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

İran'lı Metastatik Kolorektal Kanser Hastalarında Yarışan Riskler Yaşam Analizi için Bayesçi Kırılganlık Modeli

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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

ÖZET Amaç: Sadece bir nedene bağlı olayın gözlendiği yarışan riskler probleminde, neden-spesifik hazard oranları genellikle yarışan nedenler üzerindeki bağımsızlık varsayımı dikkate alınarak tahmin edilmektedir. Ancak bu varsayım pratik uygulamalarda oldukça sert olmaktadır. Bu çalışmada, kırılganlık terimi ekleyerek sayma süreci yaklaşımıyla, yarışan riskler yaşam analizindeki ve Bayesçi çerçevede bağımsızlık varsayımı problemini gevşetmek için, Finkelstein ve Esaulova (2008)'nın sonuçlarının genişletilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Sonuçlar, İran'lı metastatik kanser hastaları veri setine uygulanmıştır. Çeşitli kırılganlık dağılımları denenmiştir. Bin örneklem oluşturduktan sonra 10000 MCMC örneklemi kullanarak en iyi model için yaşam olasılığı ve %95 güven aralığı hesaplanmıştır. **Bulgular:** Sonuçlar, rektal kanserli hastalar için yaşam olasılığının kolon kanserli hastalardan daha iyi olduğunu gösterdi. **Sonuç:** Bu bulgular, özelikle orta ve küçük örneklem büyüklüklerinde, yarışan riskler, tekrarlayan olaylar ve çok merkezli klinik denemelerden elde edilen kümelenmiş yaşam verisinin modellendiği kümelenmiş veriler gibi, kayıp zamanlarının bağımsızlığı varsayımıyla ilgili belirsizlik olduğu ya da varsayımın sağlanmadığı durumlarda kullanışlı olabilir.

Anahtar Kelimeler: Bayesçi kırılganlık, yaşam; yarışan riskler; sayma süreci; bağımlılık; metastatik kolerektal kanser

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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=min) and an indicator of failure type can be observed.[1] 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.[2]

Gail or Prentice et al. reviewed the history and various techniques for analysis of survival data with competing risks.[3,4] In their paper, Taşdelen et al. studied the survival analysis in the presence of competing risks.[5] Although the choice of quantity of interest should depend on the clinical question,[6] 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,[7] 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.[2] However, this assumption can't be checked by data only.[8] In their paper, Finkelstein and Esaulova introduced a way to overcome this problem.[9] The aim of this paper is to show that 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.[9]

Bayesian approach is adopted to combine prior information with information involved in the data in the likelihood function.[2] Gasbarra and Karia studied the analysis of competing risks by Bayesian smoothing approach.[10] Arjas and Gasbarra, made an inference from right censored survival data, using the Gibbs sampler in the context of nonparametric Bayesian approach.[11] In a study by Hjort, nonparametric Bayesian estimators were introduced based on beta processes in models for life history.[12] 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.[13]

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[14] 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:

$$\begin{aligned} h_{m,sys}(t) &= \int_{a_2}^{b_2}\int_{a_1}^{b_1} h_{sys}(t,u_1,u_2)\pi(u_1,u_2|t)du_1du_2 \qquad (1)\\ &= \int_{a_2}^{b_2}\int_{a_1}^{b_1}[h_1(t,u_1)+h_2(t,u_2)]\pi_1(u_1|t)\pi_2(u_2|t)du_1du_2 \\ &= \int_{a_1}^{b_1}[h_1(t,u_1)\pi_1(u_1|t)]du_1 + \int_{a_2}^{b_2}[h_2(t,u_2)\pi_2(u_2|t)]du_2 \\ &= h_{m,1}(t)+h_{m,2}(t) \end{aligned}$$

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 $U_2=u_2$.[9]

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.[8] 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.[15-18] This approach forms the basis for extensions to random effect (frailty) models in our multiple events problem.

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

$$I_i(t)dt = E(dN_i(t)|Ft-) \quad (2)$$

Where dNi(t) is the increment of Ni 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, dNi(t) will take the value 1; otherwise dNi(t) = 0. Hence $E(dN_i(t)|Ft-)$ 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

$$I_i(t) = Y_i(t)h_0(t)\exp(X_i\beta) \quad (3)$$

Where Yi(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 = Ni(t), Yi(t), zi (i = 1 ,…, n) and unknown parameters β 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

$$P[H_0(t),\beta|D] \quad P[D|H_0(t),\beta]P[\beta]P[H_0(t)] \quad (4)$$

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

$$\prod_{i=1}^{n}[\prod_{t\geq 0} I_i(t)^{N_i(t)}]\exp[I_i(t)dt] \quad (5)$$

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

$$dNi(t) \sim Poisson(Ii(t)dt) \quad (6)$$

and it can be written as

$$I_i(t)dt = Y_i(t)\exp(X_i\beta)dH_0(t) \quad (7)$$

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

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

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 $dH^*_0(t)=rdt$ 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:

$$\prod_{i=1}^{n}[\prod_{t\geq 0} I_i(t)^{N_i(t)}]\exp[I_i(t)dt]^{\exp(U)} \quad (9)$$

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.[19,20] 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.[21]

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 1: The values of DIC for various selections of frailty distributions.

Frailty Distribution	Lognormal	Log Logistic	Gamma	Weibull
Colon	437.634	436.545	437.634	433.116
Rectum	195.900	195.771	196.126	195.106

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 10000 samples. Based on square error and absolute error loss functions, the mean and median of the samples are the estimate of the parameters respectively.[19] 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.

TABLE 2: Posterior estimation of survival parameters for colon cancer.

Parameter	Mean	Median	L	U	SD	MC error
S[1]	0.989	0.993	0.960	1.000	0.011	9.07E-05
S[2]	0.978	0.982	0.941	0.997	0.015	1.63E-04
S[3]	0.967	0.970	0.923	0.993	0.019	2.04E-04
S[4]	0.956	0.959	0.906	0.988	0.021	2.13E-04
S[5]	0.944	0.947	0.889	0.982	0.024	2.31E-04
S[6]	0.933	0.936	0.872	0.975	0.026	2.45E-04
S[7]	0.921	0.924	0.857	0.967	0.029	2.58E-04
S[8]	0.909	0.913	0.840	0.959	0.031	2.67E-04
S[9]	0.898	0.901	0.826	0.952	0.032	2.62E-04
S[10]	0.886	0.889	0.811	0.943	0.034	2.82E-04
S[11]	0.874	0.877	0.795	0.935	0.036	3.04E-04
S[12]	0.862	0.865	0.782	0.927	0.037	3.06E-04
S[13]	0.850	0.853	0.767	0.917	0.039	3.04E-04
S[14]	0.838	0.841	0.754	0.907	0.040	3.35E-04
S[15]	0.826	0.828	0.741	0.898	0.041	3.55E-04
S[16]	0.813	0.815	0.726	0.886	0.042	3.77E-04
S[17]	0.800	0.802	0.709	0.877	0.044	3.86E-04
S[18]	0.786	0.789	0.693	0.867	0.045	4.12E-04
S[19]	0.773	0.775	0.675	0.856	0.046	4.12E-04
S[20]	0.759	0.761	0.660	0.845	0.047	4.27E-04
S[21]	0.745	0.747	0.646	0.833	0.048	4.47E-04
S[22]	0.731	0.733	0.631	0.821	0.049	4.50E-04
S[23]	0.717	0.719	0.613	0.811	0.050	4.68E-04
S[24]	0.703	0.705	0.597	0.798	0.052	4.87E-04
S[25]	0.688	0.690	0.581	0.786	0.052	5.12E-04
S[26]	0.673	0.675	0.564	0.774	0.053	5.15E-04
S[27]	0.658	0.660	0.547	0.762	0.054	5.17E-04
S[28]	0.643	0.644	0.532	0.747	0.055	5.23E-04
S[29]	0.627	0.628	0.515	0.731	0.056	5.41E-04
S[30]	0.607	0.609	0.492	0.715	0.057	5.37E-04
S[31]	0.587	0.589	0.469	0.698	0.059	5.68E-04
S[32]	0.566	0.568	0.446	0.680	0.060	5.89E-04
S[33]	0.544	0.546	0.422	0.661	0.061	6.17E-04
S[34]	0.522	0.523	0.398	0.641	0.063	6.20E-04
S[35]	0.486	0.487	0.352	0.613	0.067	6.71E-04
S[36]	0.437	0.440	0.283	0.577	0.074	7.00E-04
beta	1.226	0.929	0.112	4.036	1.044	3.52E-02

L: 95% Confidence Interval (CI) Lower Bound, U: 95% CI Upper Bound,
SD: Standard Deviation, MC: Monte Carlo

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

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

Parameter	Mean	Median	L	U	SD	MC error
S[1]	0.989	0.992	0.959	1.000	0.011	1.14E-04
S[2]	0.978	0.981	0.939	0.997	0.015	1.63E-04
S[3]	0.966	0.969	0.919	0.993	0.019	2.13E-04
S[4]	0.953	0.957	0.900	0.987	0.023	2.39E-04
S[5]	0.940	0.943	0.880	0.980	0.026	2.84E-04
S[6]	0.927	0.930	0.861	0.973	0.029	3.10E-04
S[7]	0.913	0.916	0.843	0.964	0.031	3.42E-04
S[8]	0.898	0.902	0.825	0.955	0.034	3.64E-04
S[9]	0.883	0.887	0.805	0.944	0.036	3.99E-04
S[10]	0.868	0.871	0.783	0.934	0.039	4.35E-04
S[11]	0.851	0.853	0.762	0.922	0.041	4.57E-04
S[12]	0.833	0.836	0.739	0.910	0.044	5.11E-04
S[13]	0.815	0.818	0.717	0.898	0.047	5.64E-04
S[14]	0.795	0.798	0.690	0.883	0.050	5.66E-04
S[15]	0.774	0.777	0.662	0.867	0.053	6.16E-04
S[16]	0.702	0.711	0.519	0.832	0.081	9.05E-04
beta	1.665	0.575	0.001	9.658	2.762	5.29E-02

L: 95% Confidence Interval (CI) Lower Bound, U: 95% CI Upper Bound,
SD: Standard Deviation, MC: Monte Carlo

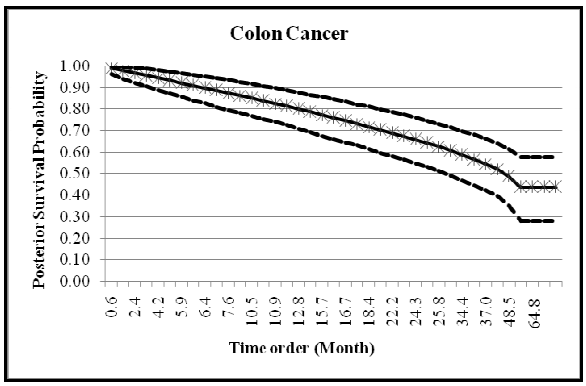

FIGURE 1: Survival curve (cross line) and its 95% confidence interval (dashed line) for patients with colon cancer.

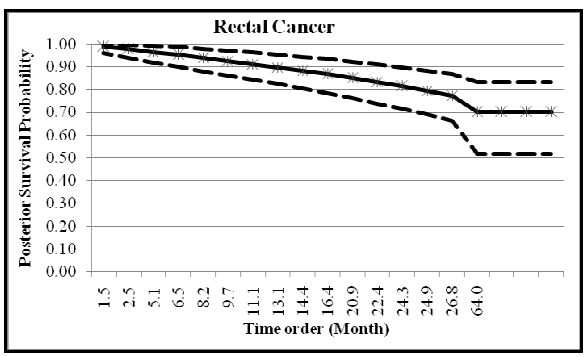

FIGURE 2: Survival curve (cross line) and its 95% confidence interval (dashed line) for patients with rectal cancer.

overall condition of the patients with rectal cancer. Other studies confirm this result in the general patients too,[22-24] But other studies showed the reverse results.[25-29] In addition, there are some arguments too.[30-34] So, there are differences in survival between two sub-sites of colo-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.[35]

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[8,36] 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,[37] 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.[21]

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

frailty terms and their priors. Therefore, by choosing various values for the parameters of priors and in addition by choosing various distributions for frailty terms, finally we found that, the Weibull distribution for frailty term with parameters 1 and beta respectively and by choosing exp(1) as prior distribution, the best value of SD would be resulted for beta. However, there weren't suggestive differences between the parameter estimates of the survival functions in the Weibull and Gamma model presented in the paper.

In this study, Gamma distribution was used as prior, other priors are also recommended.[38] In addition it is suggested to include the effect of the prognostic factor in the analysis.

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[39] and clustered data[37] such as modeling clustered survival data from multicenter clinical trials.[40]

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REFERENCES

1. Klein JP, Bajorunaite R. Inference for competing risks. In: Balakrishnan N, Rao CR, eds. Advances in Survival Analysis, Handbook of Statistics (V. 23). 1st ed. Amsterdam: Elsevier; 2004. p.291-311.
2. Klein JP, Moeschberger ML. Models for Competing Risks. Survival Analysis: Techniques for Censored and Truncated Data. 2nd ed. New York: Springer; 2003. p.50-7.
3. Gail M. A review and critique of some models used in competing risk analysis. Biometrics 1975;31(1):209-22.
4. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. Biometrics 1978;34(4):541-54.
5. Taşdelen B, Erdoğan S, Çağlıkülekçi M, Altun U. [Survival analysis in the presence of competing risks]. Turkiye Klinikleri J Biostat 2009;1(2):33-7.
6. Korn EL, Dorey FJ. Applications of crude incidence curves. Stat Med 1992;11(6):813-29.
7. Peterson AV. Bounds for a joint distribution function with fixed subdistribution functions: Applications to competing risks. Proc Nat Acad Sci 1976;73(1):11-3.
8. Kleinbaum DG, Klein M. Competing Risks Survival Analysis. Survival Analysis: A Self-Learning Text. 2nd ed. New York: Springer; 2005. p. 391-9.
9. Finkelstein M, Esaulova V. On asymptotic failure rates in bivariate frailty competing risks models. Stat Probab Lett 2008;78(5):1174-80.
10. Gasbarra D, Karia SR. Analysis of competing risks by using bayesian smoothing. Scand J Stat 2000;27(4):605-17.
11. Arjas E, Gasbarra D. Nonparametric bayesian inference from right censored survival data, using the Gibbs sampler. Statist Sinica 1994;4(3):505-24.
12. Hjort NL. Nonparametric Bayes estimators based on beta processes in models for life history data. Ann Statist 1990;18(3):1259-94.
13. Wang CP, Ghosh M. Bayesian analysis of bivariate competing risks models. Sankhya. Indian J Stat Ser B 2000;62(3):388-401.
14. Andersen PK, Gill RD. Cox regression model for counting processes: A large sample study. Ann Statist 1982;10(4):1100-20.
15. Clayton DG. A Monte Carlo method for Bayesian inference in frailty models. ometrics. 1991;47(2):467-85.
16. Clayton DG. Bayesian analysis of frailty models. Technical Report. Medical Research Cambridge: Council Biostatistics Unit; 1994.
17. Kalbfleisch JD. Nonparametric Bayesian analysis of survival time data. J Roy Statis Soc Ser B 1978;40(2):214-21.
18. Kalbfleisch JD, Prentice RL. Counting Process Formulas. The Statistical Analysis of Failure Time Data. 2nd ed. New York: John Wiley and Sons; 2002. p. 128-30.
19. Gelman A, Carlin JB, Stern HS, Rubin DB. Bayesian Inference. Bayesian Data Analysis. 2nd ed. Boca Raton, Florida: Chapman & Hall/CRC; 2004. p. 6-9.
20. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian measures of model complexity and fit (with discussion). J Roy Statis Soci Ser B (Statistical Methodology) 2002;64 (4):583-639.
21. Hsu L, Gorfine M, Malone K. On robustness of marginal regression coefficient estimates and hazard functions in multivariate survival analysis of family data when the frailty distribution is mis-specified. Stat Med 2007;26(25):4657-78.
22. Ji BT, Devesa SS, Chow WH, Jin F, Gao YT. Colorectal cancer incidence trends by subsite in urban Shanghai, 1972-1994. Cancer Epidemiol Biomarkers Prev 1998;7(8):661-6.
23. Meguid RA, Slidell MB, Wolfgang CL, Chang DC, Ahuja N. Is there a difference in survival between right- versus left-sided colon cancers? Ann Surg Oncol 2008;15(9):2388-94.
24. Toyoda Y, Nakayama T, Ito Y, Ioka A, Tsukuma H. Trends in colorectal cancer incidence by subsite in Osaka, Japan. Jpn J Clin Oncol 2009;39(3):189-91.
25. Boyle P, Langman JS. ABC of colorectal cancer. BMJ 2000;321(7264):805-8.
26. Gatta G, Faivre J, Capocaccia R, Ponz-deLeon M. Survival of colorectal cancer patients in Europe during the period 1978-1989. Eur J Cancer Prev 1998;34(14):2176-83.
27. Li FY, Lai MD. Colorectal cancer, one entity or three. J Zhejiang Univ Sci B 2009;10(3):219-29.
28. Steinberg SM, Barkin JS, Kaplan RS, Stablein DM. Prognostic indicators of colon tumors. The Gastrointestinal Tumor Study Group experience. Cancer 1986;57(9):1866-70.
29. Xu FY, Zhai MJ, Dong JK, Wang FJ, Jin YS, Zhu YM, et al. Clinical pathological factors function differently in colonic and rectal cancer prognosis J Zhejiang Univ (Medical Science) 2006;3(35):303-10.
30. Berrino F, De Angelis R, Sant M, Rosso S, Bielska-Lasota M, Coebergh JW, Santaquilani M; EUROCARE Working group. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. Lancet Oncol 2007;8(9):773-83.
31. Capocaccia R, Angelis RD, Frova L, Gatta G, Sant M, Micheli A, et al. Estimation and projections of colorectal cancer trends in Italy. Int J Epidemiol 1997;26(5):924-32.
32. Hayne D, Brown RS, McCormack M, Quinn MJ, Payne HA, Babb P. Current trends in colorectal cancer: site, incidence, mortality and survival in England and Wales. Clin Oncol 2001;13(6):448–52.
33. Wilkes G, Hartshorn K. Colon, rectal, and anal cancers. Semin Oncol Nurs 2009;25(1):32-47.
34. Zampinoa MG, Labianca R, Beretta G, Gatta G, Lorrizo K, de-Braud F, et al. Rectal cancer. Crit Rev Oncol Hematol 2004;51(2):121-43.
35. Haidinger G, Waldhoer T, Hackl M, Vutuc C. Survival of patients with colorectal cancer in Austria by sex, age, and stage. Wien Med Wochenschr 2006;156(19-20):549-51.
36. Asghari-Jafarabadi M, Hajizadeh E, Kazemnejad A, Fatemi SR. Site-specific evaluation of prognostic factors on survival in Iranian colorectal cancer patients: a competing risks survival analysis. Asian Pac J Cancer Prev 2009;10(5):815-21.
37. Sahu SK, Dey DK. A comparison of frailty and other models for bivariate survival data. Lifetime Data Anal 2000;6(3):207-28.
38. Datta GS, Ghosh JK. On priors providing frequentist validity for Bayesian inference. Biometrika 1995;82(1):37-45.
39. Cai J, Schaubel DE. Analysis of recurrent event data. In: Balakrishnan N, Rao CR, eds. Advances in Survival Analysis Handbook of Statistics (V. 23). 1st ed. Amsterdam: Elsevier; 2003. p.603-23.
40. Glidden DV, Vittinghoff E. Modelling clustered survival data from multicentre clinical trials. Stat Med 2004;23(3):369-88.