Bayesian competing risks analysis without data stratification

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ABSTRACT

Background: The Cox Proportional Hazard (CPH) model is a commonly used method to study death as the outcome of therapeutic effect. However, death may occur due to other causes not as the direct therapeutic effect. Death due to other causes is known as competing risks (CR). The conventional strategy is to handle the CR inflated death data with the stratified CPH model. However, it reduces the power of the data analysis. It is important to establish a model that can handle the CR without stratifying the data. This paper is devoted to developing the CR model.

Objective: Develop a statistical model that can handle death data analysis without stratifying in the presence of CR.

Methods: Statistical methodology is established to deal with CR. The Bayesian Inference is considered to overcome the computational difficulties. The Markov chain Monte Carlo (MCMC) was used to run the model. Model is illustrated for lung adenocarcinoma patient's data. The arm wise comparison on adenocarcinoma treated patients is performed. The computation of the competing risk model is performed in open source software OpenBugs.

Results: The proposed method helps to obtain the posterior estimates of different covariates with credible intervals. The posterior mean (SD) estimate helps to decide the best effective treatment through survival analysis in presences of CR.

Conclusions: This work is helped to work with CR data without stratifying it. It provides flexibility to analyze death data with CR by Bayesian.

1. Introduction

The primary focus of any oncology therapeutic effect study is too prolonged the duration of survival. The conventional survival analysis assumed that Competing Risk (CR) is not present in the dataset. This ignorance of CR may incorporate the misleading statistical inference about the therapeutic arm.^{1–4} It may happen that the CR is independent in nature as a cause of the therapeutic effect. The only available procedure is to discard the independent CR patient's data from survival analysis. It helps to avoid the biased inference in the clinical decision.^{5,6} However, discarding the patient's data can reduce the power of the study. In some studies, very minimal therapeutic effect benefit is expected. In this scenario, it becomes very crucial to explore the causes of death.

The deep exploration of the causes of death among treated patients gives scope for an in-depth comparison between treated arms. It is helpful to establish a decision among best effective therapy. The study can be assembled through consideration of all the patients into alive or dead. The causes of death could be disease progression or something

else. Therefore the cause of death not related to therapeutic effect is called as competing risks (CR).

A comprehensive review of CR analysis can be found in Crowder.^{7,8} There is an application on statistical analysis with CR data for system failure information.⁹ Recently, there is also an attempt to develop the CR model through Bayesian inference with incomplete trial information.¹⁰ Literature also supports about how to monitor the CR.¹¹ The choice of prior distribution for CR analysis is also documented.¹² The Bayesian analysis of CR data is explored through Weibull with the same shape and different scale parameters.¹³ However, there is not any document about how to work with CR analysis for Phase III randomized controlled trial data. This work is dedicated towards exploring the application of CR analysis in the context of randomized controlled trial.

2. Data methodology

This study makes use of publicly available of a clinical trial data which is carried out to characterize the performance of different prognostic indices on gene expression for 442 lung adenocarcinomas.

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The data is available at NCBI Gene Expression Omnibus (GEO) data repository under accession number GSE68465 (<http://www.ncbi.nlm.nih.gov/geo>). The performance of prognostic models for 442 lung adenocarcinoma was tested through a large training-testing, multi-site, blinded validation study.¹⁴ The performance of a prognostic model is measured through gene expression data set in the combination of pathological and clinical outcomes. The relapse-free and overall survival duration for all patients is measured. As an intention to treat, a few patients have selected for adjuvant chemotherapy and some of them are not. This study provides the comparison of overall survival between adjuvant and non-adjuvant chemotherapy.

However, it failed to account the CR by conventional survival analysis. In such situations, it is required to compare the efficacy of adjuvant chemotherapy through deep consideration of occurrence of death and accommodating different competing risks, which requires the development of models that consider both endpoints simultaneously. All patients are coded as status = 1 (If they died) or 0 (If they alive) at the end of the study in publicly available data sheet.

But in this work, patients died, followed by the relapse of the disease are defined as death due to therapeutic failure and coded as status = 1. Patients followed as relapse-free but died are defined as CR and coded as status = 2. Patients those are alive are defined as status = 0. The competing event is separated in this manner. It is expected that this proposed model can support further survival analysis for eventual clinical utilization.

Further, we developed a novel Bayesian framework for the survival analysis of CR inflated data. The proposed method is developed without stratifying the patient's data. A Markov model is considered to support the computational complexity. The frequentist approach to make the inference is considered. This proposed method is developed to deliver the scientific community with a tool to investigate the CR data in a randomized clinical trial.

3. A framework for survival analysis

It is obvious for a scientist who is not aware of CR but whose research involves time-to-event or time-to-death data. The analysis of such data is called as survival analysis. The event needs not to be death always. It can be the distant relapse or loco-regional relapse etc. Survival analysis is well developed and can be easily implemented in all statistical software. However, there are some situations where conventional survival analysis is not appropriate enough to analysis the time-to-death data.

The objective in survival analysis is to measure the time between the dates of diagnosis or treatment initiation to the date of death. The basic assumption of conventional survival analysis through Kaplan-Meier is that the censored observations are 'independent'.² It helps us to further assumed that the patients who are censored at a certain time point should be representative for those who are at risk at a specific time point. The "cumulative incidence function(CIF)" is defined as probability $F(t)$ of dying before time t .¹⁵ If the time of death is measured for each individual then $F(t)$ can be estimated through the relative frequency of survival times less than t . The function $F(t)$ is estimated by Kaplan-Meier estimator as.

$1 - \hat{S}(t)$ at time point t . The factor at failure time $S(t)$ is defined as $1 - \frac{d_i}{n_i}$ where d_i is death of the individual at time point i and n_i is the patients at risk at time point i .

The conventional survival analysis is not appropriate in presence of competing risks. It is required to adapt with caution. The Kaplan-Meier estimation is a method of estimating the survival probability at different time points. In presence of CR, Kaplan-Meier cannot be considered with probability. Their complement (1-KM) is defined as a probability of an event of interest in the real world where other types of events do not exist.¹⁶

CR concerns the situation where more than one cause of failure is

possible.^{16–19} It is assumed that all the failure time distributions are continuous. In the right censored, individual i is assumed to have an event time T_i and a censoring time C_i , observation are $T_i = \min(T_i, C_i)$ and $\delta_i = I(T_i \leq C_i)$, if $\delta_i = 1$, it shows that t_i is observed otherwise not. Let the event time and censoring time denoted as (T_i, C_i) and $T_i \sim S$ for $S(t) = \text{prob}(T > t)$, and having censoring distribution C_i . At any point of time, the individual who are censored can be presented by those who remain under observation.

4. A framework for Bayesian competing risks data analysis

There are some dedicated packages in widely used statistical software. Preliminary analysis of our randomized controlled trial data was performed using the R (version 3.4.0), and the cmprsk (version 2.2–7) package. The cumulative incidence was plotted through cuminc function (Fig. 3).

Similarly, in SAS the %CIF macro is helpful to estimate the cumulative incidence functions.

The conventional Cox PH model is unavoidable when lost to follow-up is nil in a long-term follow-up study. It can be accomplished with Fine-Gray model to handle competing risk events.

The nonparametric estimation through CIF is also helpful to deal with competing risks. The widely adopted approach to handle event-time data are Cox proportional hazard (CPH) modeled. However, it is not suitable tool to handle the event-time data merged with competing risks of the event. It considers the either the competing risk as censored observation or death due to the treatment effect. Therefore, the choice to work with CPH for competing risk data is the application of the cause specific sub-hazard function.

However, it is not suitable enough in terms of direct interpretation of survival probability. The other limitation of CPH is that the data should follow the proportionality assumption. If it failed to follow the proportionality assumption, then stratified CPH is suitable to work with non-proportional hazard. However, it reduces the power of study due to stratification of the entire sample size. It is better to consider dedicated approach to analysis event-time data having competing risks of event of interest.

The CR is defined as the situation in which an individual can experience more than one type of event.²⁰ It is also defined as the failure to achieve independence between the time of an event and the censoring mechanism.²¹ The situation where one type of event either preclude the occurrence of another event under investigation or fundamentally alters the probability of occurrence of this other event.²² Let C is censoring variable. The duration of observation is specified by T . The survival data can be represented as a bivariate random variable (C, T) . If $C = 1$, then T is the time at which the event occurred. If $C = 0$, then T is time at which the observation was censored. Further, C can be extended into 0, i ($i = 1, \dots, p$). If $C = 0$ then the observation is censored, and $C = i$ then observation is not censored. The term i is considered to define death due to different reasons. If death is due to treatment failure then it can be considered as $i = 1$. If death is due to other causes then it is considered as $i = 2$. In this analysis, we will restrict with the maximum value for i as 2.

$$\lambda_p(t_i) = \lim_{\delta t \rightarrow 0} \frac{\Pr(t_i < T \leq t_i + \delta t, C_i = p | T > t_i)}{\delta t} \quad (1)$$

The cumulative cause-specific hazard is defined as

$$\Delta_p(t) = \int_0^t \lambda_p(s) ds \quad (2)$$

The cause specific survival function is defined as

$$S_p(t) = \exp(-(\Delta_p(t))) \quad (3)$$

The overall survival function is defined as

$$S(t) = \exp\left(\sum_{p=1}^P -\Delta_p(t)\right) \quad (4)$$

The cause-specific density or sub-density function

$$f_p(t_i) = \lim_{\delta t \rightarrow 0} \frac{\Pr(t_i < T < t_i + \delta t, C_i = p)}{\delta t} \quad (5)$$

Let the censoring indicator for the i th individual's is defined as $\delta_{ip} = 1$ if $C_i = p \in \{1, 2, \dots, P\}$ and $\delta_{ip} = 0$ otherwise.

The covariates are defined as X_{ip} with the proportional hazard assumption as

$$\lambda_p(t_p | X_{ip}, \beta_p) = h_{0p}(t_i) \exp(\beta_p X_{ip}) \quad (6)$$

and the likelihood function is defined as

$$L_i = f_p(t_i | X_{ip}, \beta_p) \prod_{k \neq p} S(t_i | X_{ik}, \beta_k) \quad (7)$$

Further, the hazard function is extended as

$$h_i = (t_i | b_{ip}, X_{ip}, \beta) h_{0p}(t_i) \exp(\beta_p X_{ip} + b_{ip}) \quad (8)$$

$$b_{ip} \sim N(0, \Sigma) \quad (9)$$

to accommodate the cause specific frailty effects.

This analysis is performed through open source software OpenBugs (www.openbugs.net). OpenBugs is free available software. The OpenBugs code is included as Annexure at the end of this paper.

5. Analysis and results

Table 1 gives the descriptive statistics for patients in the study sample. Baseline characters observed as continuing variable are summarized through the median, while binary variables with frequencies and percentages. Fig. 1 show that the Kaplan-Meier estimates of overall survival in patients treated with Adjuvant and Non-Adjuvant arms. The median overall survival of the patients treated Adjuvant and Non-Adjuvant arms were 47 and 70.5 months respectively. The Log-rank test value on overall survival comparison is obtained with p-value 0.0015. Initially, the cumulative incidence rates of death among patients are plotted. Further, the Kaplan-Meier curves without and with considering

Table 1

Baseline characteristics of patients in the Adjuvant vs Non-adjuvant chemotherapy (N = 443).

Parameter	Adjuvant(N = 89)	Non-Adjuvant(N = 354)	All Patients
Age			
Mean	61.61	65.12	64.41
Range	36–82	33–87	33–87
Gender			
Male	40(44.94%)	183(51.69%)	223(50.34%)
Female	49(55.06%)	171(48.31%)	220(49.66%)
Tobacco Consumption			
Smoker	73(82.08%)	227(64.12%)	300(67.72%)
Non-Smoker	16(17.8%)	127(35.88%)	143(32.28%)
Disease Stage			
N0T1	5(5.62%)	109(30.79%)	114(25.73%)
N0T2	34(38.2%)	128(36.16%)	162(36.57%)
N0T3	2(2.5%)	14(3.95%)	16(3.61%)
N0T4	0(0%)	7(1.98%)	7(1.58%)
N1T1	4(4.29%)	20(5.65%)	24(5.42%)
N1T2	21(26.6%)	34(9.60%)	55(12.42%)
N1T3	1(1.12%)	6(1.69%)	7(1.58%)
N1T4	0(0%)	2(0.56%)	2(0.45%)
N2T1	4(4.49%)	7(1.98%)	11(2.48%)
N2T2	14(15.73%)	20(5.65%)	34(7.67%)
N2T3	1(1.12%)	4(1.13%)	5(1.13%)
N2T4	2(2.25%)	1(0.28%)	3(0.68%)
NXT4	0(0%)	1(0.28%)	1(0.23%)
Unknown	1(1.12%)	1(0.28%)	2(0.45%)

Fig. 1. Kaplan-Meier Curve: Without considering competing risk.

Fig. 2. Kaplan-Meier Curve: by considering competing risk as event.

the CR are plotted in Figs. 1 and 2 respectively. The duration of follow-up for both the curves is considered on overall survival. A total of 20,000 iterations with inference from the last 1s5000 iterations are considered. The posterior mean(SD) and 95% credible intervals of regression parameters are given in Table 2. It shows that Age is a positive risk factor for both the causes (i.e. death and CR). However, the impact of age for cause of CR is comparatively less(0.151) in comparison to cause as death (0.355). The arms are defined as (arm = 1 for Adjuvant and arm = 2 for Non-Adjuvant).

Table 2

Posterior estimates of the parameters observed through competing risk analysis.

Parameter	Posterior Mean(SD)	(2.5%,97.5%)
Intercept		
(β_{01})	6.034(2.623)	(2.429,12.18)
(β_{02})	-8.802(3.483)	(-15.96,-2.22)
Disease Stage		
(β_{11})	-0.113(0.361)	(-0.878,0.545)
(β_{12})	0.606(1.168)	(-1.546,3.049)
Age		
(β_{21})	0.355(0.484)	(-0.536,1.368)
(β_{22})	0.151(0.658)	(-1.118,1.479)
Arm		
(β_{31})	-0.054(0.050)	(-0.190,-0.002)
(β_{32})	0.054(0.044)	(-0.027,0.137)
Smoking		
(β_{41})	-0.045(0.019)	(-0.086,-0.007)
(β_{42})	0.027(0.056)	(-0.057,0.159)

Fig. 3. Cumulative incidence function.

Fig. 4. Competing risk frame.

The MCMC output provides the posterior mean estimate β_{31} for Non-Adjuvant arm in comparison to Adjuvant arm. The β_{31} is -0.054 with standard deviation as 0.050 . The 95% corresponding credible interval is observed with $(-0.190, -0.002)$. This β_{31} gives the inference for cohort of individuals those are shifted from censoring to death status during the study. The negative estimates of β_{31} represents that the Non-Adjuvant arm significantly prolongs the duration of survival in comparison to Adjuvant arm. However, β_{32} provides the not significant estimates about CR. The weekly arm was found better in comparison to Non-Adjuvant arm for occurrence of CR. The CR framework is presented in Fig. 4. Similar trend is also observed for the smoking status also. The regression coefficients interval for smoking status was significant for causes of death but not significant for causes with CR.

6. Discussion

The CR precludes the occurrence of the primary event of interest. The application of CIF provides better estimates in comparison to Kaplan-Meier survival estimates in this context. Fitting regression model in the presence of CR can be handled by (I) Modeling the effect of covariates on the cause-specific hazard of the outcome or (II) Modeling the effect of covariates with CIF. However, the cause-specific hazard considers the subsets of those individuals are event free. But CIF provides the best estimate of the effect of covariates on the absolute risk of

the outcome over time. During CR analysis the cause of failures could be independent or dependent in nature. The presence of covariates is used to provide information about the type's dependence between causes of death. There is an attempt to explore the distribution assumption of causes of death 7 and model the CR through the latent failure time assumption 13. Under parametric setup with Weibull distribution, the CR modeling is explored.²³ Till now the majority of methods is developed through the frequentist approach, mainly by a non-parametric procedure. But there is limited literature available on Bayesian CR modeling. The copula is found suitable to deal with CR problem.²⁴ However, it failed to consider the covariates. There is an attempt on Bayesian by the multistate model as well as as.^{25–29} The Bayesian inference is found satisfactory for semi-parametric risk data analysis in cross-over trial.³⁰ It is attempted for lifetime risk modeling on the non-terminal event.

7. Conclusion

However, there is a very rare occurrence of a non-terminal event in any trial. We have illustrated the application of the CR model into the randomized controlled trial to serve the basic objective. The basic objective is to find the best effective therapy, i.e. Adjuvant or Non-Adjuvant. It is also possible to perform regression with cause-specific models by R. But thus reduce the power of the study. There are some dedicated packages like “timereg”, “cmprsk”, “msate” to deal with CR in open source software R. These are built to carry with cumulative incidence function. But there is limited code available to deal with CR with Bayesian inference. The Bayesian can be considered as an alternative to computing the CR model. The result was further compared with the frequentist approach. It was also found similar trends in results. However, Bayesian provides a more robust and flexible interpretation. It is also possible to perform regression with cause-specific models by R. But thus reduce the power of the study as well. It is requested to write to the corresponding author about running this code with other suitable data.

This work is an extension of the Bayesian counterpart in the CR model. The tool like CPH and Kaplan-Meier estimates are well developed. However, it is not advised to adopt these tools due to their application limitations. It is required to explore the reasons for the deaths of cancer treated patients. It is incorrect to consider death due to other causes as censored. Similarly, it cannot be considered as death due to treatment failure as well. However, both the consideration makes a positive or negative impact on inference. The existing methods (like CIF or others) only dealt with different causes of death through subsetting the survival dataset. Therefore, the inference drawn from subset data is not acceptable, due to the inadequate power of the study. It becomes challenging to deal with different causes of death without subsetting the data. This work is an extension of Bayesian Inference with CR data without stratifying. We attempted the CR modeling without subsetting the dataset. It is useful for CR inflated survival data analysis. OpenBugs software is used to perform the analysis. The estimation is carried out by Markov chain Monte Carlo (MCMC) method.

Declarations of interest

The authors declare no conflict of interest.

Annexure

```
#OpenBUGS#
```

```
model {for (i in 1:N){ for (j in 1:J) {delta[i,j] <- equals(C[i], j)} #N is sample size#
```

```
for (j in 1:Td){R[i,j] <- step(t[i] - a[j] + eps)
```

```
for (k in 1:J) {dN[i,j,k] <- R[i,j]*step(a[j+1] - t[i] - eps)*delta[i,k]
```

```
dN[i,j,k] ~ dpois(lam[i, j, k])
```

```
lam[i, j, k] <- R[i,j]*exp(beta0[k] + beta1[k]*Diseasestage[i] + beta2[k]*age[i]
```

```
+beta3[k]*arm[i]+beta4[k]*smoking[i])*dL0[k,j]}}}
```

```
for (j in 1:Td) {for (k in 1:J) { dL0[k,j] ~ dgamma(mu[j,k], c)
```

```
mu[j,k] <- dL0.star[j,k]*c
```

```
dL0.star[j,k] <- max(0.1,r[k]*(a[j+1] - a[j]))}}
```

```
for (j in 1:J){ beta0[j] ~ dnorm(0,0.001)
```

```
beta1[j] ~ dnorm(0,0.001); # beta1,beta2,beta3 and beta4 are generated with prior distribution#
```

```
beta2[j] ~ dnorm(0,1)
```

```
beta3[j] ~ dnorm(0,0.001);
```

```
beta4[j] ~ dnorm(0,1)}}}
```

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cegh.2019.08.010>.

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