Multilevel joint competing risk models

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Abstract. Joint modeling approaches are often encountered for different outcomes of competing risk time to event and count in many biomedical and epidemiology studies in the presence of cluster effect. Hospital length of stay (LOS) has been the widely used outcome measure in hospital utilization due to the benchmark measurement for measuring multiple terminations such as discharge, transferred, dead and patients who have not completed the event of interest at the follow up period (censored) during hospitalizations. Competing risk models provide a method of addressing such multiple destinations since classical time to event models yield biased results when there are multiple events. In this study, the concept of joint modeling has been applied to the dengue epidemiology in Sri Lanka, 2006-2008 to assess the relationship between different outcomes of LOS and platelet count of dengue patients with the district cluster effect. Two key approaches have been applied to build up the joint scenario. In the first approach, modeling each competing risk separately using the binary logistic model, treating all other events as censored under the multilevel discrete time to event model, while the platelet counts are assumed to follow a lognormal regression model. The second approach is based on the endogeneity effect in the multilevel competing risks and count model. Model parameters were estimated using maximum likelihood based on the Laplace approximation. Moreover, the study reveals that joint modeling approach yield more precise results compared to fitting two separate univariate models, in terms of AIC (Akaike Information Criterion).

1. Introduction

Various types of data, including observational data occurring in a wide variety of fields, particularly in Medicine, Biology, Education and Social Sciences have hierarchical, nested or clustered structure. These types of data hierarchy are neither accidental nor ignorable. But, when analyzing the correlated clustered data, methods of analysis should not rely on the assumption of independence, which is a dominant assumption in traditional statistical approaches. Therefore, lately specific statistical models were developed for correlated clustered data, such as Multilevel Models [1,2]

Competing risk is an extension of classical time to event analysis or survival analysis, when individuals are under risk of failing from multiple events [3]. A key assumption of a classical time to event analysis is that, an event of interest will eventually occur in all individuals in the population (Kaplan-Meier assumption), this is violated in the presence of multiple events/ competing event data [4,5]. Thus, numerous modeling methodologies [3,4,5] are available for handling competing risk events. Also, interest increasingly has been paid to the competing risk in the presence of cluster effects since individuals may be correlated within clusters in many applications of competing risks, owing to

unobserved shared factors across individuals [6]. These data are referred to as "correlated clustered competing risks" or "multilevel competing risk". Multilevel competing risk can be modeled explicitly by using either a discrete time or continuous time competing risk hazard model due to the type of duration response. However, this analysis was focused towards discrete time hazard approach which is reviewed by Steele, Goldstein and Browne [7].

Various researchers have concentrated only on a single response although, many studies measured several/multiple responses for each individual, due to the complexity. Joint association is more complex for multilevel competing risk data, because it consists not only with multiple events, but also two correlations, between measurements on different variables for each cluster and between measurements on different individuals/subjects within a cluster [8]. The main approach undertaken here is the joint modeling of discrete time multilevel competing risk with count variable which is normally distributed after log transformation. i.e. joint association with competing risk response with continuous response. Another joint application arises with the endogeneity effect in the model. Typically endogeneity occurs when the outcome response is correlated with independent variables [9]. i.e. independent/explanatory variable is correlated with error term [10] in the model. As a second approach in this paper,a joint relationship was built through the endogeneity effect in the multilevel competing risk data.

The methodological development is motivated by a study of dengue epidemiology in Sri Lanka, 2006-2008 to assess the relationship between hospital length of Stay (LOS) (competing risk event variable), which is the outcome measurement in hospital utilization with different terminations such as discharge, transferred, dead and censored observations, and log of platelet count (continuous variable).

A comprehensive literature review was carried out which revealed the way to formulate the methodology for joint modelling of competing risk with continuous responses to the clustered data settings. When the responses are from various families of distributions, this leads to difficulties in formulating the joint distribution of those responses due to the lack of natural multivariate scenario. Joint modelling of competing risk is a highly active research area with longitudinal, repeated measurement responses. When focusing on the joint longitudinal with competing risk which is the well-known joint modelling for competing risk, many researchers [11,12,13,14] presented two marginal sub models; mixed effect sub models for the longitudinal measurement and cause specific sub model or latent failure time model [11,14] to allow for competing risk data to construct the joint structure.. The difference in this study when compared to past literature is here competing risks are modelled via discrete time hazard models with the correlated structure at the first approach. When reviewing the second approach, endogeniety effect which has been recognized several years ago in the econometric field among econometricians [15,16] have been used in here. The study of simultaneous equation method which allow endogeneity,has been extended to the multilevel models recently with the help of panel data theory since panel data and multilevel data bear some similarity [17]. But the work carried out here is novel since no such study was found in the literature where the joint modelling of multilevel discrete time competing risk data and a continuous variable was carried out through simultaneous equation method by allowing for the endogeneity effect.

2. Methodology

In this study, the authors were interested in setting up joint association between a multilevel competing risk response with multilevel continuous response. Deriving a joint distribution with the responses from different families of distributions leads to difficulties since competing risks with a survival variable with multiple events and censored observations is very different from a continuous/ normally distributed variable.

2.1. Model 1: Joint model: Multilevel discrete time competing risk hazard and multilevel normal regression

The first approach is to consider procedures for handling the joint model via two linked sub models: multilevel discrete time competing risk model and multilevel normal regression. Here normality of the second variable was achieved by applying a log transformation to the count variable. The connection

between the two responses is modeled through the association between random effects. Joint modeling was carried out via PROC GLIMMIX procedure in SAS 9.4 based on the Laplace approximation of the Maximum Likelihood Estimation.

Although the duration can be modeled explicitly either discrete time or continuous time hazard model, discrete time competing risk model was used as a proposed method to handle multiple events due to the flexibility of software. In the traditional approach to the competing risks, where the occurrence of events of interest removes the individuals from the risk of other events and each event is analyzed separately treating all other events as censored known as a binary logit model in discrete time has been proposed in here as a one sub model. A multilevel normal distribution is fitted after log transformation as the other sub model. PROC GLIMMIX procedure in SAS allows to estimate two sub marginal models jointly.

Suppose that duration are measured in discrete time intervals indexed by *t* (t=1….,T). for each discrete time interval *t* of cluster *i* for the j^{th} individuals, two responses are observed as; $Y_{1tij}^{(r)}$; binary outcome which denote whether an event has occur during the interval *t* or not for the j^{th} individual in i^{th} cluster; and second response as $Y_{2tij}^{(r)}$(log of count variable); normally distributed outcome in the time interval *t* for the j^{th} individual in i^{th} cluster for the *r* event type. Structural formulation of the model is given by,

$$Y_{1tij}^{(r)} = \begin{cases} 1\,; if\ event\ of\ type\ r\ in\ t \\ 0; if\ no\ event\ of\ type\ r\ in\ t \end{cases} ; \text{where, r} = 1,2,\dots.,\text{R} \quad (1)$$

The hazard of an event of type r in interval *t*, denoted by $h_{tij}^{(r)}$, is the probability that an event of type *r* occurs in interval *t*, given that no event of any type has occurred before the start of interval *t*. Estimate equation for each event type in multilevel discrete time competing risk model using a "logit" link function. This can be written as [7],

$$log\left(\frac{h_{tij}^{(r)}}{1-h_{tij}^{(r)}}\right) = \beta_{0j}^{(r)} + \sum_{t=1}^{t} \alpha_t^{(r)} D_{tij}^{(r)} + \beta_1^{\prime(r)} X_{tij}^{(r)} \quad (2)$$

$$\beta_{0j}^{(r)} = \beta_0^{(r)} + u_{0j}^{(r)} \quad ; where\ \left(u_{0j}^{(1)}, u_{0j}^{(2)}, \dots\dots\dots, u_{oj}^{(r)}\right) \sim \text{Multivariate Normal} \quad (3)$$

From, (2) & (3),

$$log\left(\frac{h_{tij}^{(r)}}{1-h_{tij}^{(r)}}\right) = \beta_0^{(r)} + \sum_{t=1}^{t} \alpha_t^{(r)} D_{tij}^{(r)} + \beta_1^{\prime(r)} X_{tij}^{(r)} + u_{0j}^{(r)} \quad (4)$$

And multilevel continuous sub model can be written as,

$$Y_{2tij}^{(r)} = \beta_{1j}^{(r)} + \beta_2^{\prime(r)} X_{tij}^{(r)} + \varepsilon_{ij}^{(r)} \quad (5)$$

$$\beta_{1j}^{(r)} = \beta_1^{(r)} + u_{0j}^{(r)} \quad ; where\ \left(u_{0j}^{(1)}, u_{0j}^{(2)}, \dots\dots\dots, u_{oj}^{(r)}\right) \sim \text{Multivariate Normal} \quad (6)$$

From (5) and (6),

$$Y_{2tij}^{(r)} = \beta_1^{(r)} + \beta_2^{\prime(r)} X_{tij}^{(r)} + \varepsilon_{ij}^{(r)} + u_{0j}^{(r)} \quad (7)$$

Where,

$\beta_0^{(r)}$, $\beta_1^{(r)}$– fixed intercept for the event type r,
$u_{0j}^{(r)}$ – random effects for the clusters for the event type r, $u_{0j}^{(r)} \sim N(0, \sigma^2_u)$,
$D_{tij}^{(r)}$ – Indicators for the time interval,
$\beta_0^{(r)}$, $\beta_1^{(r)}$– fixed intercept for the event type r
$\alpha_t^{(r)}$ – coefficient of the indicators for the time intervals
$\varepsilon_{ij}^{(r)}$ – random error for the individual.
$\beta'^{(r)}_1$, $\beta'^{(r)}_2$ – Fixed coefficients of the covariates/factors,
$X_{ij}^{(r)}$ – Covariates/factors

As per the model methodology given above, two sub models of competing risk and continuous variable are jointly linked separately for each and every event types *(r*=1,2,3,……,R). For simplicity, we assume that both random effects for the clusters ($u_{0j}^{(r)}$) are same and both variance (σ_u^2) are the same for the event type *r* [18,19]. In GLIMMIX procedure the structure of the variance matrix of $Y^{(r)} = (Y_{1tij}^{(r)}, Y_{2tij}^{(r)})$ as.

$$Var\left(Y^{(r)}\right) = A^{1/2} R\, A^{1/2}$$

Where, R –user specified 2 x 2 covariance matrix since two responses, A – Diagonal matrix of the variance of ($Y_{1tij}^{(r)}$, $Y_{2tij}^{(r)}$).

2.2. Model 2: Simultaneous Equation Model (SEM)

Simultaneity is an observable reason for the endogeneity of explanatory / independent variables. i.e. one or more explanatory variables are jointly associated with the dependent variable. These models are known as Simultaneous Equations Models (SEM). Also simultaneously determined variables, frequently have an equilibrium.

We can extend earlier (4) & (7) equations into a SEM as,

$$log\left(\frac{h_{tij}^{(r)}}{1-h_{tij}^{(r)}}\right) = \beta_0^{(r)} + \sum_{t=1}^{t} \alpha_t^{(r)} D_{tij}^{(r)} + \beta_1'^{(r)} X_{tij}^{(r)} + \gamma Y_{2tij}^{(r)} + u_{0j}^{(r)} \quad (8)$$

$$Y_{2tij}^{(r)} = \beta_1^{(r)} + \beta'^{(r)}_2 X_{tij}^{(r)} + \varepsilon_{ij}^{(r)} + u_{1j}^{(r)} \quad (9)$$

Where,γ – Coefficient of the covariate, $Y_{2tij}^{(r)}$

When endogeneity arises, the right hand side of (8) consists with $Y_{2tij}^{(r)}$ since $Y_{1tij}^{(r)}$ and $Y_{2tij}^{(r)}$ are jointly associated with each other. Here, $Y_{2tij}^{(r)}$ is known as the endogenous variable. Although both random effects for the clusters of two sub models are same in the standard joint multilevel scenario, random effects for the clusters, $u_{0j}^{(r)}$and $u_{1j}^{(r)}$ are not the same in SEM. It relies that, endogeniety of $Y_{2tij}^{(r)}$will lead $to\ corr(u_{0j}^{(r)}, u_{1j}^{(r)}) \neq 0$. In general, we assume that,$(u_{0j}^{(r)}, u_{1j}^{(r)}) \sim bivariate\ normal$. The suggested method is illustrated from SAS 9.2.

3. Analysis, Results and Discussion

The methodological development is illustrated by a study of Dengue patients reported in Sri Lanka in the period 2006 – 2008 within 10 districts (recorded as high incidence districts in the period from 2006-2008) The district is considered as a cluster effect. The variables that had been identified from the previous univariate studies without cluster effect by [20,21] , were used in this study by adding cluster levels' variables. Length of stay (LOS) is a duration variable which can be categorized in to three categories; 0-4 days-febrile phase, 4-6 days-critical phase and 6-10 days-recovery phase, according to the clinical course of dengue patients [22].Therefore the individuals/dengue patients were studied only within 10 days. The response, duration/LOS consists with multiple destination *r* which is equal to zero if the observation is censored, 1 if the individual is discharged, 2 if the individual transferred into another hospital and 3 if the individual dies in the hospital. So, LOS was used as a competing risk variable and other response was log of platelet count (Continuous) since there is a relationship in between LOS of dengue patients with platelet count [21,23].

Initially, data must be expanded to obtain discrete type multilevel competing risk response. Restructuring is carried out as follows (Table 1 and Table 2). Two records of individuals with 4 predefined time interval data record are taken here as an example. According to the Table 1 and Table 2, each and every individual had to be recorded for each time interval up to the time interval which is related to that individual.

Table 1 : Initial Data set example.

Individual	Duration/Time	Time Interval	Type of event	Covariate
1	5	2	2	20
2	11	4	0	35

Restructure

Table 2: Restructured Data set example.

Individual	Time Interval	Type of event	Covariate
1	1	0	20
1	2	2	20
2	1	0	35
2	2	0	35
2	3	0	35
2	4	0	35

According to the duration classification in this study, there are 4 predefined interval for 0-4, 4-6, 6-10 and >10 and 3 indicator variables (T1, T2 and T3) were used for the analysis.Two univariate model and a joint model were fitted for the two responses to compare the joint model with the univariate models in each and every approach. The Akaike Information Criteria (AIC) was used for model comparison.

Initially, all the explanatory variables were introduced to the model and the most insignificant variables were removed step by step. The parameter estimates of the obtained final joint models for the two different approaches are shown in Table 3 and Table 4. Due to the space limitation, estimated parameters for the event types: discharge and dead, are only shown in here. The same procedure can be applied for the transfer event also.

Table 3: Estimated Parameter for the model 1 & Model 2 for the Discharge Event.

Model 1				Model 2			
Competing risk		Log_platelet		Competing risk		Log_platelet	
Variable	Estimate (P value)	Variable	Estimate (P value)	Variable	Estimate (P value)	Variable	Estimate (P value)
Intercept	-2.7470 (<0.001)	Intercept	4.7171 (<0.001)	Intercept	-0.5188 (0.001)	Intercept	4.7359 (<0.001)
T1	3.0594 (<0.001)	Age	-0.0029 (<0.001)	Log_platelet	0.1684 (<0.001)	Age	-0.0026 (<0.001)
T2	3.0787 (<0.001)	Sex_male	0.04475 (<0.001)	T1	5.9568 (0.0324)	Sex_male	0.04098 (<0.001)
T3	3.8047 (<0.001)	Classificatio n_DF	0.1325 (<0.001)	T2	0.2076 (<0.001)	Classificatio n_DF	0.0977 (<0.001)
Age	0..00419 (0.006)	Classificatio n_DHF1	0.08629 (<0.001)	T3	0.4669 (0.1023)	Classificatio n_DHF1	0.0662 (<0.001)
Sex_male	0.09175 (0.029)	Rainfall	0.00001 (<0.001))	Age	0.02051 (0.002)	Placetreated _goverment	0.05136 (<0.001)
Classificatio n_DF	0.4089 (<0.001)			Sex_male	0.0489 (0.025)	Placetreated _private	-0.1224 (<0.001)
Classificatio n_DHF1	0.2911 (0.0008)			Classificatio n_DF	0.1025 (<0.001)		
Rainfall	0.00028 (0.0112)			Classificatio n_DHF1	0.1285 (0.002)		
				Rainfall	0.000179 (0.015)		

Table 4: Estimated Parameter for the model 1 & Model 2 for the Dead Event.

Model 1				Model 2			
Competing risk		Log_platelet		Competing risk		Log_platelet	
Variable	Estimate (P value)	Variable	Estimate (P value)	Variable	Estimate (P value)	Variable	Estimate (P value)
intercept	-3.1369 (0.059)	intercept	4.3785 (<0.001)	Intercept	-0.6389 (0.125)	intercept	4.3255 (<0.001)
T1	0.0532 (0.055)	Log_WBC	0.029 (0.0134)	Log_platelet	-1.5704 (0.125)	Log_WBC	0.0006 (0.1896)
T2	0.0424 (0.014)	Age	0.0028 (<0.001)	T1	3.3062 (0.052)	Age	0.0026 (<0.001)
T3	0.1611 (0.010)	Sex_male	-0.0433 (<0.001)	T2	0.0775 (0.025)	Sex_male	-0.0262 (<0.001)
Age	0.0088 (0.054)	Classification_ DF	0.1466 (<0.001)	T3	0.0128 (0.0154)	Classification_ DF	0.1547 (0.0021)
		Classification_ DHF1	0.1213 (<0.001)	Age	0.0057 (0.102)	Classification_ DHF1	0.1388 (<0.001)
		PCV	0.0017 (<0.001)			PCV	0.0012 (0.0011)

Table 5: Covariance parameter estimates.

		discharge	Dead
Model 1	Covariance (competing risk, log_platelet)	0.04912	0.05216
	Residual	0.0193	0.09094
Model 2	Covariance (competing risk, log_platelet)	0.00164	0.056
	Residual	0.09025	0.0911

According to the Table 3 and Table 4, significant variables differ in competing risks and log_platelet. A single covariate, namely, classification will be interpreted here since it can be classified as a risk variable. The rest of the covariates in the model can be similarly interpreted. The results from the model 1 for the discharge event, the odds of discharging a patient with DF is 1.12 (exp 0.4089) times the odds of discharging a patient with DHF2, while the platelet count is higher among the patients who were with DF by an amount 1.35 (10^0.1325) than those had DHF2 for the discharge patients. The Wald test statistics (p=0. 7824) for the model 2 indicated that null hypothesis can not be rejected. Thefore, exogeniety exist in the model. So, model 2 procedure can be applied to these data. When focusing on model 2 for both events; discharge and dead, showed that the direction of the estimated effects remains the same as the model 1. The odds of discharging a patient with DF is 1.108 times higher than the patient who were with DHF2, while the platelet count is higher in DF patients than the patients who were with DHF2 when the endogeneity effect exist in the model. When comparing model 1 and model 2, model 2 estimates' value (Table 3 and Table 4) are lower than model 1.

Table 5 showed that, covariance for the competing event and log_plateletis 0.04 in model 1 and random effect for the individual is 0.09 in model 1. When comparing model 1 with model 2, model 2 covariance is lower than model 1 in discharge event. Also, residual variance is similar in both models. The results for the dead event can be interpreted in the same way.

This example was mainly drawn for illustrating the methodology for the joint modelling of competing risks and continuous variable which was expected to provide improved performances rather than two univariate models. Therefore, finally fitted joint model was compared with the univariate models by the Akaike Information Criteria (AIC). The fitted model for the discharge event, shows that AIC for the joint model 1 is 21816.85 and joint model 2 is 20528, while the two univariate models had an AIC of 13674.39 for competing risk model and 9394.91 for log_platelet model, which resulted 23069.3 (13674.39 +9394.91). AIC of both joint models (model 1 and model 2) is smaller than the total AIC's of the two univariate models, suggested that joint model is more efficient than two univariate models. The results obtained from the dead event also tallies with these results.

4. Conclusion

The main objective of the study was to formulate joint models for the competing risk and count (continuous variable) with the effect of cluster. The methodology was developed by fitting two sub marginal models; multilevel discrete time competing risk and multilevel normal models, with and without exogeneity effect. The results proved that the joint models are better than the two univariate models that can be fitted separately for the two responses. Also, it was emphasized that simultaneous equation model gives better performance among two joint models, while the directions of the estimated parameters remains same in both joint models.

Extension to the study can be suggested to build up a joint relation of competing risk model with continuous or discrete type with another response for a correlated clustered data.

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