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Methodological Issues on Prognostic Imbalance in Randomized Controlled Trials (RCTs) Evaluating A Binary Outcome

Chance imbalance in baseline prognostic factors (PF) can lead to over or underestimation of treatment effects in RCTs. We simulated data from RCTs by varying risk of the outcome, effect of the treatment, power and prevalence of the PF, and sample size. Logistic regression models with and without adjustment for the PF were compared in terms of bias, standard error, coverage of confidence interval and statistical power. Covariate adjustment improves estimation accuracy and efficiency. The probability of prognostic imbalance in small trials can be substantial. Two thousand patients may be needed to minimize the chance and impact of prognostic imbalance.