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Original Article

An expectation-conditional maximization-based Weibull-Gompertz mixture model for analyzing competing-risks data: Using post-transplant malignancy data

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ABSTRACT

The aim of this study is to introduce a parametric mixture model to analysis the competing-risks data with two types of failure. In mixture context, i^{th} type of failure is i^{th} component. The baseline failure time for the first and second types of failure are modeled as proportional hazard models according to Weibull and Gompertz distributions, respectively. The covariates affect on both the probability of occurrence and the hazards of the failure types. The probability of occurrence is modeled to depend on covariates through the logistic model. The parameters can be estimated by application of the expectation-conditional maximization and Newton-Raphson algorithms. The simulation studies are performed to compare the proposed model with parametric cause-specific and Fine and Gray models. The results show that the proposed parametric mixture method compared with other models provides consistently less biased estimates for low, mildly, moderately, and heavily censored samples. The analysis of post-kidney transplant malignancy data showed that the conclusions obtained from the mixture and other approaches have some different interpretations.

Introduction

Competing-risks data is a field of survival analysis. In competing-risks context, each person can experience one of the several different types of events over the follow-up period. Survival times are defined as the time until occurrence of one competing event that prevents other event from occurring. With competing risks data, the cause-specific hazard measures the instantaneous failure rate due to one risk at a time. It is routinely estimated by constructing the Cox models on cause-specific hazards and treating time to event from the other competing risks as censored with constant hazards (1, 2).

Recently, Lunn and McNeil (3) proposed an augmented data approach to analyze competing-risks data using readily available standard programs for fitting Cox's proportional hazards regression model with censored observations. A comparison of this augmented data approach with Kaplan–Meier methods and the cause-specific hazard approach to estimate the cumulative incidence functions (CIFs) in the

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competing-risks analysis can be found in reference (4).

Fine and Gray (5) proposed a regression modeling applied directly on a CIF for particular use in competing risks analysis which extends the Cox proportional hazards model to competing-risks data by considering the subdistribution hazard (6). For any event type, this approach focuses on the hazard associated with the CIF, which expresses the effect of covariates directly on the CIF. At time t, the CIF defined the probability of having outcome by time t while other participants had experienced other events. The CIF for cause k, not only depends on the hazard of cause k but also on the hazards of all other causes. As opposed to a cause-specific analysis, which would censor the competing event(s), the Fine–Gray approach does not censor them (7, 8). The strength of the association between each predictor variable and the outcome was assessed using the subhazard ratio which is the ratio of hazards associated with the CIF (9), and standard errors of the Fine–Gray model are robust (Huber-White type) and formal check of proportionality by the use of time-varying covariate effect (6).

An alternative analysis of competing-risk data postulates a mixture model that expresses the failure time distribution in terms of the marginal distribution of failure type and the conditional distribution of time to failure, given the type of failure (10).

Suppose that there are *g* distinct types of failure and the observed failure-time vector for j^{th} individual is:

$$y_j = (t_j;\ x^T{}_j;\ d_j)\ (j = 1, \dots, n) \qquad (1)$$

Where, the t_j is the failure time or censoring time for the j^{th} individual, $x^T{}_j$ is a vector of covariates associated with the j^{th} individual, and $d_j = i$ indicates that the j^{th} individual fails due to the i^{th} type of failure and $d_j = 0$ represents a censored observation. In this situation, each individual will fail from one of the g failure types. The survival function of t is modeled as follows:

$$S(t;\ x) = \sum_{i=1}^{g} \pi_i(x) S_i(t;\ x) \qquad (2)$$

Where, $S_i(t;\ x)$ denotes the conditional survival function given failure is due to the i^{th} cause, and $\pi_i(x)$ $(i = 1,\dots,g)$ is the probability of failure from the i^{th} cause or mixing proportions; the $\pi_i(x)$ sum to one. For model 2 factors x influence both the incidence of each cause and failure time among individuals who failed from each cause. Larson and Dinse (11) were among the first to use model 2 to handle competing-risks problems. Some common lifetime distributions according to equation 2 are used for baseline hazard functions in model 2.

$$h_i(t;\ x) = h_{0i}(t)\exp\{x^T \beta_i\} \qquad (i = 1,\dots g) \quad (3)$$

Where, β_i and $h_{0i}(t,\ x)$ are a vector of regression coefficients and baseline hazard functions. For example, Gelfand et al. (12) proposed a continuous baseline hazard in the form of the summation of an arbitrary number of parametric hazards such as the Weibull. Kuk (13) considered a semi-parametric generalization of the parametric mixture model of reference. Moreover, Ng and McLachlan (10) proposed a semiparametric mixture model approach to the analysis of competing-risks data that attention is focused on inference concerning the effects of independent variables on both the probability of occurrence and the hazard rate conditional on each of the failure types.

In this study, we propose an expectation-conditional maximization (ECM)-based parametric mixture method from two distributions Weibull and Gompertz that estimations are based on maximum likelihood of the full likelihood. This model is, therefore, applicable where there are two distinct types of failure that act in a mutually exclusive manner, and the baseline failure time for each cause follows Weibull and Gompertz distributions. The proposed method does not require independent competing risks assumption. In next section, we present the proposed parametric mixture model, where parameters can be estimated by an extension of the EM algorithm that Meng and Rubin (14) termed the ECM algorithm. Then simulation and analysis of a real

dataset performed to compare this model with parametric cause-specific and Fine and Gray models.

Weibull-Gompertz Mixture Model and ECM Algorithm

In mixture context for competing risks, If population is split into 2 (g = 2) components corresponding to each type of failure with the first component as Weibull distribution and second component as Gompertz distribution that both are defined as proportional hazard models,

$$h_1(t,x) = pt^{p-1}\exp(\beta_1^T x) \qquad \theta_1 = (p, \beta_1^T),$$

$$h_2(t,x) = \exp(\mu t)\exp(\beta_2^T x) \qquad \theta_2 = (p, \beta_2^T),$$

then, for observed data y given by equation 1, the log-likelihood function for vector of unknown parameters $\theta = (\alpha^T, \theta_1, \theta_2)$, under the mixture model 2 is as follows:

$$\log L(\theta) = \sum_{j=1}^{n}\left[\sum_{i=1}^{2} I(d_j = i)\log\{\pi_i(x_j;\alpha)f_i(t_j;x_j;\theta)\} + I(d_j = 0)\log S(t_j;x_j;\theta)\right] \quad (4)$$

That $\alpha = (a, b^T)$ is parameter according to mixing proportions that is modeled to depend on x through the logistic model (15).

$$\pi_i(x,\alpha) = 1 - \pi_2(x;\alpha) = \frac{\exp(a+b^T x)}{(1+\exp(a+b^T x)} \quad (5)$$

If belonging to the i^{th} component for censored observation t_j is known then an complete-data is defined with observable vector $z_j = (z_{1j}, , z_{2j})^T$ for each censored observation t_j, where $z_{ij} = 1$ $z_{ij} = 1$ if the j^{th} individual would have failed from cause i (i = 1,2) and the log-likelihood function for complete-data is modified (15) as follows:

$$\log L_c(\theta) = \sum_{j=1}^{n}\left[\sum_{i=1}^{2} I(d_j = i)\log\{\pi_i(x_j;\alpha)f_i(t_j;x_j;\theta_i)\} + \sum_{i=1}^{2} I(d_j = 0)z_{ij}\log\pi_i(x_j;\alpha)S_i(t_j;x_j;\theta_i)\right] \quad (6)$$

But in practice for censored observation t_j, z_j is unknown and is defined as incomplete data (15, 16).

Thus, parameters can be estimated by application of the EM algorithm (16). For this algorithm, Q-function on the $(k + 1)^{th}$ iteration of the E-step is computed as:

$$Q(\theta,\theta^{(k)}) = \sum_{j=1}^{n}\left[\sum_{i=1}^{2} I(d_j = i)\log\{\pi_i(x_j;\alpha)f_i(t_j;x_j;\theta_i)\} + \sum_{i=1}^{2} I(d_j = 0)\tau_{ij}^{(k)}\log\pi_i(x_j;\alpha)S_i(t_j;x_j;\theta_i)\right] \quad (7)$$

Where,

$$\tau_{ij}^{(k)} = \frac{E(z_{ij}|y;\theta^{(k)}) = \pi_i(x_j;\alpha^{(k)})S_i(t_j;x_j;\theta_i^{(k)})}{\sum_{I=1}^{2}\pi_i(x_j;\alpha^{(k)})S_{iI}(t_j;x_j;\theta_i^{(k)})} \quad (8)$$

is the posterior probability that the j^{th} individual with censored survival time t_j would have failed due to cause i (10). By this method, Q-function in equation 7 can be decomposed into:

$$Q(\theta,\theta^{(k)}) = Q_0 + Q_1 + Q_2$$

Where,

$$Q_0 = \sum_{j=1}^{n}\left[\sum_{i=1}^{g} I(d_j = i)\log\pi_i(x_j;\alpha) + I(d_j = 0)\tau_{ij}^{(k)}\log\pi_i(x_j;\alpha)\right] \quad (9)$$

$$Q_1 = \sum_{j=1}^{n}\left[I(d_j = 1)\log f_1(t_j;x_j;\theta_1) + I(d_j = 0)\tau_{1j}^{(k)}\log S_1(t_j;x_j;\theta_1)\right] \quad (10)$$

$$Q_2 = \sum_{j=1}^{n}\left[I(d_j = 2)\log f_2(t_j;x_j;\theta_2) + I(d_j = 0)\tau_{2j}^{(k)}\log S_2(t_j;x_j;\theta_2)\right] \quad (11)$$

and in M-step of the EM algorithm α, θ_1, θ_2 can be updated separately by maximizing Q_0, Q_1, Q_2, respectively.

On differentiation of Q_0 with respect to α_i, it follows that $\alpha^{(k+1)}$ satisfies the equation,

$$\frac{\partial Q_0}{\partial\alpha} = 0 \rightarrow \sum_{j=1}^{n}[I(d_j = 1) + I(d_j = 0)\tau_{ij}^{(k)} - \pi_1(x_j;\alpha)]x_j = 0 \quad (12)$$

and differentiation of Q_1, Q_2 with respect to θ_1, θ_2 and substituting density and survival functions of Weibull and Gompertz for components 1 and 2, respectively $\theta_1^{(k+1)}, \theta_1^{(k+1)}$ satisfies the equations:

$$\frac{\partial Q_1}{\partial \theta_1} = \begin{cases} \frac{\partial Q_1}{\partial p} = 0 \to \sum_{j=1}^{n} \begin{bmatrix} I(d_j = 1)\left\{-t_j^p \ln(t_j)\exp(\beta_1^T x) + \frac{1}{p} + \ln(t_j)\right\} \\ -I(d_j = 0)\tau_{1j}^{(k)}\{t_j^p \ln(t_j)\exp(\beta_1^T x)\} \end{bmatrix} = 0 \\ \frac{\partial Q_1}{\partial \beta_1} = 0 \to \sum_{j=1}^{n} \begin{bmatrix} I(d_j = 1)\{1 = t_j^p \exp(\beta_1^T x)\} \\ -I(d_j = 0)\tau_{1j}^{(k)}\{t_j^p \exp(\beta_1^T x)\} \end{bmatrix} x_j = 0 \end{cases} \quad (13)$$

$$\frac{\partial Q_2}{\partial \theta_2} = \begin{cases} \frac{\partial Q_2}{\partial \mu} = 0 \to \sum_{j=1}^{n} \begin{bmatrix} I(d_j = 2)\left\{t_j - \frac{\{(\mu t_j - 1)EXP(\mu t_j)\exp(\beta_2^T x) + \exp(\beta_2^T x)\}}{\mu^2}\right\} \\ -I(d_j = 0)\tau_{2j}^{(k)}\left\{\frac{\{(\mu t_j - 1)EXP(\mu t_j)\exp(\beta_2^T x) + \exp(\beta_2^T x)\}}{\mu^2}\right\} \end{bmatrix} = 0 \\ \frac{\partial Q_2}{\partial \beta_2} = 0 \to \sum_{j=1}^{n} \begin{bmatrix} I(d_j = 2)\left\{1 = \frac{\{(EXP(\mu t_j) - 1)\exp(\beta_2^T x)\}}{\mu}\right\} \\ -I(d_j = 0)\tau_{2j}^{(k)}\left\{\frac{\{(EXP(\mu t_j) - 1)\exp(\beta_2^T x)\}}{\mu}\right\} \end{bmatrix} = 0 \end{cases} \quad (14)$$

The maximization for θ_1, θ_2 is implemented using ECM approach (14) instead of the EM algorithm that the M-step is replaced by two CM steps. To maximize θ_1, the first calculates $p^{(k+1)}$ by maximization of equation 10 with β_1^I fixed at $\beta_1^{T(k)}$. The second CM step calculates $\beta_1^{T(k+1)}$ by maximization of equation 10 with p fixed at $p^{(k+1)}$. Furthermore, the calculation of θ_2 with maximization of equation 11 is similar to procedure of θ_1. The solution to the second CM-step does not exist in closed form and estimations are computed iteratively by Newton-Raphson algorithm and the standard errors of estimates of the parameters can be computed by deriving the invert the information matrix. The ECM algorithm same to EM algorithm, monotonely increases the likelihood after each iteration (17, 18).

In competing risk data, cumulative incidence curve is an important curve. With mixture approach, the CIF for the first and second components according to 1 and 2 type of failures can be obtained by equations 15 and 16, (10).

$$\pi_1(x_j;\alpha)(1 - S_1(t_j;x_j;\theta_1) = \frac{\exp(a+b^T x)(1\exp\{-\exp(\beta_1^T x)t_j^p\})}{(1+\exp(a+b^T x))} \quad (15)$$

$$\pi_1(x_j;\alpha)(1 - S_2(t_j;x_j;\theta_2) = \frac{\exp(-\exp(\beta_2^T x)\{\exp(\mu t_j)-1\}/\mu)}{(1+\exp(a+b^T x))} \quad (16)$$

That α, θ_1, θ_2 are the maximum likelihood estimates.

A simple and informative way of checking the proportional hazards assumption in the parametric mixture model is provided by plotting $\log(-\log(1-F_i(t)/\pi_i))$ versus time for each level of the variable, where $F_i(t)$ is the estimated CIF, is the estimated final CIF (10). Approximately parallel lines should result to support the proportional hazards assumption for the conditional distributions.

Simulation Experiments

In this section, we present the results of simulation experiments for comparing the proposed parametric method with parametric cause-specific and Fine and Gray models approach. In this simulation, we considered the sample size n = 1000 and two distinct events of failure (g = 2). The covariate x was a continuous variable, which was generated independently from the N(0; 1) distribution. We assume the component-hazard functions $h_i(t; x)$ (i = 1; 2) are Weibull and Gompertz distributions with proportional hazards,

$h_1(t, x) = pt^{p-1} \exp(\beta_{01} + \beta_1 x)$
$h_2(t, x) = \exp(\mu t) \exp(\beta_{02} + \beta_2 x)$

The true parameter values were (β_{01}, β_1, p, β_{02}, β_2, μ = 0.5; −0.5; 1.5; 0.5; 0.5; 0.2). For the parameters in the logistic model 5, we used a = 0.25 and b = 3. Given that an entity belongs to the first component, a sample failure time due to event 1 was generated according to $h_1(t)$ using the inverse transform method. Similarly, for an entity belonging to the second component, a sample failure time due to event 2 was generated according to $h_2(t)$. For each entity, the censoring time was generated from a uniform distribution U(c1; c2), where c1 and c2 are some constants. If the j^{th} failure time were greater than the j^{th} censoring time, it was taken to be censored at this censoring time. In the study, we considered four different sets of values for c1 and c2 so that comparison under different levels of censoring could be investigated. For each simulation set, we generated 100 independent samples and fitted the simulated data using the proposed mixture parametric method. Furthermore, we fitted cause-specific parametric and Fine and

Gray models to the simulated data. Notice that some of parameters in these models cannot be estimated. The average bias, the mean square error (MSE) for parameters are reported in table 1.

From table 1, it can be seen that the proposed parametric mixture method, compared with other models, provides consistently less biased estimates for low, mildly, moderately, and heavily censored samples. The semi-parametric Fine and Gray approach generally has greater bias and MSE, which is to be expected because the true model is a two-component mixture of parametric distributions. In mixture model, with increasing level of censoring, bias and MSE for parameters will increase. It is true except for p parameter of Weibull component that has not monotonic increase. In the proposed model, the most value of bias and MSE, for low, moderately and, in particular, for heavily censored samples, belongs to b of the logistic part.

Analysis of Post-transplant Malignancy Data

Behzad Einollahi et al. conducted a large multicenter study on 12,525 renal recipients, accounting for up to 59% of all kidney transplantation in Iran during 22 years follow-up period since October 1984 up to December 2008. The majority of their patients received a kidney from a living unrelated donor (87.5%), followed by 9.8% and 2.7% of patients who received from living related and deceased donor, respectively. They collected 266 (2%) biopsy-proven post-transplant malignancy cases of 26 different types from 16 transplant centers in Iran (19).

Table 1. Average bias, MSE of estimates from the proposed parametric mixture method, parametric cause-specific and Fine and Gray models

Fine and Gray model		Specific model		Mixture model		Parameter	Average percent censored	Censoring distribution
MSE	Average bias	MSE	Average bias	MSE	Average bias			
		1.0778	-1.0382	0.00010	0.0084	β_{01}	5.77 Low	Uniform (3,8)
1.41658	1.1902	0.90518	0.9514	0.00014	-0.0101	β_1		
		0.0445	-0.2109	0.00002	-0.0023	p		
		1.38104	-1.1752	0.00006	0.0042	β_{02}		
1.75695	-1.3255	0.96749	-0.9836	0.00007	0.0051	β_2		
		0.00264	-0.0513	0	-0.0002	μ		
				0.00009	0.0022	a		
				0.00051	-0.0118	b		
		1.07842	-1.0385	0.00022	0.0135	β_{01}	11.5 Mild	Uniform (2,7)
1.34235	1.1586	0.88945	0.9431	0.00036	-0.0179	β_1		
		0.03797	-0.1948	0.00002	-0.0017	p		
		1.40133	-1.1838	0.00009	0.007	β_{02}		
1.64558	-1.2828	0.97518	-0.9875	0.00014	0.0096	β_2		
		0.00216	-0.0463	0.00001	0.001	μ		
				0.0001	0.0027	a		
				0.00044	0.0075	b		
		1.07884	-1.0387	0.00047	0.0208	β_{01}	21.77	Uniform (1,6)
1.25395	1.1198	0.87069	0.9331	0.00063	-0.0242	β_1	Moderate	
		0.03111	-0.1763	0.00004	-0.0047	p		
		1.42798	-1.195	0.00012	0.008	β_{02}		
1.52498	-1.2349	0.98448	-0.9922	0.0004	0.0184	β_2		
		0.00162	-0.04	0.00004	0.0057	μ		
				0.00009	0.0023	a		
				0.00261	0.0471	b		
		1.05611	-1.0277	0.00168	0.0405	β_{01}	40.98	Uniform (1,3)
1.0496	1.0245	0.81219	0.9012	0.00285	-0.0528	β_1	Heavy	
		0.00979	-0.0987	0.00004	0.0019	p		
		1.46604	-1.2108	0.00068	0.0248	β_{02}		
1.27374	-1.1286	1.00885	-1.0044	0.00265	0.0507	β_2		
		0.00116	-0.0328	0.00023	0.0143	μ		
				0.00018	0.0095	a		
				0.0247	0.1558	b		

MSE: Mean square error

To illustration clarify the proposed parametric mixture method, we considered to assess the incidence of death and chronic graft loss after malignancy as a competing risk data in this patient. We analyzed a subset of these data by considering one risk factor, defined by one categorical variable: type of cancer [Kaposi's sarcoma (KS), Non Kaposi's sarcoma (non-KS), post-transplantation lymphoproliferative disorder (PTLD), genitourinary and reproductive system, solid (GU and RS)] and considered two types of failure as competing risks after malignancy: (i) chronic graft loss and (ii) death with functioning graft.

Chronic graft loss and death were seen, respectively, in 27 (10.2%) and 53 cases (19.9%) and 186 cases (69.9%) accounted as censored. Incidence rate of chronic graft loss was 4.4 per 100 person-years while incidence rate of death with functioning graft was 8.6 per 100 person-years. Thus, incidence rate of death was approximately 2 times higher than the incidence rate of chronic graft loss. Furthermore, distributions of patient survival time and graft survival time after malignancy were near to Gompertz and Weibull distributions, respectively. The proposed mixture parametric approach was adopted, and the result is presented in table 2. For comparison, we also fitted parametric cause-specific and Fine and Gray models. The results are presented in tables 3 and 4, respectively.

Based on the Fine and Gray approach from table 4, we found that type of cancer is a significant risk factors associated with the cumulative incidence of death. Hazard of non-KS cancer is similar to KS cancers but PTLD, GU and RS and solid cancers increase hazard of death versus KS cancers. However, hazard of chronic graft lost is similar to all types of cancer. In this model, type of cancer is not an important factor on the time to develop chronic graft lost. According to table 3, The parametric cause-specific model also indicates that the type of cancer has a significant effect associated with hazard of death similar to Fine and Gray approach. However, hazard of chronic graft lost for PTLD, GU, and RS cancer is similar to KS cancers. Furthermore, non-KS cancers decrease hazard of graft lost versus KS cancers, while solid cancers increase mentioned hazard. However, a drawback of the cause-specific hazard and Fine and Gray approach is that the competing causes of failure are not jointly estimated; that is, a separate model is fitted for each failure cause, treating other failure causes as censored. A factor that has strong influence on the cause-specific hazard function may have no effect on the CIF; Thus, a direct comparison of parameter estimates corresponding to the various failure types is complicated under the cause-specific hazard approach (3-5, 20).

By the mixture approach, we simultaneously estimate the logistic coefficients and the regression coefficients. Thus, the risk factors affecting the incidence of failures and the time to death and chronic graft lost were interpreted.

With the analysis of the post-transplant malignancy data using the proposed ECM-based parametric mixture method, it is found out from table 2 that the non-KS cancer not only increases the probability of chronic graft lost but also prolongs the time to this event but does not have a significant effect on time to death versus KS cancer. The PTLD cancer reduces the probability of chronic graft lost and time to death but does not have a significant effect on time to chronic graft lost versus KS cancer.

Table 2. Maximum likelihood estimates (with standard errors) for ECM-based parametric mixture method

Coefficient	Components		Logistic part
	Death outcome	Chronic graft lost	
Cancer			
KS	Base category	Base category	Base category
Non-KS	0.09 (1.04)	-2.29* (1.03)	1.98* (0.89)
PTLD	1.18* (0.41)	0.41 (0.49)	-1.14* (0.38)
GU and RS	-0.47 (0.50)	2.77* (0.59)	-2.91* (0.56)
Solid	0.32 (0.45)	3.03* (0.55)	-2.81* (0.53)

*P < 0.05. KS: Kaposi's sarcoma, Non-KS: Non Kaposi's sarcoma, PTLD: Post-transplantation lymphoproliferative disorder, GU and RS: Genitourinary and reproductive system, ECM: Expectation-conditional maximization

The GU and RS and solid cancers reduce the probability of chronic graft lost and time to this event but have no significant effect on time to death versus KS cancer. Furthermore, based on parametric mixture method, the most hazards of death and chronic graft lost were related to PTLD and solid tumors, respectively.

Table 3. Maximum likelihood estimates (with standard errors) for parametric cause-specific method

Coefficient	Events	
	Death outcome	Chronic graft lost
Cancer		
KS	Base category	Base category
Non-KS	-1.91 (1.06)	-2.2* (1.05)
PTLD	1.56* (0.41)	0.32 (0.49)
GU and RS	1.51* (0.50)	0.85 (0.6)
Solid	2.25* (0.45)	1.35* (0.56)

*P < 0.05. KS: Kaposi's sarcoma, Non-KS: Non Kaposi's sarcoma, PTLD: Post-transplantation lymphoproliferative disorder, GU and RS: Genitourinary and reproductive system, ECM: Expectation-conditional maximization

Table 4. Maximum likelihood estimates (with standard errors) for Fine and Gray method

Coefficient	Events	
	Death outcome	Chronic graft lost
Cancer		
KS	Base category	Base category
Non-KS	-1.79 (1.05)	-2.04 (1.05)
PTLD	1.45* (0.41)	-0.09 (0.48)
GU and RS	1.33* (0.47)	0.43 (0.57)
Solid	1.93* (0.43)	0.65 (0.54)

*P < 0.05. KS: Kaposi's sarcoma, Non-KS: Non-Kaposi's sarcoma, PTLD: Post-transplantation lymphoproliferative disorder, GU and RS: Genitourinary and reproductive system

From tables 3 and 4, it can be seen that the results obtained by Fine and Gray model and cause-specific parametric lead to similar conclusions on the effect of type of cancer hazard on death but its effect on the time to death and chronic graft lost are different from the result of parametric mixture method.

Discussion

We have proposed an ECM-based parametric mixture method for the regression analysis of competing-risks data. In contrast to Fine and Gray and cause-specific parametric model, the proposed method does not require independent competing risks assumption (10). Estimation is undertaken by maximum likelihood via the ECM algorithm. The proposed estimation procedure via the ECM algorithm is stable and the likelihood is monotonic increasing after each iteration. The mixture model 2 considers the influence of factors on both the probability of occurrence and the hazard rate conditional on each of the failure types using the logistic model and the proportional hazards model. A factor that is important for the probability of occurrence may not be important for the failure risk. In particular, the probability of occurrence for the i^{th} cause is estimated based on the information on the uncensored observations and the posterior probabilities equation 8 of failure for the censored observations. The mixture model 2 allows us to determine the effect of factors on these two quantities simultaneously.

We also performed some simulation studies. It was found that when the true model is a mixture of Weibull and Gompertz distributions, the bias and MSEs of the estimates obtained by the former (Fine and Gray and cause-specific parametric) approach were larger. According to the mixture model, increasing the level of censored, increases bias and MSE. It is exceptional for p parameter of Weibull component that is not monotonic increasing.

Similarly, when it was applied to the real data, mixture model took a longer time to converge. The conclusions obtained from the mixture and other approaches have some different interpretations. The reason may be that mixture method is a parametric model and estimate parameters of components jointly. It may be also because of this fact that competing risks are not independent, which is an essential assumption in formal models of competing risk.

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References

1. Prentice RL, Kalbfleisch JD, Peterson AV,

Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. Biometrics 1978; 34(4): 541-54.
2. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002.
3. Lunn M, McNeil D. Applying Cox regression to competing risks. Biometrics 1995; 51(2): 524-32.
4. Tai BC, Machin D, White I, Gebski V. Competing risks analysis of patients with osteosarcoma: a comparison of four different approaches. Stat Med 2001; 20(5): 661-84.
5. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association 1999; 94(446): 496-509.
6. Pintilie M. Competing risks: a practical perspective. Hoboken, NJ: John Wiley & Sons; 2006.
7. Beyersmann J, Schumacher M. Time-dependent covariates in the proportional subdistribution hazards model for competing risks. Biostat 2008; 9(4): 765-76.
8. Latouche A, Porcher R, Chevret S. A note on including time-dependent covariate in regression model for competing risks data. Biom J 2005; 47(6): 807-14.
9. Grunkemeier GL, Jin R, Eijkemans MJ, Takkenberg JJ. Actual and actuarial probabilities of competing risks: apples and lemons. Ann Thorac Surg 2007; 83(5): 1586-92.
10. Ng SK, McLachlan GJ. An EM-based semi-parametric mixture model approach to the regression analysis of competing-risks data. Stat Med 2003; 22(7): 1097-111.
11. Larson MG, Dinse GE. A mixture model for the regression analysis of competing risks data. Journal of the Royal Statistical Society 1985; 34(3): 201-11.
12. Gelfand AE, Ghosh SK, Christiansen C, Soumerai SB, McLaughlin TJ. Proportional hazards models: a latent competing risk approach. Journal of the Royal Statistical Society 2000; 49(3): 385-97.
13. Kuk AYC. A semiparametric mixture model for the analysis of competing risks data. Australian Journal of Statistics 1992; 34(2): 169-80.
14. Meng XL, Rubin DB. Maximum likelihood estimation via the ECM algorithm: A general framework. Biometrika 1993; 80(2): 267-78.
15. McLachlan G, Peel D. Finite mixture models. Hoboken, NJ: John Wiley & Sons; 2000.
16. Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data via the EM algorithm. Journal of the Royal Statistical Society 1977; 39(1): 1-38.
17. McLachlan G, Krishnan T. The EM algorithm and extensions. Hoboken, NJ: John Wiley & Sons; 1996.
18. Meng XL. On the rate of convergence of the ECM algorithm. Ann Statist 1994; 22(1): 326-39.
19. Einollahi B, Rostami Z, Nourbala MH, Lessan-Pezeshki M, Simforoosh N, Nemati E, et al. Incidence of malignancy after living kidney transplantation: a multicenter study from Iran. J Cancer 2012; 3: 246-56.
20. Fine JP. Analysing competing risks data with transformation models. Journal of the Royal Statistical Society 1999; 61(4): 817-30.