Bayesian Frailty for Competing Risks Survival Analysis in the Iranian Metastatic Colorectal Patients

Iran’lı Metastatik Kolorektal Kanser Hastalarında Yarışan Riskler Yaşam Analizi için Bayesçi Kırılganlık Modeli

ABSTRACT Objective: In the competing risks problem, wherein only the event due one cause is observed, the cause-specific hazard rates are usually estimated by considering the independence assumption on the competing causes. However, this assumption is too rigorous in the practical situations. This paper aimed to extend the results of Finkelstein and Esaulova (2008), in order to relax the problem of independence assumption in the competing risks survival analysis with counting process approach by exerting frailty term and in the Bayesian framework. Material and Methods: The results were applied on Iranian metastatic colorectal cancer patients’ data set. Several frailty distributions were tried. The survival probability and their 95 percent confidence interval were calculated based on the best model and using 10000 MCMC samples after burning 1000 samples. Results: The results showed better survival for the patients with rectal cancer than with colon cancer. Conclusion: These findings may be useful for many situations at which there is uncertainty about or the independence assumption of failure times is not hold, such as competing risks, recurrent events and clustered data including modeling clustered survival data from multicenter clinical trials, especially in the case of moderate to small sample size.

Key Words: Bayesian frailty, survival; competing risks; counting process; dependency; metastatic colorectal cancer


Anahtar Kelimeler: Bayesçi kırılganlık, yaşam; yarışan riskler; sayma süreççi; bağımlılık; metastatik kolorektal kanser


In various medical studies, the event of interest occurs by several possible causes. For example, in patients with colorectal cancer (CRC), there are at least two ways a patient would die; death by colon cancer or
death by rectal cancer. In the other word there is two latent failure times (say $T_1$ and $T_2$) which only one of them i.e. the minimum failure time ($X_{\text{min}}$) and an indicator of failure type can be observed. Therefore, in the competing risks problem, occurrence of the event by one cause prevents it by other cause(s) or makes it unobservable or un-interpretable.

Gail or Prentice et al. reviewed the history and various techniques for analysis of survival data with competing risks. In their paper, Taşdelen et al. studied the survival analysis in the presence of competing risks. Although the choice of quantity of interest should depend on the clinical question, but in many cases, the primary interest is the marginal survival probability or hazard rate of that latent failure time. But, this is not identifiable without exerting further assumptions on the correlation structure of the failure times, and usually cause-specific survival or hazard for the cause of interest is estimated by treating other failures as censored. It is noteworthy that the cause-specific hazard or survival is equal to the marginal one, only when the assumption of the independent failure times is fulfilled. However, this assumption can’t be checked by data only. In their paper, Finkelstein and Esaulova introduced a way to overcome this problem. The aim of this paper is to show how the results of Finkelstein and Esaulova, can be extended to relax the problem of independence assumption in the competing risks survival analysis with counting process approach by exerting frailty term as a random variable and introducing priors for this variable, in the Bayesian framework.

Bayesian approach is adopted to combine prior information with information involved in the data in the likelihood function. Gasbarra and Karia studied the analysis of competing risks by Bayesian smoothing approach. Arjas and Gasbarra, made an inference from right censored survival data, using the Gibbs sampler in the context of non-parametric Bayesian approach. In a study by Hjort, nonparametric Bayesian estimators were introduced based on beta processes in models for life history. Wang and Ghosh introduced a stage-wise noninformative prior elicitation strategy utilized for absolutely continuous bivariate exponential distributions in Bayesian analysis of bivariate competing risks models.

The rest of the paper is set as following sections: in the second section of the paper the findings of Finkelstein and Esaulova is introduced, the likelihood construction based on counting process approach of Andersen and Gill for survival times and considering gamma frailty is discussed in the section 3, application of the results is illustrated in section 4 on a colorectal cancer real data set and finally the conclusions are made in the section 5 of this paper.

### MATERIAL AND METHODS

#### FINDINGS OF FINKELSTEIN AND ESAULOVA

Finkelstein and Esaulova, in addressing the problem of bivariate frailty competing risks model showed that: by assuming that the risks are dependent via a bivariate frailty ($U_1$, $U_2$), when the components of the system are independent conditional on independent $U_1$ and $U_2$, then the mixture failure rate of the system can be constructed by the sum of mixture failure rate of individual components, so that:

\[
h_{m,xy}(t) = \int \int h_{m,y}(t,u_1,u_2)\pi(u_1,u_2|t)du_1du_2
\]

\[
= \int \int [h_1(t,u_1) + h_2(t,u_2)]\pi(u_1|t)\pi(u_2|t)du_1du_2
\]

\[
= \int [h_1(t,u_1)]\pi(u_1|t)du_1 + \int [h_2(t,u_2)]\pi(u_2|t)du_2
\]

\[
h_{m,1}(t) + h_{m,2}(t)
\]

Therefore, if the frailty terms $U_1$ and $U_2$ are considered independent and $T_1$ and $T_2$ are conditionally on $U_1$ and $U_2$ are independent, the joint hazard function of two competing events can be estimated by a sum of two individual hazards conditioned on $U_1=U_1$ and $U_2=U_2$. One of the most important problems encountering within the competing risks analysis is the independence assumption of the survival times. In the classical analysis, the crude or cause-specific hazard ratios are usually estimated based on this assumption. Since the assumption can’t be checked by data, the analyses are performed by ignoring this assumption and this produces the biased estimations. The findings of Finkelstein and Esaulova, ma-
ke a clue to overcome this problem by adding a frailty term in the model, afterwards survival times would be independent. In the other words, this could make an adjustment to the model. In the next section, we further use this idea to model competing risks by including frailty terms in the model and considering priors for these random variables and the problem would be addressed in the Bayesian survival framework.

**Likelihood Construction Based On Counting Process And Independent Frailties**

Based on the results of the previous section, for computing the hazard function of the system (which in this paper is considered as two variables, without losing the generalizability), it is sufficient to compute the conditional hazard function of each cause of failure separately given the frailty components for each cause. Therefore in this section the likelihood is constructed for the data by exerting frailty random variables into the likelihood function, suitable priors considered for the variables, hazard function and finally the parameters of interest i.e. survival probabilities and their Standard Error (SE) are estimated.

Several authors have discussed Bayesian inference for censored survival data where the integrated baseline hazard function is to be estimated non-parametrically. Kalbfleisch, Kalbfleisch and Prentice, Clayton and Clayton, formulates the Cox model using the counting process notation introduced by Andersen and Gill and discusses estimation of the baseline hazard and regression parameters using Markov Chain Monte Carlo (MCMC) methods. This approach forms the basis for extensions to random effect (frailty) models in our multiple events problem.

For subjects \( i = 1, ..., n \), the processes \( N_i(t) \) are observed which count the number of failures occurred up to time \( t \). The corresponding intensity process \( I_i(t) \) is given by

\[
I_i(t) = E(dN_i(t) \mid Ft-)
\]

(2)

Where \( dN_i(t) \) is the increment of \( N_i(t) \) over the small time interval \([t, t+dt)\), and \( Ft- \) represents the available data just before time \( t \). If subject \( i \) is observed to fail during this time interval, \( dN_i(t) \) will take the value 1; otherwise \( dN_i(t) = 0 \). Hence \( E(dN_i(t) \mid Ft-) \) corresponds to the probability of subject \( i \) failing in the interval \([t, t+dt)\). As \( dt \) 0 (assuming time to be continuous) then this probability becomes the instantaneous hazard at time \( t \) for subject \( i \). This is assumed to have the proportional hazards form

\[
I_i(t) = Y_i(t)h_0(t)\exp(X_i\beta)
\]

(3)

Where \( Y_i(t) \) is an observed process taking the value 1 or 0 according to whether or not subject \( i \) is observed at time \( t \) and \( h_0(t)\exp(X_i\beta) \) is the familiar Cox regression model. Thus we have observed data \( D = N_i(t), Y_i(t), z_i (i = 1, ..., n) \) and unknown parameters \( \beta \) and \( H_0(t) = \int h_0(t) dt \) which the latter to be estimated non-parametrically.

The joint posterior distribution for the above model is defined by

\[
P[H_0(t), \beta \mid D] \propto P[D \mid H_0(t), \beta] P(\beta) P[H_0(t)]
\]

(4)

It is needed to specify the form of the likelihood \( P(\beta) P(H_0(t)) \) and prior distributions for \( \beta \) and \( H_0(t) \). Under non-informative censoring, the likelihood of the data is proportional to

\[
\prod_{i=1}^{n} \prod_{t=0}^{T_i} I_i(t)^{N_i(t)} \exp[I_i(t)dt]
\]

(5)

This is essentially as if the counting process which increments \( dN_i(t) \) in the time interval \([t, t+dt)\) are independent Poisson random variables with means \( I_i(t)dt \):

\[
dN_i(t) \sim \text{Poisson}(I_i(t)dt)
\]

(6)

and it can be written as

\[
I_i(t)dt = Y_i(t)\exp(X_i\beta)dH_0(t)
\]

(7)

Where \( dH_0(t) = h_0(t)dt \) is the increment or jump in the integrated baseline hazard function occurring during the time interval \([t, t+dt)\). Since the conjugate prior for the Poisson mean is the gamma
distribution, it would be convenient if $H_0(t)$ were a process in which the increments $dH_0(t)$ are distributed according to gamma distributions. We assume the conjugate independent increments prior suggested by Kalbfleisch, namely

$$dH_0(t) \sim \text{Gamma}(c \cdot dH^*_0(t), c)$$ (8)

Here, $dH_0(t)$ can be considered as a prior guess at the unknown hazard function, with $c$ representing the degree of confidence in this guess. Small values of $c$ correspond to weak prior beliefs. In the example below, we set $dH^*_0(t) = r dt$ where $r$ is a guess at the failure rate per unit time, and $dt$ is the size of the time interval.

After inserting frailty term we would have:

$$\prod_{i=1}^{n} \left[ \sum_{t > 0} \left( \frac{U_i(t)}{t^{\gamma_i}} \right) \exp[U_i(t)] dt \right] \exp(U)$$ (9)

Several distributions such as Lognormal, Log Logistic, Gamma and Weibull may be used as frailty distribution. The distributions for this term were used so that they provide the mean equal to 1 and a variance which should be estimated via modeling.

**PATIENTS**

Data were acquired from cancer registry center of Research Center of Gastroenterology and Liver Disease (RCGLD), Shahid Beheshti Medical University, Tehran, Iran. All patients with metastatic CRC diagnosis according to the pathology report of cancer registry were eligible for this study. Based on this criterion, a total of 94 patients (67 (71.3%) with colon cancer, 27 (28.7%) with rectal cancer were included in the study. The follow up time was defined as 1 January 2002 (as the date of diagnosis) up to the 1 October 2007 as the time of the death from the disease (as the exact failure time) or survival (as the censoring time). Deaths were confirmed through the telephonic contact to relatives of patients. Metastatic patients were chosen according to the spread of tumor to distant surfaces or organs (M-stage) of American Joint Committee on Cancer (AJCC) TNM (Tumor, Node, and Metastasis) staging criterion. Based on the site topography of cancer, the colon and rectal were separated to define the sites of the cancer. This research was conducted in accordance with the principles set forth in the Helsinki Declaration 2008 (available at: http://www.wma.net/en/30publications/10policies/b3/index.html).

In this data set, colon and rectal cancers were considered as the competing events of death, wherein the death from colon (rectal) cancer prevent the death from the other cause to be observed.

**RESULTS**

In this section, the results of two last sections are evaluated by a real data set. In the analysis, the hazard of the colon and rectal cancers was separately computed by Lognormal, Log Logistic, Gamma and Weibull distributions for frailty terms. Deviance Information Criterion (DIC) was computed as a measure of model selection among the distribution mentioned above; models with smaller DIC would be preferred to the models with larger DIC. The results showed that there were not considerable differences among the values of DIC for these distributions for colon and rectal cancer data (Table 1).

Therefore, other analyses were followed by Gamma frailty model which has been proved to be a robust choice for frailty distribution in practical situations.

Analyses were performed by WINBUGS 1.4 software (available free at: http://www.mrc-bsu.cam.ac.uk/bugs/winbugs). In each set of analyses, a total of 11000 MCMC samples were drawn and the quantities of interest were estimated based on 10000 of them after burning 1000 samples. The convergence of the samples to the parameter value was monitored by history plots which plot the sampled parameter versus iteration number in a sequences of chains. Since they result approximately the same value, the convergence of the samples was

<table>
<thead>
<tr>
<th>Frailty Distribution</th>
<th>Lognormal</th>
<th>Log Logistic</th>
<th>Gamma</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>437.634</td>
<td>436.545</td>
<td>437.634</td>
<td>433.116</td>
</tr>
<tr>
<td>Rectum</td>
<td>195.900</td>
<td>195.771</td>
<td>196.126</td>
<td>195.106</td>
</tr>
</tbody>
</table>

TABLE 1: The values of DIC for various selections of frailty distributions.
confirmed for each of quantities estimated. In addition, the Monte Carlo (MC) Error for each parameter was computed. As a rule of thumb, the simulation should be run until the Monte Carlo error for each parameter of interest is less than about 5% of the sample standard deviation.

Subsequently the parameter of the frailty term, survival probabilities and their 95% confidence intervals were computed based on these 10,000 samples. Based on square error and absolute error loss functions, the mean and median of the samples are the estimate of the parameters respectively. In patients with colon cancer, the survival probability declines from 0.989 to 0.437 (Table 2). The MC error for all parameter estimates is far less than 5% of the sample standard deviation, which is a confirmation of the model convergence. Also, in patients with rectal cancer, the survival probability declines from 0.989 to 0.702 (Table 3). The MC error for all parameter estimates is far less than 5% of the sample standard deviation, which in this case is a confirmation of the model convergence, too.

The survival of the patients with colon cancer decrease to about 0.44 after 64 months and continued in this value until the end of study (Figure 1). In the other hand, the survival of the patients with rectal cancer decrease to approximately 0.7 after about 64 months and continued in this value until the end of study (Figure 2). In these figures it can be seen that approximate one and two year survival of the patients with colon cancer were 0.813 and 0.658 respectively. In the other hand, these approximate probabilities were 0.898 and 0.833 respectively. Therefore, the survival of patients with rectal cancer is better than that of patients with colon cancer.

## DISCUSSION AND CONCLUSION

In this paper, the results of Finkelstein and Esaulova, were extended to relax the problem of independence assumption in the competing risks survival analysis with counting process approach by exerting several frailty terms as random variables, finally choosing Gamma distribution for this quantity and introducing Gamma prior for this variable, and then the posterior survival probabilities were computed in the Bayesian survival framework. The results were applied on Iranian metastatic colorectal cancer patients’ real data set.

Based on our findings, overall survival of the metastatic patients with rectal cancer was better than those of colon cancer. This shows the better
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Other studies confirm this result in the general patients too, but other studies showed the reverse results. In addition, there are some arguments too. So, there are differences in survival between two sub-sites of colon-rectum and this can recommend further specific study of colon and rectum and possibly their prognostic factors.

In the line with our study, in a paper by Haidinger et al, the one and five year survival of Male patients with colon cancer, was not statistically different from that of patients with rectal cancer but higher survival, tough not statistically significant, was observed in Female patients with rectal cancer.

When the independence assumption does not hold, this not only affect the variance of the parameter estimates but also it affects the parameter value itself and this make some deviance (bias) in the value of hazard ratios (survival probabilities) form their real estimates, hence some incorrect or deviant interpretations might have been made in biological context. By inserting frailty component, both the parameter estimates and their SE’s have been adjusted for model misspecifications on both aspects of accuracy and precision.

In our paper, similar to other studies, Gamma distribution has been used for frailty variable, since simulation results showed that the biases are generally 10% and lower, even when the true frailty distribution deviates substantially from the assumed Gamma distribution. This suggests that the Gamma frailty model can be a suitable practical choice in real data analyses if the regression parameters and marginal hazard function is of primary interest and individuals are exchangeable with respect to their dependencies.

However, the variance parameter of this distribution had high variation. We think that the possible reason for this problem is due to the skewed distribution of the variance parameter i.e. beta (this is a variance parameter and its sampling distribution is right skewed). Since this is the nature of the distribution for variance parameter, high values of SDs are unavoidable.

Our guess to slightly improve the precision of the parameter went among the distributions of the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Median</th>
<th>LU</th>
<th>SD</th>
<th>MC error</th>
</tr>
</thead>
<tbody>
<tr>
<td>S[1]</td>
<td>0.989</td>
<td>0.992</td>
<td>0.959</td>
<td>1.00</td>
<td>0.011</td>
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<tr>
<td>S[2]</td>
<td>0.978</td>
<td>0.981</td>
<td>0.939</td>
<td>0.997</td>
<td>0.015</td>
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<tr>
<td>S[3]</td>
<td>0.966</td>
<td>0.969</td>
<td>0.919</td>
<td>0.993</td>
<td>0.019</td>
</tr>
<tr>
<td>S[4]</td>
<td>0.953</td>
<td>0.957</td>
<td>0.900</td>
<td>0.987</td>
<td>0.023</td>
</tr>
<tr>
<td>S[5]</td>
<td>0.940</td>
<td>0.943</td>
<td>0.880</td>
<td>0.980</td>
<td>0.026</td>
</tr>
<tr>
<td>S[6]</td>
<td>0.927</td>
<td>0.930</td>
<td>0.861</td>
<td>0.973</td>
<td>0.029</td>
</tr>
<tr>
<td>S[7]</td>
<td>0.913</td>
<td>0.916</td>
<td>0.843</td>
<td>0.964</td>
<td>0.031</td>
</tr>
<tr>
<td>S[8]</td>
<td>0.898</td>
<td>0.902</td>
<td>0.825</td>
<td>0.955</td>
<td>0.034</td>
</tr>
<tr>
<td>S[9]</td>
<td>0.883</td>
<td>0.887</td>
<td>0.805</td>
<td>0.944</td>
<td>0.036</td>
</tr>
<tr>
<td>S[10]</td>
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<td>0.871</td>
<td>0.783</td>
<td>0.934</td>
<td>0.039</td>
</tr>
<tr>
<td>S[11]</td>
<td>0.851</td>
<td>0.853</td>
<td>0.762</td>
<td>0.922</td>
<td>0.041</td>
</tr>
<tr>
<td>S[12]</td>
<td>0.833</td>
<td>0.836</td>
<td>0.739</td>
<td>0.910</td>
<td>0.044</td>
</tr>
<tr>
<td>S[13]</td>
<td>0.815</td>
<td>0.818</td>
<td>0.717</td>
<td>0.898</td>
<td>0.047</td>
</tr>
<tr>
<td>S[14]</td>
<td>0.795</td>
<td>0.798</td>
<td>0.690</td>
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<tr>
<td>S[15]</td>
<td>0.774</td>
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<td>0.662</td>
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<td>S[16]</td>
<td>0.702</td>
<td>0.711</td>
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<td>0.081</td>
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<tr>
<td>beta</td>
<td>1.665</td>
<td>0.575</td>
<td>0.001</td>
<td>9.658</td>
<td>2.762</td>
</tr>
</tbody>
</table>

**TABLE 3:** Posterior estimation of survival parameters for rectal cancer.

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**FIGURE 1:** Survival curve (cross line) and its 95% confidence interval (dashed line) for patients with colon cancer.

**FIGURE 2:** Survival curve (cross line) and its 95% confidence interval (dashed line) for patients with rectal cancer.
The finding of the paper may be useful for many situations at which there is uncertainty about or the independence assumption of failure times is not hold, such as competing risks problem with more than two causes of failure, recurrent events and clustered data such as modeling clustered survival data from multicenter clinical trials.

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