Influence of censoring on conclusions of FDA-approved cancer drugs using the modified time to treatment failure

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Background:

• Time-to-treatment failure (TTF), which regards both disease progression and treatment interruption as events, is a common measure that can be used as a sensitivity analysis for informative censoring
• For excessive censoring in the control group, TTF exaggerates the effect size instead of penalizing the bias.
• The modified TTF (mTTF), considers censoring as events only for excessive censoring in the intervention group.
• We examine whether excessive censoring in the intervention could affect the results of randomized controlled trials (RCTs) leading to FDA-approved drugs using mTTF.

Methods:

• In this cross-sectional study, phase II-III RCTs of FDA drugs approved based on time-dependent surrogate endpoints between 2010 and 2020 were collected.
• Individual patient data were reconstructed from the published Kaplan-Meier (KM) curves of the intention-to-treat population.
• Reverse KM method (i.e., events and censoring are flipped) was used to quantify excess censoring between study groups.
• mTTF sensitivity analysis was conducted and statistical significance was calculated using the log-rank test.

Results:

• A total of 101 studies comprising 60,697 patients met the inclusion criteria.
• The most common surrogate endpoint was PFS 86 (85.1).
• The median HR for surrogate endpoints was 0.54 (IQR, 0.41 to 0.63) and the median p-value was 3.0*10^{-5} (IQR, 2.8*10^{-8} to 1.5*10^{-3}).
• Following adjustment for excess censoring using the mTTF the median HR was 0.68 (IQR, 0.52 to 0.84) and the median p-value was 4.2*10^{-3} (IQR, 2.5*10^{-6} to 0.12).
• Across all trials, 35 (34.6%) lost statistical significance using the mTTF.

Main takeaways

We introduce mTTF as a practical sensitivity analysis tool for the effect of excessive censoring in the intervention group.

Our findings suggest that some studies are associated with an excessive drop-out rate favoring the intervention group.

Excessive censoring in trial arms may indicate informative censoring bias in some FDA-approved treatment trials.

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Example of modified Time-to-treatment failure (mTTF)
In this example (S-TRAC study), following mTTF sensitivity analysis the trial loses significance. We reconstruct KM plots (A) and build reverse KM plots (B) identifying excessive censoring (C) mTTF sensitivity analysis is done (D).