A Model-based Test for Treatment Comparison based on Left-truncated and Interval-censored Survival Data

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Introduction

Survival Analysis
Time to event data (also called survival data) occurs frequently in many fields, such as medicine, epidemiology, biology, engineering, finance, and environmental science. Analyzing such data allows us to

- find the survival probabilities beyond certain times, and
- determine factors that affect survival time (e.g. treatment) and thus compare treatments.

Features of Survival Data
Censoring and truncation are two common features of survival data. For example,

- In follow-up studies, patients are only observed periodically. The exact survival time T of an individual may not be observed but only known to be in an interval, $(L, R]$, resulting in ***interval-censored data***.
- Besides, in studies allowing late entry, only individuals whose survival times are larger than certain times can be included in the analysis, resulting in ***left-truncated data***.

Censoring and truncation make traditional statistical methods inapplicable and post challenges in analyzing survival data.

Objective

In this research, we develop a new model-based test to compare treatments based on left-truncated and interval-censored (LTIC) data.

Method

Reverse Hazard Function

$$\eta(t) = \lim_{\Delta t \to 0} \frac{P(t - \Delta t \le T \le t | T \le t)}{\Delta t}, t \ge 0,$$

an instantaneous failure rate, given an individual fails before time t.

Model
Assume a reversed proportional hazards regression model for T:

$$\eta(t|Z) = \eta_0(t) e^{\beta Z},$$

where $Z = 0$ or 1 is a treatment indicator, $\eta(t|Z)$ is the reversed hazard function for treatment Z, $\eta_0(t)$ is an unspecified baseline function, and β is a regression parameter. Under the assumed model,

$$F(t|Z) = F_0(t)^{e^{\beta Z}},$$

where F and F_0 are cumulative distribution functions for groups 1 and 0, respectively.

Hypothesis
Often, we are interested in test $H_0: \beta = 0$, meaning that there is no difference in survival between two treatments.

Data
For a sample of size n, the LTIC data is

$$\{(L_i, R_i], K_i, z_i;\ i = 1, \dots, n\},$$

where K_i is the truncation time and z_i is the treatment indicator of individual i. T_i is observable only if survival time $T_i > K_i$.

Method (cont'd)

Proposed Test
We propose a linear rank-type test based on the derived score function,

$$U_{(\beta=0, F_0)} = \sum_i^n z_i\, c_i(F_0).$$

Since F_0 is unknown, replaced by its nonparametric MLE, we obtain $U_{(\beta=0,\ \hat{F}_0)}$. Using permutation, we obtain $V_{(\beta=0,\ \hat{F}_0)}$, an estimate of the variance of $U_{(\beta=0, F_0)}$. We then propose the ***test statistic***

$$W = \frac{U_{(\beta=0, \hat{F}_0)}}{\sqrt{V_{(\beta=0, \hat{F}_0)}}} \dot{\sim} N(0,1),$$

which is asymptotically normal as $n \to \infty$. The null hypothesis would be rejected if $|W| > z_{\alpha/2}$.

Simulation Study

Setting
To evaluate the performance of the proposed test, we investigated the *size & power* of the test, and the *distribution of the test statistic*, and compared them to an existing method based on simulated data.

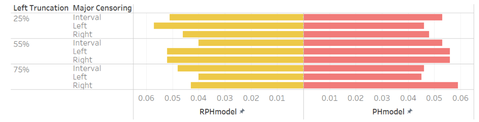
Different settings were considered based on

- Sample size: n = 200 and 400
- Model for survival time:
  - Reversed Proportional hazards (PRH) model: true
  - Proportional hazards (PH) model: false
- Proportions of left-truncation: 25%, 55%, and 75%, and
- Major type of censoring: left, interval, right

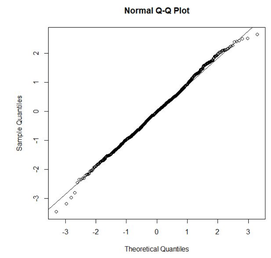
In each setting, 1000 sets of LTIC data were generated.

Results

1. *Test Size*
The graph below shows that the proposed test has a correct size. It means that the test rejects H_0 with a correct probability (0.05) when there is no difference in survival between treatments ($\beta = 0$), even with a false PH model.



2. *Distribution of Test Statistic*
Under different settings, the normal-QQ plots show that the test statistic follows a normal distribution.



n = 400, LT 25%, RPH

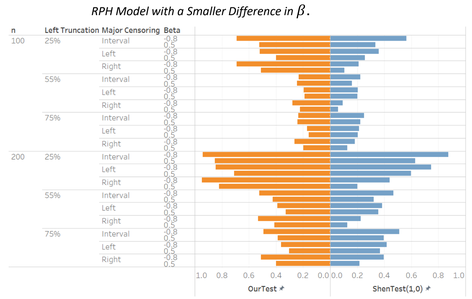
Simulation Study (cont'd)

Results

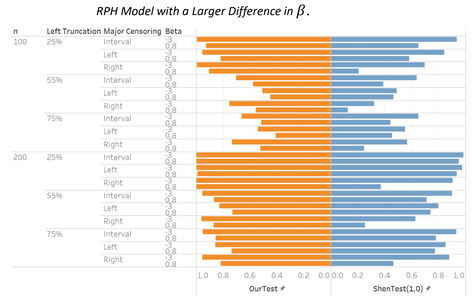
3. *Power Comparison to Existing Method*
When there is a difference in survival distribution between treatments ($\beta \neq 0$), we compared the power between the proposed test to Shen's test. Shen's test is a family of nonparametric rank-based tests requiring two weight parameters (Shen, 2015). The comparisons are between our test and Shen's test with its best weight parameters.

The first two graphs below show that, under an RPH model, our test overall outperforms Shen's test. The third graph below shows that out test is comparable to Shen's test with a false model.

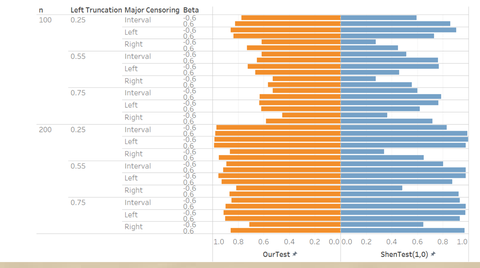
RPH Model with a Smaller Difference in β.



RPH Model with a Larger Difference in β.

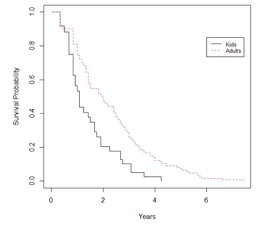


PH Model with a Larger Difference in β.



Application

The proposed test is applied to a set of AIDS blood transfusion data collected by the CDC. The survival time of interest is AIDS incubation time. It is left-truncated as cases of transfusion-related AIDS before July 1, 1982 were excluded. For illustration, censoring intervals were artificially generated to obtain LTIC data. One objective is to compare two age groups: kids (33) and adults (72).



Estimated Survival Functions

The *p*-values using the proposed test are smaller than 0.05. We conclude that kids and adults have different incubation times.

MV	Thetad	Test Statistic	Our P	Test Statistic	Shen(0,0)	Test Statistic	Shen(0,1)	Test Statistic	Shen(1,0)	Test Statistic	Shen(0.5,0.5)
18	2/3	1.9549	0.0253	1.3342	0.0911	1.5908	0.0558	2.8081	0.0025	1.7508	0.04
24	1/2	1.7589	0.0393	4.0138	0	2.2536	0.0121	3.093	0.001	2.3252	0.01
36	1/3	1.8357	0.0332	0.8937	0.1857	0.105	0.4582	2.5527	0.0053	1.081	0.1399

Conclusion

1. A new linear rank-type test is developed under an RPH model for analyzing LTIC data.
2. The proposed performs well based on extensive simulation studies.
3. There is no need to choose weight parameters.
4. The proposed test can be generalized to compare more than 2 treatments.

Limitation and Future Study

1. The proposed test assumes an RPH model. Model checking techniques are needed when analyzing real data.
2. For investigating the robustness of the proposed test, other models other than a PH model should be used.

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