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Letter to the Editor

Prognostic relevance of epilepsy at presentation in lower-grade gliomas

We read with great interest a recent paper by Berendsen et al. on the prognostic relevance of epilepsy at presentation in patients diagnosed with glioblastoma (GBM).[1] The authors found that epilepsy was an independent prognostic factor for longer survival in GBM patients.

We commend the authors for performing the largest study to date on the association between epilepsy at presentation and survival in GBM patients. However, we have concern regarding the statistical methods used to select the variables for inclusion into multivariate analysis. In this paper, the variables were selected based on statistically significant difference on chi-square analysis between epilepsy and non-epilepsy groups. For example, IDH1 mutational status was not included in the multivariate analysis because it did not correlate with epilepsy status (chi-square test; $P = .98$). We believe that this approach can be biased because variables that did not correlate with epilepsy on chi-square testing may still be a significant predictor of survival by either the log-rank test or univariate Cox regression. Our threshold for entering variables to be tested in multivariate analysis is not only demonstration of clinical significance in prior studies but also significance on the univariate survival analysis.

The reported incidence of epilepsy is higher in lower-grade gliomas (LGGs) than GBMs.[2,3] Refractory epilepsy is also more common in LGGs, occurring in 30%–35%.[2] Few studies have investigated the association between epilepsy and survival in LGGs.[4] Consequently, we reviewed hospital records for all adult patients with histologically confirmed LGGs (grades II and III) between 2012 and 2016. This study was conducted following approval by the ethical committee and institutional review board of Xiangya Hospital. Statistical analyses were performed using SPSS 20.0 (IBM). *P* values $<.05$ were considered significant.

We identified 113 LGG patients. The median follow-up was 37 months. According to the presence of epileptic seizure at presentation, patients were divided into 2 groups: 42 patients with epilepsy and 71 patient without epilepsy. Epilepsy was not a significant predictor of progression-free survival (log-rank test; $P = .094$) or overall survival (OS) (log-rank test; $P = .131$). We also analyzed the significance of epilepsy in the 477 patients from the Cancer Genome Atlas. The median follow-up was 107 months. Epilepsy was significantly associated with longer OS (log-rank test; $P = .048$) on Kaplan-Meier analysis, with a median survival of 109 months (95% CI: 88–150) in the epilepsy group versus 79 months for patients without epilepsy (95% CI: 51–108). However, epilepsy was not a significant predictor of OS ($P = .642$) after correcting for age, KPS, tumor location, WHO grade, histological classification, radiotherapy, and chemotherapy (Table 1).

Table 1. Multivariate analysis of prognostic factors affecting survival

	Overall Survival		
Factor	B	HR (95% CI)	*P* Value
Epilepsy			.642
Age	.060	1.062 (1.040–1.084)	**<.01**
KPS	−.038	.963 (.941–.985)	**.001**
Histologic subtype			.285
Tumor grade	−.847	.429 (.236–.778)	**.005**
Radiotherapy			.530
Chemotherapy	1.038	2.823 (1.705–4.673)	**<.01**
Tumor location			.968

Abbreviations: B, coefficient value; CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance status.
**P* value $<.05$ for multivariate analysis.

In conclusion, the inclusion of variables into multivariate survival analysis should not be based on significance from the chi-square test. Epilepsy may not have a prognostic significance on survival in LGGs as it does in GBMs. Further studies are needed to verify this finding.

Conflict of interest statement. None declared.

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Reply to Letter

Response to: "Prognostic relevance of epilepsy at presentation in lower-grade gliomas"

We thank Zhou et al for their interest and comments regarding our article.[1]

We acknowledge the theoretical interest of taking the isocitrate dehydrogenase 1 (IDH1) mutational status of tumors into account in the multivariable survival analysis of glioblastoma patients presenting with or without epilepsy. We also agree that the inclusion of IDH1 status in this analysis should not depend on its mere correlation with epilepsy and have indeed not to proceed in such a way in our analysis. As discussed in our article, tissue to determine IDH1 status was only available for 360 of the 647 glioblastoma patients, a limitation of our retrospective study. However, restricting our analysis to these patients would have led to selection bias. Indeed, and as stated in our manuscript, these 360 patients showed significant differences with respect to age, tumor location, resection and postoperative treatment, and proportion of patients presenting with epilepsy compared with our complete patient cohort.[1] Moreover, these patients showed a significantly longer survival (median overall survival [OS]: 376.0 days from surgery, 95% CI: 337.4–414.6) compared with patients not included in the IDH1 analysis (median OS: 196.0, 95% CI: 159.2–232.8, log-rank test, $P<.0005$). Of note as well, IDH1 mutation was observed in only 21 of 360 patients (5.8%). Since IDH1 status did not correlate to epilepsy at presentation (χ^2 test, $P=.98$), it is unlikely that IDH1 mutation is the underlying factor that explains the prognostic effect of epilepsy at presentation in glioblastoma patients.

We also thank Zhou et al for sharing their preliminary analysis on the prognostic relevance of epilepsy at presentation in an institutional cohort of 113 lower-grade gliomas and in 477 patients from The Cancer Genome Atlas (tumor grade undescribed). With use of a univariable log-rank test, they did not observe any significant association between survival and epilepsy at presentation in their institutional cohort ($P=.131$). In the dataset of The Cancer Genome Atlas, a *history* of seizure was associated with survival in univariable analysis ($P=.048$), but not after correction for age, KPS, tumor location, World Health Organization grade, histological classification, radiotherapy, or chemotherapy ($P=.682$). This analysis of Zhou et al in fact addresses a different research question than that investigated in our paper, as they report on the prognostic relevance of epilepsy in lower-grade gliomas. In order to interpret the results of this analysis, however, more information regarding baseline characteristics of the patients included in their study is needed, in particular regarding the distribution of grade II and grade III patients in their cohorts. Indeed, the median follow-up of their institutional cohort (37 mo) seems very short for low-grade glioma patients compared with the published median survival of grade II glioma patients,[2] suggesting an overrepresentation of grade III astrocytic tumors or immature follow-up data. Additionally, it would be very interesting for Zhou et al to address their own question on the role of IDH1 mutational status, which is more frequently found in lower-grade tumors.[3] We are looking forward to reading a future report of their analyses, and in particular the results of a multivariable analysis with their institutional data.

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