized predictions of 3-, 5-, and 10-year survival probabilities. Scenario: The patient has requested a comprehensive evaluation of his prognosis to aid in determining whether to proceed with radiotherapy treatment.

who underwent biopsy or subtotal resection, we observed a predominance of astrocytomas (73%), 1p19q noncodeletion (67.9%) (consistent with previous studies[36,37]), and TERT promoter wildtype status (63.6%). These findings underscore the potential importance of molecular features in affecting the GTR rates in IDH-mutant gliomas. This knowledge informs surgical planning and may aid in predicting the likelihood of achieving GTR in these patients. It is important to recognize that our study was limited to a retrospective analysis of the pathological and molecular characteristics specific to the non-GTR group. Consequently, we cannot claim that these molecular characteristics directly lead to non-GTR outcomes. The occurrence of non-GTR is a complex clinical issue involving a multitude of factors, including tumor location and size,[38] molecular features,[39,40] and the patient's preoperative condition.[41] This complexity highlights the necessity for systematic investigation through future prospective cohort studies.

Recognizing the multifaceted nature of the prognostic factors in IDH-mutant gliomas, we employed a multivariate Cox proportional hazards regression model to construct a comprehensive nomogram. This predictive tool incorporates a range of clinically relevant variables including age, TERT promoter status, extent of resection, pathological grade, and radiotherapy status. The model demonstrated robust performance across 3 independent cohorts, with time-dependent ROC analyses consistently yielding AUC values > 0.75. Notably, our nomogram represents an advancement over previous prognostic models[7,42] by integrating both molecular markers and treatment-related factors, thereby offering more nuanced and personalized prediction. Decision curve analysis further corroborated the superior clinical utility of our model compared with the WHO grading system in predicting 5-year OS.

We developed an online calculator based on the nomogram to facilitate the practical application of our findings. Our team engaged in continuous dialogue with frontline clinicians, ensuring an intuitive and straightforward interface for swift and efficient utilization. The feedback from clinicians has been overwhelmingly positive, emphasizing the calculator's utility in facilitating their decision-making processes. Based on this feedback, several improvements have been implemented, including enhanced response times and the addition of user-friendly prompts, further streamlining the user experience. This user-friendly interface allows clinicians to input patient-specific data and obtain rapid estimations of 3-, 5-, and 10-year survival probabilities. Beyond mere prognostication, this tool offers valuable insights into the potential impacts of various treatment modalities on individual patient outcomes. Moreover, it serves as a powerful decision support system, enabling the identification of patients likely to benefit from standard therapies, as well as those who may require more aggressive or innovative approaches (Figure 4).

While our model represents a significant step forward in prognostic modeling of IDH-mutant gliomas, it is important to emphasize that it should complement, rather than replace, clinical judgment. Physicians should integrate the model predictions with patient-specific factors and the latest empirical evidence to formulate optimal treatment plans.

Our study has several limitations. First, despite validation across 3 independent cohorts, our patient population was derived from high-level medical centers in China, potentially limiting generalizability to community hospital settings. Differences in treatment protocols across different centers could also be an important variable. Although we have made efforts to validate our model across multiple independent cohorts to ensure its broad applicability, inconsistencies in treatment protocols between institutions may still have some impact on the results. Second, the relative rarity of certain clinical feature combinations may have resulted in their underrepresentation in our training cohort, necessitating caution when interpreting predictions for such cases. Finally, while our model encompasses numerous prognostic factors, it may not capture all relevant variables, such as specific chemotherapy regimens. In addition, unmeasured variables such as patient comorbidities might also influence the prognosis, which has not been thoroughly explored in the current study. Recent studies have shown a strong connection between DNA methylation levels and the prognosis of IDH-mutant gliomas, with low G-CIMP status in recurrent IDH-mutant gliomas often indicating a poor prognosis and displaying biological characteristics similar to IDH-wildtype gliomas.[15,43–45] Our current study is primarily focused on utilizing existing biological markers alongside treatment processes to offer predictive insights for the diagnosis and treatment of IDH-mutant gliomas. In future studies, we plan to further explore molecular markers, including DNA methylation, to enhance our predictive model and increase its accuracy and practicality in clinical applications.

During our analytical process, we also detected outliers primarily attributed to atypical clinical characteristics or unusual molecular marker configurations. For instance, patients belonging to extreme age groups or those with specific tumor subtypes demonstrated significantly divergent predictive outcomes compared to the broader cohort. To address these discrepancies, we will explore how to seamlessly integrate the online calculator with electronic health record systems, enabling clinicians to access and update patient data in real-time and provide more precise personalized treatment recommendations. In addition, as technologies like machine learning continue to evolve, we expect to leverage these advanced technologies to further optimize our model, enhancing its predictive accuracy and clinical utility.

In conclusion, we have developed and validated a robust, individualized prognostic tool for patients with IDH-mutant gliomas. This nomogram not only provides personalized survival estimates but also offers a valuable framework for treatment optimization. Our findings highlight the intricate nature of IDH-mutant glioma management and underscore the need for continued research on tailored therapeutic approaches. Future directions may include validation in larger, more diverse cohorts, incorporation of additional molecular and treatment-related variables, and integration with complementary predictive modalities, such as radiomics or liquid biopsy. Ultimately, this study represents a significant step toward more precise and personalized care for patients with IDH-mutant gliomas.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords:

IDH-mutant glioma | nomogram | prognosis prediction | clinical decision-making

LAY SUMMARY

IDH-mutant gliomas are common brain tumors that need surgery. Removing as much of the tumor as possible during surgery can help patients live longer. The authors of this study wanted to see which factors make it difficult to remove these tumors. To do this, they reviewed the data of 650 patients with these tumors from 3 separate centers in China. Their results showed that specific features of the tumor and genetic markers were linked to less successful tumor removal. Using this data, they developed an online calculator that combined patient factors with treatment and tumor features to help doctors predict how long a patient may live after surgery.

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Conflict of interest statement

The authors declare no conflict of interest.

Authorship Statement

Houshi Xu and Yue Wang are joint doctoral students at Peking Union Medical College Hospital and Huashan Hospital, affiliated with Fudan University. YM, ZS and JW conceived, supervised, and designed this study. HX, BL, and RZ: Data analysis and manuscript writing. LS, YW, and SJ collected the clinical data. HX, HC, MS and JC: Data processing and web tool building. KL, HN and ZZ: Reviewing and editing. Hong Kong and Shanghai Brain Consortium (HSBC) is a consortium led by the brain tumor researchers at Huashan Hospital, Fudan University, Shanghai and Chinese University of Hong Kong (https://www.surgery.cuhk.edu.hk/btc/hsbc/). All authors have contributed to the manuscript and approved the submitted version.

Data Availability

All processed data and R codes used in this study were obtained from the corresponding author upon reasonable request. Source codes will be available at https://github.com/mvpsc30/nomogram_IDHmut_glioma when this manuscript is accepted.

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