

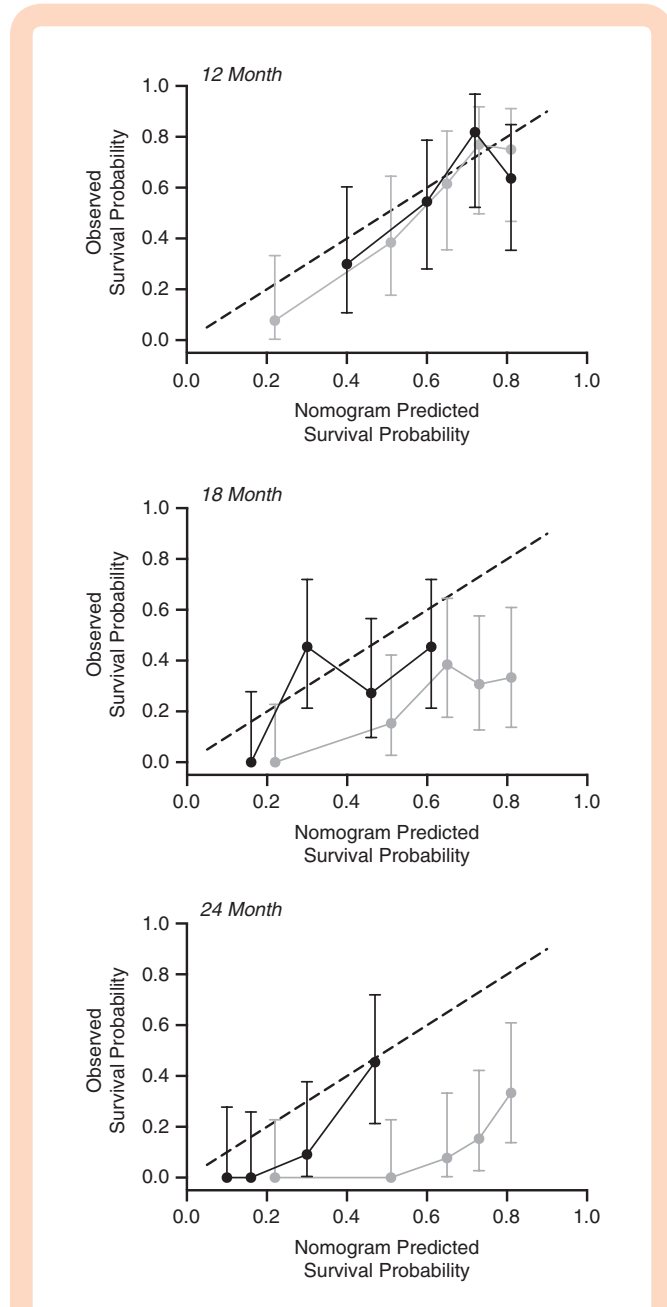
## Letter to the Editor

### Performance of a nomogram for IDH-wild-type glioblastoma patient survival in an elderly cohort

We carefully examined the article “An independently validated nomogram for isocitrate dehydrogenase-wild-type glioblastoma patient survival” by Gittleman et al.<sup>1</sup> This valuable publication describes the development and validation of a survival nomogram for individuals newly diagnosed with isocitrate dehydrogenase (IDH)-wild-type glioblastoma (GBM). The prognostic algorithm was trained using a patient population with a mean age of 63 years (standard deviation 11 years) and employs a variety of prognostic factors. Because of the wide range of patient ages in the training (29–88 years) and validation (24–85 years) data sets, and the observation that age contributes nearly 25% of possible points in their nomogram, we sought to test nomogram performance in a cohort of older patients treated at Duke. This study was approved by the Duke Health Institutional Review Board.

We included a cohort of 63 patients age  $\geq 70$  years with GBM (71.4% pathologically confirmed as “glioblastoma, IDH-wildtype” per revised 2016 WHO classification). Our data set revealed a similar survival profile compared with Gittleman et al. using a multivariable Cox proportional hazards model with the same set of measured and imputed prognostic variables that they reported.<sup>1</sup> Specifically, our hazard ratio (HR) for *MGMT* status (methylated vs. unmethylated) was 0.42 (95% confidence interval [CI], 0.24–0.74), for concurrent TMZ/radiotherapy (yes vs. no) was 0.27 (95% CI, 0.12–0.58), for KPS  $\geq 70$  was 0.27 (95% CI, 0.09–0.79), and for age was 1.08 (95% CI, 1.02–1.14). The HR for age in our multivariate model was notably higher than in their model (1.08 vs. 1.02 per additional year). Similar to their findings, extent of surgical resection was not a significant prognostic variable in our data. The HR for extent of surgical resection (biopsy vs. gross total [GTR]) was 3.44 (95% CI, 0.90–1.76;  $P = .10$ ) and for subtotal resection (STR) vs. GTR was 1.45 (95% CI, 0.54–3.94;  $P = .46$ ).

Patient data were input into the nomogram to calculate total points and associated 12-, 18- and 24-month survival predictions for all patients that received GTR or STR. The nomogram worked reasonably well for this subset of older GBM patients. The estimated versus observed 12- and 18-month survival probabilities intersected the 45° line of identity, indicating that the predicted survival probabilities approached the observed value within a 95% CI (Fig. 1, black bars). Brier scores



**Fig. 1** The estimated versus observed probabilities for 12-, 18-, and 24-month survival predictions against the 45° line of identity. Black lines with circular symbols represent data from patients receiving subtotal or gross total resection ( $N = 43$ ). Gray lines with circular symbols represent data including an additional 20 subjects undergoing biopsy-only procedures.

to assess prediction accuracy were 0.23, 0.20, and 0.10 for 12-, 18-, and 24-month survival, respectively.

Biopsy-only procedures are more common in older GBM patients, especially those with a low KPS.<sup>2,3</sup> In our sample, 32% of patients underwent biopsy-only (100% of patients with KPS < 70). However, the published nomogram accommodates only GTR and STR as options. When we included 20 patients receiving biopsy-only, treating these as equivalent to STR and assigning 6 points in the nomogram, the nomogram did a poor job estimating 18- and 24-month survival. In both instances, the nomogram was overly optimistic in this (admittedly unintended) use case (Fig. 1, gray bars).

In summary, we observe that the nomogram performs well among older GBM patients when excluding those who do not undergo resection. The nomogram showed some evidence of overestimating 24-month survival probabilities. GBM patients older than 65 years have substantially shorter survival compared with younger patients (6 vs. 14.6 months).<sup>4-6</sup> Thus, 24-month survival probabilities provided by the nomogram may extrapolate beyond most observed event times in older GBM patients. A limitation to our study is the relatively small sample size. Larger cohorts of older GBM patients are warranted to test the nomogram in the future. Such work should include patients undergoing biopsy-only procedures and incorporate narrower survival windows (e.g., 6-month survival) to increase applicability to the older GBM patient population.

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