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Research Paper Mathematics

Clinical Trial Data Analysis Using Competing Risk Models

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ABSTRACT

Competing risks arise in studies when subjects are exposed to more than one cause of failure. The standard Kaplan-Meier method for survival analysis does not yield valid results for a particular risk if failures from other causes are treated as censored. A useful quantity for the competing risk analysis is the cumulative incidence function (CIF). Tuberculosis treatment contains at least few drugs and the toxicity may occur due to any one of the drugs which could affect cure of the patient. This paper presents the application of a cause specific hazard model in the analysis of toxicity data in the treatment using multi-drug regimens

KEYWORDS : Cumulative Incidence Function (CIF), Cause-Specific Hazard Model, Cox PH Model, Multi-drug regimen, Tuberculosis treatment, toxicity

Introduction

The standard survival analysis considers the time until an event occurs. In clinical trial a person can experience toxicity due to one of several drugs and the toxicity times of other drugs are competing risks (Pintilie, 2007). Survival time analysis by standard methods, such as the Kaplan-Meier (KM) method (Kaplan and Meier, 1958) and the standard Cox model (Lunn and McNeil, 1995), not distinguish different causes in the presence of competing risks. Alternative approaches use the cumulative incidence estimator by the Cox models on cause-specific and on subdistribution hazards models (Fine and Gray, 1999).

Censoring may occur for multiple reasons including loss to follow-up, participant withdrawal, and study termination prior to observation of the target event. If it is reasonable to assume that those participants remaining in the risk set are representative of all who would be at risk for the target event, then we have independent censoring. Under this assumption, testing of group effects and modeling of the survival function may be carried out with the KM method. The marginal probability of the event, the cumulative incidence function (CIF), may then be estimated by 1−KM. In the presence of covariates, evaluation of group and covariate effects on the hazard function and then the modeling of the hazard and survival functions may be performed with the Cox proportional hazards method (Gooley et al., 1999). Additionally, other events may occur that preclude the occurrence of the target event. The analysis of each cause-specific hazard is the standard analysis procedure for these data, allowing for the covariate effects on the hazard of the target event to be evaluated in the presence of competing risk events. Computationally, individuals who experience the competing event are censored at that event time, and there is no difference between varying causes of censoring. Separate cause-specific proportional hazards models may then be fitted for each failure type, assuming only independent censoring (Kalbfleisch and Prentice, 2002).

Generally, for non-informative censoring event, the covariate effects are often estimated with the Cox proportional hazards method (Cox, 1972). While this approach is valid for evaluating the cause-specific hazard of the target event, in practice the analysis of the complimentary cause-specific hazard of a particular event is often excluded. The estimates of the target event probabilities are either overestimated with the 1−KM estimate or foregone completely (Gaynor and Feuer, 1993). When the marginal probabilities are of interest, we may model the proportional hazards of the sub-distribution, and therefore directly assess covariate effects on the probability of the-target event in the presence of competing risk. The proportional hazards models for the sub-distribution, also known as the cumulative incidence function is for a specific failure type in a competing risks analysis (Prentice et al., 1978). We then apply and compare cause-specific Cox proportional hazards models with proportional sub distribution hazards models.

Cox regression approach for specific hazards

This model assumes a non-parametric baseline hazard function. One way for estimating such a model is to estimate a proportional hazard parametric model with a step function that is constant between every two consecutive event times thus estimating the most detailed hazard function possible (Klein and Andersen, 2005). If the ranked event times are $t_1<t_2<;....< t_n$ then we estimate the baseline step function as

$$\lambda(t)=\begin{cases} h_1 & \text{if; } 0<t\le t_1 \\ h_2 & \text{if; } t_1<t\le t_2 \\ \vdots & \\ h_Q & \text{if; } t_{Q-1}<t\le \infty \end{cases} \qquad (1)$$

where $h_1,h_2,\ldots,h_Q$ are parameters to be estimated together with the β parameters in $h(t)=\lambda(t)\exp(\beta X)$.

Model specification

Define, for each individual, the pair (T,C) where T is the failure time, and C is the failure cause. T is assumed to be a continuous and positive random variable, while C takes values in the finite set {1,2,…,k}. Assume that the individual fails from one and only one cause. The joint distribution of (T,C) is completely specified through either the cause-specific hazards, $h_j(t)$ and through the cumulative incidence functions $F_j(t)$. They are relevant when two or more causes of failure act simultaneously, but the smallest failure time and its type only are observed. In other words, each failure time is potentially right censored by every other failure times. The recent approach to competing risks is considering the joint distribution of failure time T and cause of failure C, two observable random variables (Kalbfleisch and Prentice, 1980; Crowder, 2001).

Cause-specific Hazard Function

Various approaches have been suggested in competing risks analysis. One intuitive way is to use the cause-specific hazard function (Chiang, 1970) which is defined as

$$h_j(t\mid x)=\lim_{\Delta t\to 0}\frac{P(t\le T<t+\Delta t, J=j\mid T\ge t;x)}{\Delta t} \quad j=1,\ldots,m \qquad (2)$$

The function $h_j(t;x)$ represents the instantaneous failure rate from cause j at time t in the presence of other failure types, given a covariate vector x. In the context of competing risks, the Cox proportional hazard model is often used to evaluate the covariate effects (Prentice et al., 1978) and is defined as follow

$$h_j(t\mid x)=h_{0j}(t)\exp(x\beta_j) \quad ; \quad j=1,2,\ldots,m \qquad (3)$$

where $h_{0j}(t)$ is the baseline hazard function β_j is a column vector of covariate coefficients of cause j. The model does not imply the failure

rate with removal of some or all other failure types and the model of cause j does not restrict the proportional hazard form of other failure types.

Cumulative Incidence Function

The cumulative incidence function helps to determine patterns of failure and to assess the extent to which each component contributes to overall failure. The Kaplan-Meier (KM) method has been a widely used tool for estimating survival function and cumulative incidence function, a complementary of survival function. This method is conceptually easy to understand and easy to calculate. However, if there is more than one type of event (or failure), and if these events are dependent, KM estimates are biased (Gray, 1988). This bias arises because the KM method assumes that all events are independent, and thus, censors events other than the event of interest. The CIF is an important quantity related to one risk in the context of competing risks. The CIF curve provides a better incidence curve associated with one risk that 1–KM. It also provides a meaningful interpretation in terms of failure due to one risk regardless of whether competing risks are independent (Zhang and Fine, 2008).

The cumulative incidence function from type j failure is defined by,

$$F_j(t) = P(T \le t, C = j), \quad j = 1,2,...,k \qquad (4)$$

and corresponds to the sub-distribution function for the probability of a subject failing from cause j in the presence of all the competing risks.

The cause-specific cumulative hazards $\Lambda_j(t)$, the overall hazard $\lambda(t)$, the overall cumulative hazard $\Lambda(t)$ and the overall survival function S(t) are defined, respectively, as:

$$\Lambda_j(t) = \int_0^t h_j(t)dt \; ; \; j = 1,2,...,k$$

$$h(t) = \lim_{\Delta t \to 0} \frac{P(T < t + \Delta t \mid T \ge t)}{\Delta t} = \sum_{j=1}^{k} h_j(t) \qquad (5)$$

$$\Lambda(t) = \int_0^t h(u)\mathbf{d} \quad = \sum_{j=1}^{k} \Lambda_j(t)' \qquad \text{and} \qquad (6)$$

$$S(t) = P(T > t) = e^{-\Lambda(t)} \qquad (7)$$

The survival function can be factorized into the following k functions $S_j(t) = e^{-\Lambda_j(t)}$ as follows

$$S(t) = e^{-\sum_{j=1}^{k} \Lambda_j(t)} = \prod_{j=1}^{k} e^{-\Lambda_j(t)} = \prod_{j=1}^{k} S_j(t) \qquad (8)$$

The sub-density functions $f_j(t)$ from cause j, the marginal distribution F(t) of T, and the marginal distribution of C are respectively given by:

$$f_j(t) = \frac{d}{dt} F_j(t) = h_j(t) S_j(t) \qquad (9)$$

$$F(t) = P(T \le t) = \sum_{j=1}^{k} F_j(t), \qquad \text{and} \qquad (10)$$

$$\pi_j(t) = P(C = j) = \lim_{t \to \infty} F_j(t) \; ; \quad j = 1,2,...,k \qquad (11)$$

Competing Risk Problem in Clinical Trials

The patients who were not responded the treatment (at least for two drugs that is Isoniazid and Rifampicin) is called multidrug-resistant tuberculosis (MDR-TB) patients. The MDR-TB patients were treated with the TB drugs of Injection Kanamycin, Ethinomide, other anti-TB drugs (Cycloserine, Ofloxacin, Ethambutol, PAS and Capreomycin). The patients may develop toxicity for one or more drugs and it may lead to failure of treatments. The event of interest for the analysis is toxicity during treatment. A majority number of patients develop toxicity due to Kanamycin and Ethinomide. The other drugs effect is minimal. Hence, in this work, the toxicity is categorized in to three types: due to Kanamycin (K), Ethinomide (Eth) and others.

The aim is to estimate the specific cause effect using the Cause specific hazards function and Cumulative Incidence Function.

The data consists of 86 multidrug-resistant tuberculosis (MDR-TB) patients' details from the National Institute for Research in Tuberculosis, ICMR, Chennai.

Results

Probability values for the effect of Inj. Kanamycin Toxic

Failure time (month)	CIF	StdErr	Lower 95% Limits	Upper 95% Limits
0	0.00000	0.00000	0.00000	0.00000
2	0.01333	0.01333	0.00112	0.06444
3	0.02828	0.01990	0.00525	0.08875
4	0.04421	0.02523	0.01151	0.11319
6	0.11013	0.03976	0.04781	0.20175
7	0.12661	0.04236	0.05852	0.22208
8	0.14443	0.04516	0.07023	0.24423
9	0.18246	0.05069	0.09605	0.29075
13	0.20650	0.05476	0.11158	0.32153
17	0.23589	0.06037	0.12950	0.36036
19	0.26528	0.06506	0.14864	0.39704
20	0.29467	0.06903	0.16878	0.43207
22	0.32826	0.07382	0.19115	0.47240
24	0.37024	0.08095	0.21667	0.52439
30	0.42272	0.09088	0.24545	0.58989
33	0.50519	0.11344	0.27229	0.69879
36	0.60415	0.13428	0.30235	0.80872

The above table shows the probability values for different months. The lowest probability value for the month of 4 is 0.04421 (4%) and the end of the followed-up period 36 month shows the estimated probability is 0.60415 (60%).

Probability values for the effect of Ethinomide toxic

Failure time (months)	CIF	StdErr	Lower 95% Limits	Upper 95% Limits
0	0.00000	0.00000	0.00000	0.00000
1	0.04651	0.02284	0.01502	0.10626
2	0.07194	0.02852	0.02914	0.14097
3	0.08600	0.03141	0.03746	0.16000
5	0.10123	0.03444	0.04669	0.18053
7	0.11788	0.03767	0.05693	0.20289
8	0.13588	0.04106	0.06818	0.22685
10	0.17703	0.04853	0.09428	0.28097
12	0.26144	0.05948	0.15405	0.38205
13	0.28316	0.06168	0.17037	0.40675
15	0.30628	0.06401	0.18773	0.43301
16	0.32941	0.06606	0.20555	0.45866
20	0.35623	0.06886	0.22540	0.48915
22	0.38689	0.07239	0.24728	0.52444
25	0.42776	0.07896	0.27245	0.57431
36	0.54221	0.13072	0.26590	0.75363

The probability values for the cause specific to Ethinomide toxic in the month of 7 is 0.11788 (12%) and the end of the followed-up period 36 month shows the estimated probability is 0.54221 (54%).

Probability values for the effect of OTHER drugs toxic

Failure time (months)	CIF	StdErr	Lower 95% Limits	Upper 95% Limits
0	0.00000	0.000000	0.00000	0.00000
1	0.08140	0.029659	0.03563	0.15154
2	0.15488	0.039797	0.08688	0.24081
3	0.19330	0.043816	0.11606	0.28530
5	0.20674	0.045135	0.12645	0.30073
7	0.25081	0.049397	0.16069	0.35126
8	0.28139	0.051988	0.18505	0.38558
9	0.29736	0.053282	0.19787	0.40337
10	0.31409	0.054637	0.21129	0.42201
12	0.33168	0.056066	0.22537	0.44158
14	0.35256	0.058191	0.24127	0.46561
16	0.39573	0.062042	0.27489	0.51402
20	0.41990	0.064278	0.29341	0.54113
21	0.44626	0.066782	0.31331	0.57067
22	0.49900	0.070511	0.35509	0.62706
23	0.52847	0.072613	0.37800	0.65830
29	0.59583	0.077253	0.42919	0.72835
30	0.62951	0.078417	0.45642	0.76103
31	0.70361	0.079848	0.51590	0.82968
32	0.74066	0.079082	0.54728	0.86112
33	0.77771	0.077249	0.57964	0.89057
36	0.91108	0.062607	0.67333	0.97831

The probability values for the cause specific to other TB drugs for the month of 2 is 0.15488 (15%) and the end of the followed-up period 36 month shows the estimated probability is 0.91108 (91%).

Estimates for the cause specific to Kanamycin								
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Wt	1	-0.00190	0.01939	0.0096	0.9220	0.998	0.961	1.037
Age	1	-0.02362	0.02462	0.9203	0.3374	0.977	0.931	1.025
Gender	1	0.05951	0.49799	0.0143	0.9049	1.061	0.400	2.817
-2LL	137.810							

The above table shows that the results of cause-specific Cox proportional hazard models, for the cause specific to Kanamycin toxic and the other drugs toxic were censored. The lower hazard value (0.977) shows for weight and the other two hazard values for age and gender shows also similar results.

Estimates for the cause specific to Ethinomide								
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio onfidence Limits	
Wt	1	-0.00926	0.02082	0.1976	0.6567	0.991	0.951	1.032
Age	1	-0.04851	0.02452	3.9139	0.0479	0.953	0.908	1.000

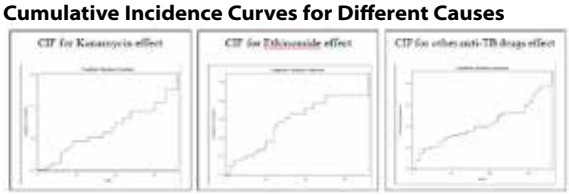
Estimates for the cause specific to Ethinomide								
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio onfidence Limits	
Gender	1	0.97551	0.51247	3.6236	0.0570	2.653	0.972	7.242
-2LL	164.704							

The above table result shows the hazard values for the cause specific Ethinomide toxic and the other drugs toxic were censored. The lower hazard ratio for age 0.953 and the higher hazard value gender is 2.653.

Estimates for the cause specific OTHER drugs								
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Wt	1	-0.01552	0.01372	1.2800	0.2579	0.985	0.958	1.011
Age	1	0.00302	0.01408	0.0459	0.8304	1.003	0.976	1.031
Gender	1	0.56156	0.36296	2.3938	0.1218	1.753	0.861	3.571
-2LL	299.361							

The cause specific to other anti-TB drugs (Cycloserine, Ofloxacin, Ethambutol, PAS and Capreomycin) the hazard ratio shows the higher hazard value for gender 1.753 and the other two hazard values for weight and age shows similar values.

Cumulative Incidence Curves for Different Causes



From the above three CIF curves clearly shows the higher estimated probability values for the cause specific to other anti-TB drugs toxic.

Discussion

The cause-specific proportional hazards model and proportional subdistribution hazards model are the methods applied to calculate the estimates of the effect of toxic developed by the Kanamycin, Ethinomide and other anti-TB drugs. For quantifying the prognostic effect of covariates, a natural choice would be to estimate them with cumulative incidence functions. Comparisons of the cumulative incidence for specific types of effect may provide additional information about the treatment differences. The cause related to the other anti-TB drugs in 36th month shows 91% estimated probability whereas the other estimated probabilities values for Kanamycin is 60% and Ethinomide is 54%. The CIF curves also clearly shows the higher estimated probability values for other anti-TB drugs toxic.

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