Evaluating Effects of Changing Treatments in Longitudinal Studies

Xiaolei Zhou, Beth Sherrill, Yun Wu, Lee Bennett, Jianmin Wang

RTI Health Solutions, Research Triangle Park, NC, United States

BACKGROUND

- In studies evaluating treatment effects for endpoints such as overall survival, patients are expected to change treatments during follow-up due to disease progression, adverse events, or other reasons.
- It is often of interest to compare efficacy endpoints across the entire treatment pattern, assessing the effects of the sequence of initial treatments and second- or even third-line treatments.
- However, in practice, researchers often either ignore second-line treatments or simply stratify patients by whether they received second-line treatment. These simplistic approaches do not take full advantage of the longitudinal information.
- The use of time-varying covariates in Cox models can provide valuable insights into treatment sequencing (e.g., in oncology research). However, these methods are not used widely, even in situations where they are clearly applicable.

OBJECTIVES

- The intent of this presentation is to highlight the usefulness of survival analyses that assess time-varying covariates, such as treatment changes.
- We present simulations to demonstrate how to appropriately account for second-line treatment when evaluating the effect of first-line treatments.

TIME-VARYING COVARIATES METHODOLOGY

Why Commonly Used Methods Are Not Always Appropriate

Example: When comparing overall survival between two treatments, ideally, patients would stay in the initial treatment until death or last follow-up such that:

$$\text{Cox model Log } h(t) = \alpha(t) + \beta_1 Trt_A \quad \text{(Model \#1)}$$

where t = time, Log h(t) is the logarithm of the hazard at time = t, $\alpha(t)$ is the underlying hazard function for the reference group, and Trt_A = 1 for patients in Treatment A (Trt A) and 0 for patients in Treatment B (Trt B) (Figure 1).

- In oncology settings, patients may start maintenance therapy, start another anticancer treatment, or stop therapy at any time during the follow-up period for various lengths of time.
- Therefore, it may not be appropriate to assume a constant log HR (i.e., proportional hazards).

Time-Varying Covariates

- To create a time-varying covariate for treatment, an indicator is set to change from 0 to 1 when the treatment starts, such that the hazard changes when treatments change. We denote it as Trt (t).
- The specific model and its interpretation must reflect clinical assumptions.

Other Considerations When Building a Model Containing Time-Varying Covariates

- Does the order in which treatments are received impact the effect?
- Is treatment duration of interest (in addition to sequencing)? If so, the time-dependent covariate may be constructed to accumulate time on treatment instead of as a simple indicator.
- How are gaps between treatments handled? Is the hazard expected to remain constant, return to baseline, or something in between?
- What is the impact of sample size? If very few patients have a certain treatment pattern, one may consider excluding them, collapsing across similar patterns, and/or building a simplified model with fewer parameters.

METHODS

Overview

- Three different scenarios were described to reflect different clinical understandings of the association between risk of death and treatment:

Scenario I: Risk determined only by initial treatment

Scenario II: Risk determined only by current treatment

Scenario III: Risk determined by current treatment with diminished, but lingering, treatment effect when treatment stops

- For each scenario, 1,000 different datasets were simulated (i.e., 3,000 datasets) with predefined risks of death associated with each treatment.
- Because risks were predefined for each scenario and used to simulate the datasets, the true treatment effects were known.
- Three Cox models (with and without time-varying covariates, and with different parameter definitions) were used to analyze each dataset, and the hazard ratio comparing Trt A with Trt B was estimated.
- Results were compared with the true treatment effects to evaluate bias of the estimates.

Dataset Simulations

- Each dataset was constructed with a sample size of 3,000 patients
- Patients were initially randomized 1:1 to active Trt A and Trt B, followed by possible crossover or start of another treatment, Treatment C (Trt C).
- In practice, Trt C could be a second-line treatment or no treatment. For these scenarios, we considered switch to Trt C as the end of active treatment (i.e., observation or best supportive care).

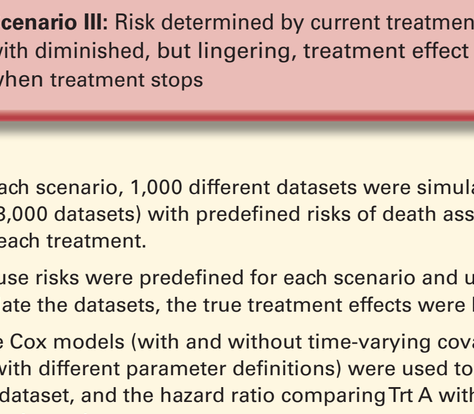
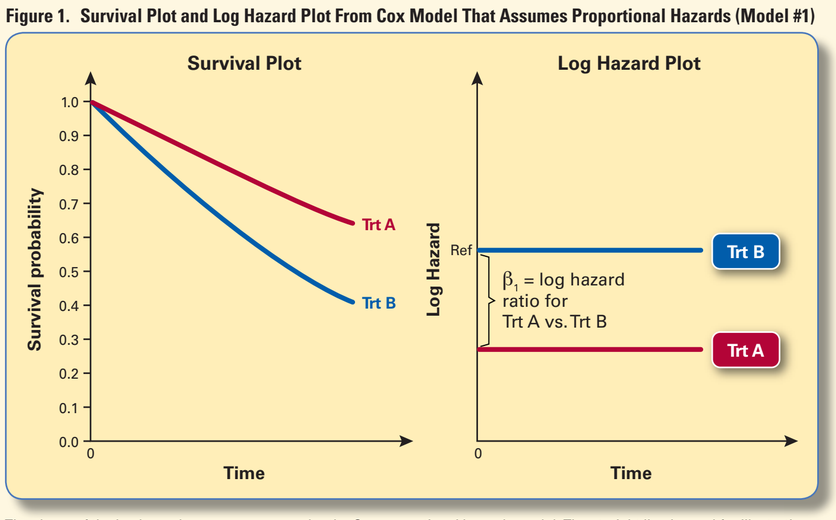


Figure 1. Survival Plot and Log Hazard Plot From Cox Model That Assumes Proportional Hazards (Model #1)



The shape of the log hazard curve may vary under the Cox proportional hazards model. The straight line is used for illustration purposes.

- During the follow-up period, the change of treatment was randomly generated to occur at any time after 100 days from the initiation of the assigned treatment or not at all.
- An event time for death for each patient was randomly generated, using predefined risk rates for first-line and second-line treatment (Table 1).
- Patients were followed for 3 years starting from the initiation of the first treatment. If there was no death, 25% of the patients remained in the study by the end of the 3 years.

Table 1. Simulated Scenarios With Predefined Risk Rates

Scenario	Predefined Risks	Simulation Settings	Known True HRs
I	Rate of death per person-day if starting on Trt A (R_a)	R_a = 1/1,500	HR for A vs. B = R_a/R_b = 0.667
	Rate of death per person-day if starting on Trt B (R_b)	R_b = 1/1,000	
II	Same initial risks when starting treatment	R_a = 1/1,500 R_b = 1/1,000	HR for A vs. B = R_a/R_b = 0.667
	When treatments change, risk is changed, without regard to previous treatment; for example, rate of death per person-day on Trt A after receiving Trt B ($R_{a|b}$) is the same as R_a	$R_{a|b} = R_a$ = 1/1,500 $R_{b|a} = R_b$ = 1/1,000	
	When patients go off treatment, the risk of death increases to the level of untreated patients (R_c)	R_c = 1/600	HR for C vs. A = R_c/R_a = 2.5 HR for C vs. B = R_c/R_b = 1.667
III	Same initial risks when starting treatment	R_a = 1/1,500 R_b = 1/1,000	HR for A vs. B = R_a/R_b = 0.667
	When treatments change, risk is changed, without regard to previous treatment (same as Scenario II)	$R_{a|b} = R_a$ = 1/1,500 $R_{b|a} = R_b$ = 1/1,000	
	When patients go off treatment, the risk of death increases, but not as much as if they had never been treated In other words, the rate of death per person-day on no treatment is smaller here than in Scenario II; it depends on whether previous treatment was Trt A ($R_{c|a}$) or Trt B ($R_{c|b}$) In the simulations, we set the lingering, diminished effect after stopping treatment to be 1.5 times the risk while taking each treatment	$R_{c|a}$ = 1/1,000 $R_{c|b}$ = 1/667	HR for C|A vs. C|B = $R_{c|a}/R_{c|b}$ = 0.667 HR for C|A vs. A = $R_{c|a}/R_a$ = 1.5 HR for C|B vs. B = $R_{c|b}/R_b$ = 1.5

HR = hazard ratio; R = rate of death per person-day.

Table 2. Cox Models

	Model #1 (Baseline Covariates Only) Figure 1	Model#2 (Time-Dependent Covariates) Figure 2	Model #3 (Time-Dependent Covariates, With Parameter for Diminishing Effect of Stopping Treatment) Figure 3
Cox model	Log h(t) = $\alpha(t) + \beta_1 Trt_A$	Log h(t) = $\alpha(t) + \beta_1 Trt_A$ (t) + $\beta_2 Trt_C$ (t)	Log h(t) = $\alpha(t) + \beta_1 Trt_A$ (t) + $\beta_2 Trt_C$ (t)
Covariate definitions	Trt_A = 1, if initial treatment = A = 0, if initial treatment = B	Trt_A (t) = 1 if treatment at time (t) = A = 0 otherwise	Trt_A (t) = 1 if treatment at time (t) = A = 0 if treatment at time (t) = B OR after switch to no treatment (Trt C): = 1 if treatment before switch was A = 0 if treatment before switch was B
		Trt_C (t) = 1 if treatment at time (t) = C = 0 otherwise	Trt_C (t) = 1 if treatment at time (t) = C = 0 otherwise
Parameter definitions	β_1 = log HR for Trt A vs. Trt B	β_1 = log HR for Trt A vs. Trt B	β_1 = log HR for Trt A vs. Trt B
		β_2 = log HR for Trt C vs. Trt B	β_2 = logarithm of factor by which treatment effect is diminished after stopping
		($\beta_1 - \beta_2$) = log HR for Trt A vs. Trt C	
Formula to obtain HR (A vs. B)[a]	Exp(β_1)	Exp(β_1)	Exp(β_1)
Model assumptions	Risk determined only by initial treatment Treatment effect is constant over time	Risk determined only by current treatment Treatment effect does not depend on the order it was received	Risk upon stopping treatment does not return to risk without treatment
Assumptions match which scenario	I	II	III

[a] Trt B is the reference for each model.

Detailed Simulation Specifications

1. Generate random censoring times (T_c) from Uniform[0,1460] distribution and truncate at 1,096 if greater than 1,096.
2. Generate random treatment switch times (T_{sw}) from Uniform[100, 800] distribution.
3. If $T_{sw} < T_c$, select second-line treatment using a Bernoulli trial with 30% switch to Trt C.
4. Generate event time on first treatment (T_1) from exponential distribution using the predefined risk parameter for first-line treatment (R_a or R_b).
5. If $T_1 > T_{sw}$, generate event time on second treatment (T_2) using appropriate risk parameter for second-line treatment ($R_{a|b}$, $R_{b|a}$, $R_{c|a}$, or $R_{c|b}$).
6. Determine event/censoring time and indicator variables for the specific scenario.
7. Fit three Cox models (Table 2).
8. Repeat steps 1 through 8 for each scenario 1,000 times.
9. Average parameter estimates from the Cox models, convert them to hazard ratios, and compare to the true value derived from the predefined risk parameters.

Figure 2. Representative Log Hazard Plot From Cox Model #2

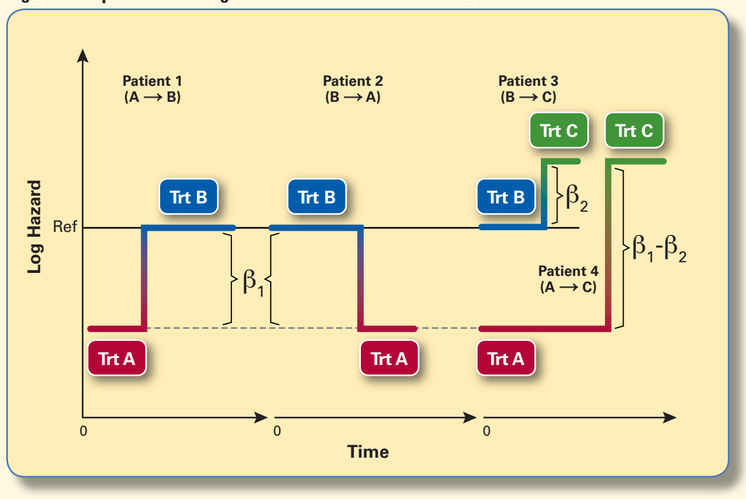
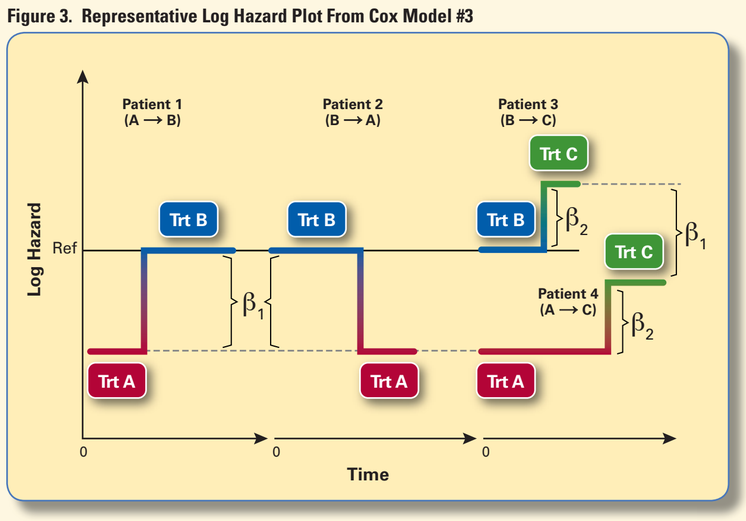


Figure 3. Representative Log Hazard Plot From Cox Model #3



RESULTS

- For scenarios I and II, the model that was constructed to match the clinical underpinnings of the simulated dataset provided the closest approximation to the preset hazard ratio for comparing Trt A with Trt B (known hazard ratio for A vs. B = 0.667) (Table 3).
- For scenario III, both models #2 and #3 gave unbiased estimates of the known hazard ratio for Trt A vs. Trt B.

Table 3. Estimated Parameters and Hazard Ratios From Cox Models[a] With Shading Where Results Match Simulated Scenarios

Scenario	Parameter	Model #1 (Baseline Covariates Only)	Model #2 (Time-Dependent Covariates)	Model #3 (Time-Dependent Covariates, With Parameter for Lingering But Diminished Effect After Stopping Treatment)
I	β_1	–0.404 (0.056)	–0.161 (0.060)	–0.188 (0.057)
	β_2	NA	–0.071 (0.100)	0.016 (0.096)
	HR A vs. B	**0.668**	**0.851**	**0.829**
II	β_1	–0.125 (0.054)	–0.403 (0.061)	–0.331 (0.055)
	β_2	NA	0.515 (0.081)	0.706 (0.078)
	HR A vs. B	**0.882**	**0.668**	**0.718**
III	β_1	–0.193 (0.056)	–0.407 (0.062)	–0.407 (0.057)
	β_2	NA	0.204 (0.090)	0.410 (0.085)
	HR A vs. B	**0.824**	**0.666**	**0.666**

NA = not applicable.

[a] Mean parameter estimates (SD) are based on 1,000 simulations. Estimated hazard ratios were calculated using the exponential of the mean estimated parameter β_1.

- In these simulations, the model that best reflected the clinical scenario also was usually the best statistical fit to the data based on the likelihood statistic (Table 4).

Table 4. Percentage of Simulations That Showed Best Fit[a]

Scenario	Model #1 (Baseline Covariates Only)	Model #2 (Time-Dependent Covariates)	Model #3 (Time-Dependent Covariates, With Parameter for Lingering But Diminished Effect After Stopping Treatment)
I	100%	0%	0%
II	0%	92.5%	7.5%
III	0%	8.1%	91.9%

[a] For each simulation, three models were fit. The model with the greatest likelihood was picked as best fit.

Models #2 and #3 look identical, but parameter definitions and interpretations are different (further illustrated in Figures 2 and 3).

LIMITATIONS

- Simulated datasets were devised to follow predefined sets of risks, such that we could compare results to the known hazard ratios. In real-life situations, the true hazard ratio is not known.
- These simulations assumed that treatment switches are random. In real-life situations, this is typically not the case, and other baseline and/or time-dependent covariates will be necessary.

CONCLUSIONS

- The technique of incorporating time-varying covariates in analyses of time-to-event endpoints provides a flexible analysis method to evaluate treatment effects in complex situations in which patients receive a sequence of treatments.
- The model must be selected carefully to reflect clinical understanding of the treatment impact.
- This approach has wide applications, most notably in oncology research.

CONTACT INFORMATION

Beth Sherrill, MS
Global Head, Biometrics

RTI Health Solutions
200 Park Offices Drive
Research Triangle Park, NC 27709

Phone: +1.919.541.1233
Fax: +1.919.541.7222
E-mail: bsherrill@rti.org

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