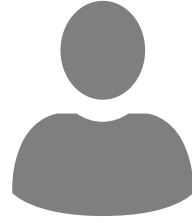


Using a time-varying covariate in the Cox proportional hazards model discerns early/late treatment efficacy. Use with caution.

Use of time-varying covariate in assessing disease remission in the early and late phases of treatment with application to RITAZAREM trial.  Marianna Nodale, Simon Bond



TRIAL BACKGROUND

RITAZAREM, an open-label, multi-centre RCT, aims to assess the efficacy of rituximab compared to the current standard of care in the prevention of relapse in ANCA-associated vasculitis.

Design: N = 170 patients, 1:1, 90% power at $\alpha = 5\%$ for HR = 0.42.

Outcome: time to disease relapse.

Primary analysis: Cox proportional hazard model for overall efficacy

Clinical question: does treatment effect *persist* after the patient stops taking the drug?

Statistical analysis: Cox proportional hazard model with treatment interaction which includes a time-varying covariate to investigate early/late treatment effect.

$$I \quad (\text{time} \leq \text{stop drug} = \tau)$$

Is the time-varying covariate model robust?

METHODOLOGY RESEARCH

1. Censoring and relapse times simulated with a Weibull distribution (sample N = 167, 83 events).
2. Relapse times after change point simulated with a conditional Weibull distribution.
3. Simulated $HR_{\text{early}} \neq HR_{\text{late}} \in (0.3, 0.9)$
4. True change point for HR $\tau = 20$.
5. Analysis change point 10-30.

RESULTS

Simulations (n=1000) investigate the operational characteristics of the model under a variety of assumptions:

- A. Null hypothesis
- B. Constant overall efficacy
- C. Late efficacy
- D. Early efficacy
- E. Different early/late efficacy
- F. Wrong change point τ

DISCUSSION

- Null/constant efficacy \Rightarrow small sample size bias, controlled by increasing N.
- Different HR and mismatch between assumed/true $\tau \Rightarrow$ large bias, worsened by increasing N.

