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Assessing time-trend bias in glioblastoma prognosis over two decades of clinical trials

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Abstract

Background: The time-trend bias represents a potential limitation in the use of external controls in glioblastoma (GBM) trials. In this study, we assessed whether outcomes for newly diagnosed GBM (ndGBM) patients treated with the standard Stupp protocol in clinical trials have changed over the past two decades.

Methods: We retrieved individual patient survival pseudo-data from Stupp protocol arms reported in trials published over the last twenty years. Survival distributions were approximated using Weibull distributions, and an Accelerated Failure Time (AFT) model was used to evaluate any potential time trend by correcting for identified key prognostic factors.

Results: MGMT methylation status and Karnofsky Performance Status emerged as the main determinants of survival differences among clinical trials. Both in a multivariable regression that included all candidate prognostic factors and after adjustment for the main determinants, publication year showed no impact on the outcome of the Stupp protocol control arms. The performance of the model was validated using three independent Phase 3 cohorts, providing additional evidence for the absence of time-trend bias.

Conclusions: No evidence of time-trend bias was observed in Phase 3 GBM trials over the past two decades once major prognostic factors were accounted for.

Keywords: Stupp protocol; glioblastoma; historical controls; time-trend bias.

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