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Survival Analysis vs Longitudinal Modeling With Multiple Imputation–A False Dichotomy

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To the Editor

We read with interest the article by Fu et al[1] and were struck by their strong statements regarding the validity of survival analysis and their dismissal of multiple imputation as a statistical tool in observational studies with missing data. We were most concerned by their assertion that survival analysis is not impacted by missing data while multiple imputation leads to biased results. Both multiple imputation and survival analysis (eg, Kaplan-Meier estimates or a proportional hazards model) rely on the missing at random assumption,[2] according to which the probability that an observation is missing can be predicted from the observed data. In both types of analyses, results may be biased if missingness is related to patient characteristics that have not been observed. In the survival context, this amounts to assuming that censored patients (eg, patients who discontinued treatment or were lost to follow-up) had the same outcome risk as noncensored patients.[3] When this noninformative missingness assumption is violated, both survival analysis and multiple imputation can lead to biased estimates. Patients with neovascular age-related macular degeneration with poor vision outcomes are more likely to discontinue treatments and medical visits. This may lead to missing visual acuity (VA) data.[4] This form of right censoring clearly violates the missing at random assumption and may have induced bias in the study by Fu et al.[1] Additionally, no censoring criteria were described in the authors' Methods section, suggesting that patients who had prolonged intervals with multiple missed visits or injections were still included in the study. An advantage of longitudinal modeling, with or without multiple imputation, is the ability to flexibly incorporate assessments conducted at variable length intervals. In contrast, such an irregular observation scheme results in interval-censored data in a survival analysis because precise event times are unknown. Because missed visits and therefore longer intervals between observations have been shown to be associated with worse VA outcomes,[5] this becomes an important consideration that survival analysis has no mechanism to address without multiple imputation.

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We think survival analysis and longitudinal modeling with multiple imputation for missing data are different approaches that answer different questions, each with their own benefits and limitations. Fu et al[1] are correct that survival analysis is advantageous in dealing with differential length of follow-up, a common issue in observational studies. However, this approach limits the ability to model the dynamic change of VA during treatment for age-related macular degeneration. The authors' survival analysis, which censored the data at the first occurrence of a good VA outcome (eg, 20/40 or better), ignores the frequent occurrence of VA worsening later on. Their survival curves, with a plateau for VA outcome of 20/40 or better, represent the anticipated early VA gain from anti-vascular endothelial growth factor treatment, but the article is silent on the later VA loss. Longitudinal modeling with multiple imputation is advantageous in this situation because it captures the dynamic changes of VA. No single statistical method is perfect; out-right dismissal of one form of analysis limits our ability to fully understand the data.

Conflict of Interest Disclosures:

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