Original Article

State of art the competing risks survival analysis for cancer patients

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Background and aim: In the competing risks problem, the cause-specific hazard rates are usually estimated by considering the independence assumption. However, this assumption may not be fulfilled in various practical situations. This paper addresses the problem of independence assumption in the competing risks survival analysis by including frailty component in the model. The finding was used to analyze the colorectal cancer patients' data.

Methods: The Weibull distribution for competing risks including Gamma frailty was introduced and fitted on colorectal cancer data. The findings showed a substantial adjustment for model accuracy and precision by inserting frailty component, so that both the parameter estimates and their SE's have been adjusted.

Conclusions: The findings may be useful for situations at which the independence assumption of failure times is not satisfied such as competing risks and multicenter clinical trials.

Keywords: Survival; frailty; independence; colon; rectum

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Introduction

In some medical studies, the outcomes may occur by several potential causes. For example, in patients with colorectal cancer (CRC), there are at least two ways a patient would experience death outcome; experiencing death by colon cancer or by rectal cancer. In the simplest form of competing risks problem, there are two latent failure times (say T_1 and T_2) which only one of them [i.e., the minimum failure time (X = min)] could be observed along with an indicator of failure cause (1). Therefore, occurrence the outcome by one cause prevents the other cause(s) or makes them unobservable or un-interpretable (2).

Gail [1975] or Prentice *et al.* [1978] and Taşdelen *et al.* [2009] assessed the history and a variety of procedures for analysis of survival data in the presence of competing risks (3-5). Although the effect size of interest is dependent on the clinical question (6), but in many situations, the main focus is on marginal survival probability or marginal hazard rate for each cause. This means that eliminating or adjusting for other causes, the cause of interest how affects the outcome. For example, by considering the deaths caused by colon cancer, what is the probability of occurring death caused by rectal cancer?

Since there are correlations among outcomes occurring by the causes, marginal survival probability or marginal hazard rate would not be estimable without applying additional assumptions on the correlation structure of the failure times (7). Marginal survival probability or marginal hazard rate are equal to the marginal ones, only when the assumption of independence of failure times is satisfied (2). It is popular (and easier) to estimate cause-specific survival probability or hazard rate for the cause of interest considering as censored the outcomes by other causes. For

example the survival probability or hazard rate for colon cancer is estimated considering the independent of death or censoring in colon and rectal cancer. The results obtained by the analyses which ignore this assumption produce biased estimations (8,9) considering the accuracy and precision of the estimates (10). In the other hand, this assumption can't be checked by data itself and only a sensitivity analysis could be performed (2).

Various ways could be used to relax the problem of independence assumption in the competing risks survival analysis (11). As one of useful procedures, utilizing frailty models taking into account the correlation as a frailty component in the model will do a correction on model (10).

Adjusting the classic competing risks models using frailty

Finkelstein and Esaulova [2008], in addressing the problem of bivariate frailty competing risks model showed that by assuming dependent risks via a bivariate frailty (U_1, U_2), when the components of the system are conditionally on independent U_1 and U_2 are independent, then the mixture failure rate of the system can be constructed by the sum of mixture failure rate of individual components (11).

After applying the findings of Finkelstein and Esaulova [2008], survival times would be independent. In our study, we further use this idea to model competing risks by including frailty terms in the model. We constructed the likelihood function for the data by making use of Gamma frailty and applying the frailty distribution into the likelihood and taking integral with respect to u we have:

$$L_{marg}(\lambda,\rho,\beta|u)=\int_0^{\infty}\prod_{i=1}^{n}\{[h_0(y_i)u\exp(x_i^t\beta)]^{\delta_i}\exp[-H_0(y_i)u\exp(x_i^t\beta)]\}\times\frac{u^{1/\theta-1}\exp(-u/\theta)}{\theta^{1/\theta}\Gamma(1/\theta)}du$$

By taking the logarithm from equation above and summing over *k* competing events, the marginal log likelihood Klein [1992] is as follow (12):

$$l_{marg}(\lambda,\rho,\beta|u)=\sum_{j=1}^{k}\{[d_j\log\theta-\log\Gamma(1/\theta)+\log\Gamma(d_j+1/\theta)]-(d_j+1/\theta)\log(1+\theta\sum_{j=1}^{n_i}[H_0(y_{ij})\exp(x_{ij}^t\beta)])+\sum_{i=1}^{n_j}\delta_{ij}[x_{ij}^t\beta+\log h_0(y_{ij})]\}$$

Based on this function, the effect of covariates was considered in the likelihood function and the parameters of interest were estimated along with their standard error (SE).

Addressing the findings on examples of colorectal cancer data

In this section, the findings of the method are addressed by a real data set on colorectal cancer. The findings have been published elsewhere (10) (and they are used as example here); however a brief introduction is followed.

Data were gathered in cancer registry center of Research Center of Gastroenterology and Liver Disease (RCGLD), Shahid Beheshti Medical University, Tehran, Iran. All patients with CRC diagnosis according to the pathology report of cancer registry were eligible for this study. A total of 1,219 patients [802 (65.8%) with colon cancer, 392 (32.2%) with rectal cancer] were entered in the study. The follow up time was defined as 1st January 2002 (the date of diagnosis) up to the 1st October 2007 as the time of the death from the disease or survival (censoring). Deaths were confirmed through the telephonic contact to relatives of patients.

For all patients, the demographic and clinico-pathological characteristics (*Table 1*), were used in the analysis. Based on site topography of the cancer, colon and rectal cancers were considered as competing risks of death. The hazard of the colon and rectal cancers was computed by the Weibull regression with Gamma frailty to adjustment for the problem of independence assumption. Additionally the Weibull regression model without Gamma frailty was also fitted on the data. All analyses have been conducted using STATA 10 statistical software and a fixed value (=1) for Weibull scale parameter considered.

Results

For colon cancer (*Table 1*), the frailty parameter was significant (parameter estimate =1.65, SE =1.27 and P value =0.033), therefore a significant heterogeneity existed which was caused by the dependence of the two competing risks. Although for rectal cancer (*Table 2*), the frailty parameter wasn't significant (parameter estimate =1.77, SE =2.20 and P value =0.180), however a suggestive effect was observed (0.77 deviates from 1) and this amount substantially affect the parameter estimate and their SE's.

In the second to fourth columns of *Tables 1,2*, the results (including regression coefficients, SE's and P values) of ordinary regression are shown which were based on independence assumption of the survival times of patients

Table 1 Results of Weibull regression models in approaches with and without frailty parameters for colon cancer

Characteristics	Ordinary Weibull model			Weibull model with Gamma frailty		
	B[a]	SE	P value	B[a]	SE	P value
Age at diagnosis (years)						
<45	*	–	–	*	–	–
45-65	–0.12	0.22	0.63	–0.26	0.25	0.44
>65	0.54	0.52	0.07	0.55	0.67	0.16
Gender						
Male	*	–	–	*	–	–
Female	–0.29	0.17	0.21	–0.28	0.23	0.36
Marital status						
Single	*	–	–	*	–	–
Married	–0.58	0.27	0.23	–0.50	0.39	0.44
BMI						
18.6-24.9	*	–	–	*	–	–
<18.5	0.72	0.60	0.01	0.86	0.98	0.04
25-29.9	–1.00	0.11	0.00	–1.17	0.12	0.00
>30	–0.02	0.38	0.96	–0.07	0.46	0.88
Tumor size (mm)						
<20	*	–	–	*	–	–
>20	–0.07	0.25	0.79	–0.03	0.34	0.94
Pathologic stage						
Early	*	–	–	*	–	–
Advanced	0.64	0.43	0.00	0.89	0.79	0.01
Tumor grade						
Well differentiated	*	–	–	*	–	–
Moderately differentiated	–0.45	0.17	0.09	–0.55	0.19	0.09
Poorly differentiated	0.65	0.57	0.03	1.20	1.86	0.03
Weibull shape parameter	1.20	0.10	0.03	1.45	0.21	0.52
Frailty parameter	–	–	–	1.65	1.27	0.033

[a], regression coefficient; *, reference category; SE, standard error; BMI, baby mass index. Reference: (10).

with colon and rectal cancers. This assumption couldn't be checked in this data, so there may be some uncertainty (bias and incorrect SE) in these results. In the following columns of tables, the results of Weibull model with gamma frailty are shown. In this approach, both the parameter estimates and their SE's have been adjusted for model misspecifications.

Conclusions

In this study, the problem of not taking into consideration the independence in competing risks were addressed by using Weibull distribution for competing risks by introducing Gamma frailty in the models. The results were investigated using examples on a colorectal cancer data set. The findings showed a substantial adjustment for model (including regression coefficients and Weibul Shape parameter) by frailty component. The dependency of the risks not only affect the variance of the parameter estimates but also affects the parameter value itself (8). In the frailty approach, both the parameter estimates and their SE's have been adjusted for model misspecifications. Therefore frailty model will adjust model on both aspects of accuracy and precision. This finding may be useful for many situations

Table 2 Results of Weibull regression models in approaches with and without frailty parameters for rectal cancer

Characteristics	Ordinary Weibull model			Weibull model with Gamma frailty		
	B[a]	SE	P value	B[a]	SE	P value
Age at diagnosis (years)						
<45	*	–	–	*	–	–
45-65	0.26	0.44	0.45	0.42	0.68	0.35
>65	0.65	0.84	0.14	0.86	1.34	0.13
Gender						
Male	*	–	–	*	–	–
Female	–0.04	0.30	0.90	0.07	0.43	0.86
Marital status						
Single	*	–	–	*	–	–
Married	–0.28	0.47	0.65	–0.29	0.62	0.73
BMI						
18.6-24.9	*	–	–	*	–	–
<18.5	0.23	0.62	0.63	0.15	0.69	0.79
25-29.9	–0.88	0.15	0.02	–1.03	0.17	0.03
>30	–0.97	0.28	0.19	–1.15	0.27	0.18
Tumor size (mm)						
<20	*	–	–	*	–	–
>20	0.00	0.35	0.99	–0.03	0.42	0.95
Pathologic stage						
Early	*	–	–	*	–	–
Advanced	1.44	1.44	0.00	1.64	2.31	0.00
Tumor grade						
Well differentiated	*	–	–	*	–	–
Moderately differentiated	0.59	0.56	0.06	0.74	0.85	0.07
Poorly differentiated	–0.21	0.51	0.74	–0.13	0.64	0.85
Weibull shape parameter	1.37	0.15	0.00	1.57	0.29	0.02
Frailty parameter	–	–	–	1.77	2.20	0.18

[a], regression coefficient; *, reference category; SE, standard error; BMI, body mass index. Reference: (10).

at which there is uncertainty about or the independence assumption of failure times is not hold, such as competing risks, recurrent events (13), clustered data (14) multicenter clinical trials (15). Like some other studies (14), as one of limitations of this study, only one distribution has been used frailty variable in this study. However, other distributions such as Log-Normal, Log-Logistic, Gompertz and Generalized Gamma are also recommended. Additionally only Gamma distribution has been used for frailty variable which has been suggested as suitable distribution (16). But other distributions could be recommended. Also this framework could be shift and addressed by Bayesian framework (17).

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