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Letter to the Editor

A validated prognostic nomogram for patients with newly diagnosed lower-grade gliomas in a large-scale Asian cohort

The nomogram represents a statistical model that incorporates multiple risk factors to estimate individualized survival probabilities. Recently, Gittleman et al presented a nomogram which provides an important tool for individualized survival prediction for newly diagnosed low-grade gliomas (LGGs).[1] In this study, however, some limitations should be noted. Firstly, the LGG populations enrolled represented a relatively small sample size in cohorts of both the Ohio Brain Tumor Study (OBTS; $n = 98$) and The Cancer Genome Atlas (TCGA; $n = 238$), which may decrease the statistical power leading to bias. Secondly, the ethnicities of the populations in both cohorts were primarily limited to American patients (91.8% and 95.7% Caucasians in OBTS and TCGA, respectively). Since the incidence and survival rates are different between ethnicities,[2,3] the extrapolation of these findings to other race/ethnic groups, especially Asian populations, with the highest number of incident cases per year,[4] should be further substantiated. Thirdly, postsurgical adjuvant treatment was not included in the Gittleman nomogram model. According to the latest European Association for Neuro-Oncology/Society for Neuro-Oncology consensus criteria, the addition of chemotherapy to radiotherapy has demonstrated in LGG improvements in both progression-free survival and overall survival (OS).[5,6] Hence, it is also important to consider postsurgical treatment strategies for comprehensive evaluation.

The above limitations therefore obviously raised questions on interpreting these results in a broader clinical setting. Adding to the information provided by Gittleman et al,[1] we developed a new nomogram for Asian patients by reviewing the cohort from the Chinese Glioma Genome Atlas (CGGA; http://www.cgga.org.cn). The clinicopathological characteristics of the patients are presented in Figure 1A, B. A total number of 582 patients with newly diagnosed LGG were included; the median age was 39.93 years, and 242 (42%) were female. In the CGGA, the samples were collected between 2004 and 2016. There were 218 events (deaths; 37.5%) over a median follow-up time of 121.6 months (range, 2.5–160.8 mo). Stratifying by molecular subtype, the Kaplan–Meier curves showed that the isocitrate dehydrogenase mutant/codeletion (IDHmut/codel) subtype had the best survival (median survival has not been reached), followed by the IDHmut/noncodel subtype (median survival = 79.4 mo), while IDH wildtype (wt) had the worst prognosis (median survival = 52.0 mo) (Figure 1A). Additionally, while no difference in OS was observed between CGGA and TCGA ($P = 0.129$; Figure 1A), we found that CGGA-IDHwt patients had better survival than TCGA-IDHwt ($P < 0.001$). This may be explained by the fact that the CGGA cohort includes younger patients than TCGA ($P < 0.001$), as well as by discrepancies of tumor grade distribution (47.3% World Health Organization [WHO] grade II in CGGA compared with 21.4% grade II in TCGA; $P < 0.001$). Subsequently, Cox regression analysis (Figure 1B, right) showed that younger age at diagnosis, WHO grade II versus III, IDHmut-codel versus IDHwt, and the IDHmut/noncodel versus the IDHwt were significantly associated with better prognosis ($P < 0.001$, respectively). The adjuvant treatment following surgery showed a trend toward improved survival (Figure 1B, right).

The nomogram to estimate 60-, 90-, and 120-month survival probabilities was established (Figure 1C). Verifying the Gittleman study, our nomogram showed that age at diagnosis was the largest contributor to patient survival, followed by molecular subtype, WHO grade, treatment, and sex. Cross-validation showed that the concordance index (C-index) for the model prediction was 0.827 (Figure 1D; left), ensuring reliable performance. The calibration plot showed that the observed and the nomogram predicted OS curves were well aligned (Figure 1D; left). In addition, we validated our nomogram for LGG patients who received postsurgical adjuvant therapy through cross-validation and the calibration plot (C-index: 0.804; Figure 1D, right).

In conclusion, the Gittleman nomogram is also valid for Asian cohorts. Importantly, we show that the incorporation of postsurgical treatment conditions can expand the clinical use of the Gittleman nomogram without impairing its validity. While our presented model includes the largest sample size to date for LGG patients, this nomogram would be strengthened by including other important variables such as pre- and postoperative tumor volume in future work when imaging data are available. Overall, this nomogram should be a useful tool for counseling patients in clinical practice including treatment decisions, follow-up, and prognosis. In this context, we have made a free online tool for this nomogram (https://rrlnnomogram.shinyapps.io/LGG_Nom_Asian/).

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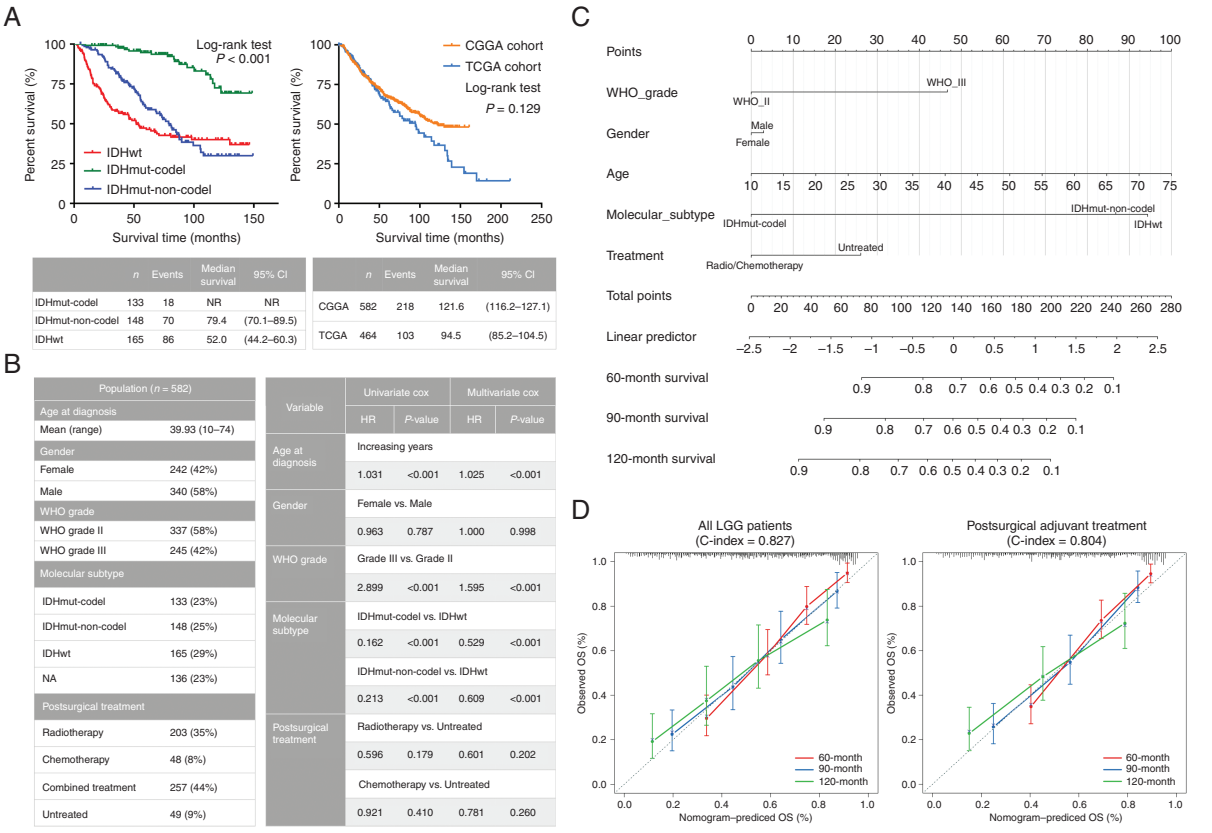

	n	Events	Median survival	95% CI
IDHmut-codel	133	18	NR	NR
IDHmut-non-codel	148	70	79.4	(70.1–89.5)
IDHwt	165	86	52.0	(44.2–60.3)

	n	Events	Median survival	95% CI
CGGA	582	218	121.6	(116.2–127.1)
TCGA	464	103	94.5	(85.2–104.5)

B

Population (n = 582)	
Age at diagnosis	
Mean (range)	39.93 (10–74)
Gender	
Female	242 (42%)
Male	340 (58%)
WHO grade	
WHO grade II	337 (58%)
WHO grade III	245 (42%)
Molecular subtype	
IDHmut-codel	133 (23%)
IDHmut-non-codel	148 (25%)
IDHwt	165 (29%)
NA	136 (23%)
Postsurgical treatment	
Radiotherapy	203 (35%)
Chemotherapy	48 (8%)
Combined treatment	257 (44%)
Untreated	49 (9%)

Variable	Univariate cox		Multivariate cox	
	HR	P-value	HR	P-value
Age at diagnosis	Increasing years			
	1.031	<0.001	1.025	<0.001
Gender	Female vs. Male			
	0.963	0.787	1.000	0.998
WHO grade	Grade III vs. Grade II			
	2.899	<0.001	1.595	<0.001
Molecular subtype	IDHmut-codel vs. IDHwt			
	0.162	<0.001	0.529	<0.001
	IDHmut-non-codel vs. IDHwt			
	0.213	<0.001	0.609	<0.001
Postsurgical treatment	Radiotherapy vs. Untreated			
	0.596	0.179	0.601	0.202
	Chemotherapy vs. Untreated			
	0.921	0.410	0.781	0.260

Fig. 1 (A) Kaplan–Meier survival curves for patients with newly diagnosed LGG by molecular subtype from CGGA (left); and by study (right). *P*-values from log-rank tests. (B) The summary of clinicopathologic features (left) and results of univariable and multivariable Cox regression analysis (right) in CGGA LGG cohort. (C) Nomogram to estimate 60-, 90-, and 120-month survival for patients with newly diagnosed LGG. (D) The calibration curves for predicting prognosis at each time point in all LGG patients (left) and patients who recieved postsurgical adjuvant treatment (right).

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Conflict of interest statement. The authors have no relevant competing interests to disclose.

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