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Immortal time bias in retrospective analysis: Is there a survival benefit in patients with glioblastoma who received prolonged treatment of adjuvant Valganciclovir?

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Dear Editor:

We read with interest "Effects of valganciclovir as an add-on therapy in patients with cytomegalovirus-positive glioblastoma: A randomized, double-blind, hypothesis-generating study".[1] Stragliotto *et al.* reported a randomized study, VIGAS, which showed no significant difference in tumor growth or median survival in the Valganciclovir arm. However, the explorative analysis showed a significantly better median survival of 24.1 months in patients receiving >6 months of Valganciclovir *versus* 13.1 months in patients receiving 0–6 months of treatment. In addition, the same group conducted a retrospective study of 50 patients who received Valganciclovir, which showed the median survival was 25.0, 30.1 and 56.4 months for all patients, patients with at least 6 months of treatment and patients with continuous use, respectively.[2] The result was significantly better than contemporary controls (13.5 months, $p < 0.001$). The authors suggested that long-term Valganciclovir treatment may be required for a clinical effect on outcome. Indeed, there seemed to be a "dose-response relationship"—the patients who received longer course of treatment had better outcome. Nonetheless, it is likely that "immortal time bias" could explain this result.[3–6]

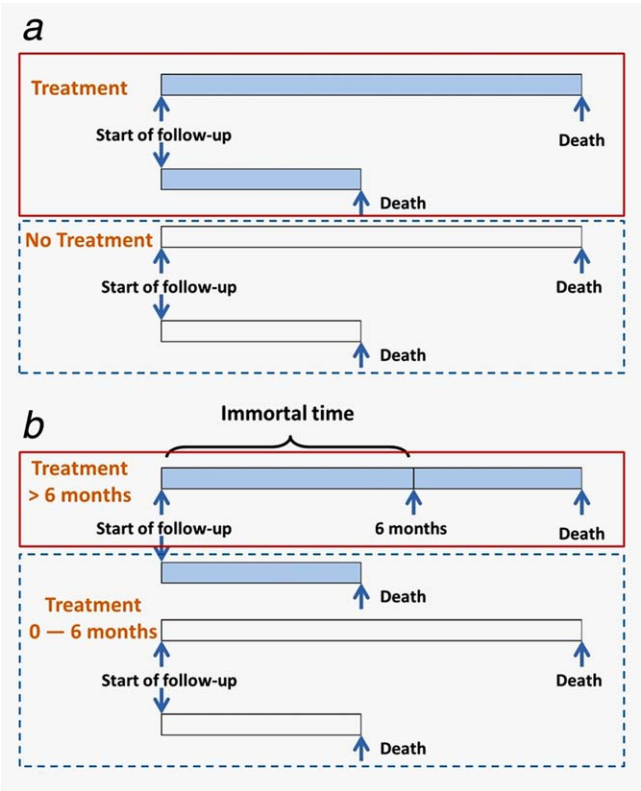

Figure 1. (*a*) An imaginary randomized study with ineffective treatment. The exposure is defined as "receiving treatment." The survivals of the exposed group (red solid square) and non-exposed group (blue dash square) are the same. (*b*) If the exposure is redefined as "receiving treatment > 6 months," the survival of the exposed group (red solid square) would certainly be better than the non-exposed group (blue dash square), because only patients who survive long enough (>6 months) can be classified as exposed, and all patients who die within 6 months will be classified as non-exposed. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

"Immortal time" refers to a time span in the follow-up period during which the outcome could not have occurred because of exposure definition. For example, death "cannot" occurred in the first 6 months of follow-up in the group of patients who received at least 6 months of treatment (Fig. 1). More extremely, if a cohort is defined as a group of patients who received 10 years of treatment, the survival would certainly be longer than 10 years. In conventional survival analysis, the immortal time bias confers a spurious survival advantage to the treated group. The work of van Walraven *et al.* demonstrated that, in leading clinical journals, more than 40% of studies containing survival analyses with a time-dependent factor were susceptible to immortal time bias.[7] Fortunately, the bias could be prevented using time-dependent analysis,[3,6] such as Cox regression with treatment status as a time-dependent covariate. We are looking forward that reanalysis of the original data can be performed.

Yours sincerely,
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Letter to the Editor

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