Published in final edited form as:

Stat Methods Appl. 2016 June ; 25(2): 251–267. doi:10.1007/s10260-015-0302-2.

Joint Modeling of Covariates and Censoring Process Assuming Non-Constant Dropout Hazard

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Abstract

In this manuscript we propose a novel approach for the analysis of longitudinal data that have informative dropout. We jointly model the slopes of covariates of interest and the censoring process for which we assume a survival model with logistic non-constant dropout hazard in a likelihood function that is integrated over the random effects. Maximization of the marginal likelihood function results in acquiring maximum likelihood estimates for the population slopes and empirical Bayes estimates for the individual slopes that are predicted using Gaussian quadrature. Our simulation study results indicated that the performance of this model is superior in terms of accuracy and validity of the estimates compared to other models such as logistic non-constant hazard censoring model that does not include covariates, logistic constant censoring model with covariates, bootstrapping approach as well as mixed models. Sensitivity analyses for the dropout hazard and non-Gaussian errors were also undertaken to assess robustness of the proposed approach to such violations. Our model was illustrated using a cohort of renal transplant patients with estimated glomerular filtration rate as the outcome of interest.

Keywords

Censoring; discrete survival model; informative dropout; longitudinal data; non-constant hazard; random effects; maximum likelihood estimation

1. Introduction

Graft rejection is a major complication after renal transplantation that results in reverting back transplanted patients to renal replacement therapy in the form of dialysis (Nankivell and Alexander 2010). Thus, close monitoring of renal function over time after renal transplantation is essential so that complications as such could be detected. Measuring the

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Conflict of interest: None declared.

changes in renal function over time is more predictive of patient's long-term graft function (Kasiske, et al 2001). Estimated glomerular filtration rate (eGFR) is the distinct marker used to assess kidney function and progression to kidney failure. Despite its significance, few studies have looked at the eGFR changes expressed by slope and allograft survival (Wu, et al 2010). Thus, monitoring changes of eGFR levels over time is more informative of the progression of renal disease than just observing eGFR values on their own. Fluctuation in eGFR levels is usually gauged in terms of the rate of change over time referred to as slope estimation. However, when patients experience graft rejection, eGFR levels can no longer be measured since patients in this case go back on dialysis and are dropped out of the study. This complication results in informative dropout which is a special type of non-ignorably missing data that eventuates in studies where the dropout probability and early termination depend on the subject's true rate of change of the measured outcome pertaining to the censored individual (Wu and Bailey 1988, 1989).

Recent studies that examined the relationship between slope of eGFR and trends in renal function relied on the ordinary least squares (OLS) estimates for the slopes; thus disregarding the presence of informative dropout and treating it as being non-informative (Wu et al 2010). Such an assumption results in biased estimates and inaccurate inferences; hence, proper methods of analysis should be conducted to account for this type of dropout (Schluchter 1992).

Different approaches have been proposed to analyze longitudinal data with informative dropout. This includes the shared parameter models that entail linking and modeling both the outcome and the missing process by assuming a random effect model for the outcome and treating the random effect as a covariate. The shared parameter models encompass approaches such as the one proposed by Wu and Carroll (1988), Wu and Bailey (1988) and Follmann and Wu (1995). The approximate sample selection (Manning et al 1987) was a class of models that addressed the problem of informative missingness but are known to be computationally intensive and difficult to implement (Follman and Wu 1995). A two-part model that accommodates for the longitudinal studies has been described in Horrocks and Heuvel (2009). However, two-part models could generate biased estimates since the error in the estimation of the random effects is not accounted for (Wang et al 2000). Fitting the full model and maximizing the full likelihood function is a favorable approach compared to other approaches such as the two-part models (Fieuws and Verbeke 2006). Joint modeling and fitting the full model was considered as an approach for estimation that adjusts for informative dropout under the assumption that the dropout hazard is constant over time (Mori et al 1994). A recent study conducted by Jaffa et al. (2012) presented a likelihood based approach in which censoring was modeled as logistic constant hazard that accounted for covariate effects. The constant dropout hazard assumption is not frequently encountered in most clinical settings. For instance, the deterioration of renal function after kidney transplant is known to be at its highest risk during the first 12 months post-transplantation since this period represents the early adaptation phase to the renal allograft after transplantation (Seron et al 2005). A likelihood based model that assumed a non-constant hazard without covariate effects in a bivariate setting was proposed by Jaffa et al (2011). The repeated measures for every individual subject were reduced to the naïve ordinary least square estimates (OLS) that assume that these observations are not correlated.

The challenge has been in having a model that accounts for both assumptions of non-constant hazard and covariate effects that consequently results in an increase in the number of parameters to be estimated. In the present study we have developed a likelihood based model in which we accounted for both assumptions concurrently. The novelty and key feature of this approach reside in modeling changes in an outcome over time with varying probability of censoring and incorporating covariate effects intuitively in the censoring process in addition to overcoming the computational complexity of generating estimates for the large number of parameters.

The clinical motivation behind this manuscript was driven by the fact that a significant decline in eGFR is the final common pathway leading to chronic renal failure. Once eGFR is impaired or decreased, progression to renal failure or end stage renal disease occurs at an increased rate (Tonelli et al, 2011). Although the level of eGFR is known to be modulated by a number of covariates or risk factors such as age, gender, and race (Derose et al., 2013; Douville et al, 2009; Kramer et al, 2003; Yokoyama et al, 2009; Yokoyama et al, 2009;), the nature of these risk factors are not yet fully determined (Yokoyama et al, 2009). Therefore, assessing the risk factors that contribute to the decline in eGFR, is of high clinical significance.

In the current manuscript we aimed to address this key clinical issue by proposing a new model that generates accurate and unbiased estimates that determine the effects of targeted risk factors on eGFR levels. Repeated measures of eGFR were taken longitudinally until the patient experienced the clinical outcome of graft rejection/graft failure which is considered the end result of kidney function. Knowledge that renal failure occurred provides the information that eGFR level decreased to negligible levels since last measurement was obtained. While our proposed model accounts for this information, other naïve approaches such as those that are based on Ordinary Least Squared (OLS) ignore it and evaluate the rate of eGFR change only up to the last available measurement. Thus, naïve approaches ignore the information that renal failure occurred and result in biased estimates and inaccurate inferences (Schluchter 1992). Therefore, our objective was to model and estimate the rate of change of eGFR used as a measure of risk for graft failure over time for the population and individual subjects following renal transplantation and to identify the risk factors that can impact the decline in eGFR levels accounting for patients' informative dropout.

2. The Model

Consider a set of $i=1, \dots, n$ independent subjects, with outcome y_{ik} measured at $k=(t_{i1}, t_{i2}, \dots, t_{im_i})$ where the time points $(t_{i1}, t_{i2}, \dots, t_{im_i})$ are the actual times of measurement and are assumed to be prespecified and not occurring in a random fashion. The number of visits m_i for subject i is assumed to be greater than or equal to 2 for all subjects in the study so that individual slopes can be estimated. Specifically the number of visits should be in the range of $2 \leq m_i \leq p$ where p represents the number of prespecified time points that are assumed to be not necessarily equally spaced. Hence, the underlying distribution for the number of observations is left truncated and subjects that have less than two observations are excluded from the study. The data is assumed to follow a monotone missing pattern, wherein the subjects are observed until they drop out from the study and will no longer be followed, and

hence no further measurements will be recorded on these patients for the duration of the study.

The underlying model for y_{ik} is assumed to be

$$y_{ik} = \alpha_i + \beta_i t_{ik} + e_{ik}, \quad (1)$$

with random effects α_i and β_i and random error e_{ik} which is assumed to be normal with mean zero and variance σ_e^2 . The outcome y_{ik} is assumed to be normally distributed and could therefore accommodate negative values. Transformation could be applied to normalize the outcome only when not normal. Even in this case, we were able to show that the impact on the estimates is minimal when the outcome is not normal (Table 3). Hence the transformation that ensures positive values such as log transformation is not necessary.

Given that interest is in slope estimation we summarize the observations for every individual using generalized least square estimates. Moreover, patients who undergo kidney transplantation are those with kidney failure and are on dialysis, hence eGFR levels at baseline prior to transplantation are meaningless and could be discarded. In this regard, Kaplan Meier survival analysis confirmed that there is no significant difference in survival between the group of patients whose baseline pre-transplant eGFR levels is less than 15 ml/min/1.73 m² and those who are above this cutoff point (P-value = 0.5). The first group refers to the patients with kidney failure while the latter corresponds to those who have severe to mild kidney damage prior to transplantation (Perazella and Reilly 2003). Failure to capture a significant difference in survival between the two groups of patients indicates that the pre-transplant baseline eGFR levels do not affect kidney function post-transplantation.

Accordingly, for each individual subject the following model was assumed:

$$1) \quad \beta_i \sim Normal \left(\theta_0 + \sum_{j=1}^z \theta_j X_{ij}, \sigma_\beta^2 \right); \quad (2)$$

Based on this assumption, the underlying individual subjects' slopes β_i are normally distributed with a mean $\theta_0 + \theta_1 X_i$ that is a function of the various covariates X_i .

Conditional on the individual slopes β_i the number of observations m_i for every individual subject is assumed to have a discrete non-constant hazard model that is a function of the individual slopes β_i and is defined as follows

$$m_i | \beta_i \sim \text{Discrete censoring distribution with} \\ Pr(M=m_i | \beta_i) = h_{im_i}^{R_i} \prod_{k=1}^{m_i-2} (1 - h_{ik}) \quad (3)$$

where h_{ik} is the discrete hazard that indicates the probability of dropping out in interval k given that i^{th} individual is still in the study as in the previous interval. The indicator variable

$R_j = 0$ if the subject was seen at the last follow-up time and $R_j = 1$ if the subject dropped out of the study at or before the last follow-up time point. Hence the censoring model is right truncated since the study may terminate before observing the withdrawal of every subject from the study. Right truncation is taken care of by R_i which when equals to zero indicates that the study has terminated and the i^{th} subject was still enrolled in the study. Moreover, according to assumption 1, β_i 's are based on covariate effects X_i 's; hence, intuitively the censoring process is also determined by these covariates and has the following logistic model

$$\log it(h_{ik}) = \gamma_k + \gamma_1 \beta_i \quad \text{that is} \quad h_{ik} = \frac{\exp(\gamma_k + \gamma_1 \beta_i)}{1 + \exp(\gamma_k + \gamma_1 \beta_i)} \quad (4)$$

The $k = m_i - 2$ censoring parameters are denoted as γ_k . If γ_1 is different than zero, then this indicates that the censoring process is informative and if it equals to zero then this indicates a non-informative censoring.

Given the individual slope β_i and the number of observations m_i for every subject, the GLS estimates for individual subjects $b_{i, GLS}$ ($i = 1, 2, \dots, n$) follow a normal distribution with mean β_i and variance $\sigma_{b_i}^2$ (assumption 3).

$$3) \quad b_{i, GLS} | m_i, \beta_i \sim \text{Normal} \left(\beta_i, \sigma_{b_i}^2 \right). \quad (5)$$

The GLS estimates $b_{i, GLS}$ and the variances $\sigma_{b_i}^2$ and σ_ε^2 were estimated using SAS proc MIXED.

The likelihood function corresponding to this model can be described as follows:

$$\begin{aligned} L &= \prod_{i=1}^n f(\beta_i, m_i, b_{i, GLS}) = \prod_{i=1}^n f(b_{i, GLS} | m_i, \beta_i)^* f(m_i, \beta_i) \Rightarrow \\ L &= \prod_{i=1}^n f(\beta_i) f(m_i | \beta_i) f(b_{i, GLS} | m_i, \beta_i) \end{aligned} \quad (6)$$

Given that β_i is not observed so it is considered as the random effect and the likelihood function is integrated over it to get a marginal likelihood that has the following form

$$\begin{aligned}
L &= L(\theta_0, \theta_1, \gamma_k, \gamma_1) = \prod_{i=1}^n f f(m_i, b_{i, GLS}) f(\beta_i) d\beta_i = \prod_{i=1}^n f f(\beta_i) f(m_i | \beta_i) f(b_{i, GLS} | \beta_i, m_i) d\beta_i \\
&= \prod_{i=1}^n \int \frac{1}{\sqrt{2\pi}\sigma_\beta} \exp \left\{ -\frac{1}{2} \left(\frac{\beta_i - \left(\theta_0 + \sum_{j=1}^z \theta_j X_{ij} \right)}{\sigma_\beta} \right)^2 \right\} * h_{im_i}^{R_i} \prod_{k=1}^{m_i-2} (1 - h_{ik}) * \frac{1}{\sqrt{2\pi}\sigma_{b_i}} \exp \left\{ -\frac{1}{2} \left(\frac{b_{i, GLS} - \beta_i}{\sigma_{b_i}} \right)^2 \right\} d\beta_i
\end{aligned}
\tag{7}$$

A direct maximization of the marginal likelihood generates the maximum likelihood estimate (MLE) of the intercept θ_0 and the population slopes θ_j that correspond to the various z covariates, in addition to the consistent estimates of the other parameters of interest $(\gamma_k, \gamma_1, \sigma_\beta^2)$. Specifically, the likelihood function was maximized using the Gaussian quadrature tools embedded in SAS Proc NLMIXED (Littell et al 2006). The likelihood function integrated over the random effect was defined in this procedure and maximized by the “model general” option. Empirical Bayes estimates for the individual slopes β_i were predicted using the adaptive Gaussian quadrature described in Pinheiro and Bates (1995). The quasi-Newton optimization algorithm (Fletcher 1987) was utilized as a method of obtaining the MLEs for the model's parameters of interest. An outline of the algorithm that was implemented to obtain the empirical Bayes estimates for the individual slopes using the Gaussian quadrature is presented in Appendix A.

3. Cohort of renal transplant patients with eGFR measurements

The motivating example behind this study was centered on determining the progression of renal disease over time following renal transplantation in a cohort of patients who underwent kidney transplantation in the year 2000 at the Medical University of South Carolina (MUSC). Demographical information and clinical measures were collected on 110 renal transplant patients, with a mean age of 43.34 years divided between 46 female recipients (42%) and 64 male recipients representing 58% of the total sample size. There were 47 (43%) Caucasian recipients, 60 (55%) African-Americans, 2 Asians and 1 Hispanic. Regarding the donors characteristics, 80 (73%) donors were Caucasians, 24 (22%) were African-Americans, and 6 Hispanics. With respect to the gender distribution and vital status of the donors, 72 donors were males (65%), and 38 (35%) were females; 21 (19%) were living donors and 89 (81%) were deceased.

The degree of matching between donors and recipients was considered in terms of gender and race. In this context, 41 male patients received kidneys from male donors; while 23 male recipients had female donors. Regarding the female recipients, 15 female patients received kidneys from female donors; while 31 female recipients had male donors. In terms of matching in race, 62 recipients had the same race as their donors. Specifically, for Caucasian recipients, 42 of them had Caucasian donors; while 4 had African-American donors, and 1

had Hispanic donor. Regarding African-American recipients, 19 of them had African-American donors; 38 had Caucasian donors, and 3 had Hispanic donors.

Repeated measures of the patients' eGFR levels were recorded over time as a marker to assess kidney function. The normal range of eGFR varies from 90 to 120 ml/min/1.73m² and reduction in eGFR levels is indicative of reduced renal function and potential risk for graft rejection. Levels of eGFR were calculated using the 4-variable equation of the Modification of Diet in Renal Disease (MDRD) study that depends on serum creatinine, age and gender (Levy et al 1999). Specifically eGFR is computed as follows:

$$\text{Glomerular filtration rate} = 186.3 \times [\text{creatinine (mg/dl)}]^{-1.154} \times [\text{age (years)}]^{-0.203} \times 0.742 (\text{if female}) \times 1.212 (\text{if African-American})$$

(8)

These patients were followed for 3 years post renal transplant and repeated measures of eGFR were computed at baseline pre-transplant (month 0), and at 1, 3, 6, 12, 24 and 36 months post-transplantation. Measurements of eGFR levels were available at these time points until the patient experiences renal failure and hence drops out from the study and reverts back to dialysis. About 18% of the patients experienced graft rejection related dropout that resulted in informative dropout and had therefore incomplete measurements of eGFR levels.

The dropout hazard in interval k knowing that the patient was still enrolled in the study before or at interval k was not constant. Specifically, the probability of dropping out between follow-up months 3 and 6 was 2.8%, months 6 and 12 was 2.88%, months 12 and 24 was 7.92%, and months 24 and 36 was 4.32%. Here we realize that patients were at the highest risk of graft rejection between months 6 and 12 following transplantation. This result is in concordance with previous findings that demonstrated that the highest risk of graft rejection arises in the first year post-transplant (Seron et al 2005). Given that the dropout probability is not constant over time, a non-constant hazard approach should be employed to better model the censoring process for this cohort of renal transplant patients. Univariate Cox proportional hazard analysis performed on this cohort showed that the slope estimates of eGFR are significantly associated with censoring ($P\text{-value} < 0.0001$) indicating that the censoring mechanism is related to the slopes of eGFR. Thus, eGFR is the study variable that impacts the hazard of kidney failure and the individual's early termination from the study and hence triggers the problem of informative dropout.

The mean value for eGFR in the cohort of renal transplant patients is 43.95 ml/min/1.73m². The estimated slope corresponding to eGFR over time is 1.4 ($P\text{-value} < 0.0001$) indicating that as time increases by 1 month, eGFR increases by 1.4 ml/min/1.73m². Moreover, to assess the effect of eGFR on time-to-event that is time-to-graft rejection in our renal transplant dataset we implemented a hierarchical random-intercepts and hierarchical random-intercepts and slopes models. Our results suggested that eGFR is significantly

associated with time-to-graft rejection (P-value = 0.0005) and indicated that as eGFR levels increases by 1 ml/min/1.73m² the time-to-graft rejection increases by 0.0628 months. Along the same lines the hierarchical random-intercepts and slopes model showed that eGFR was also significantly associated with time-to-graft rejection (P-value = 0.0008) and that the time-to-graft rejection was increased by 0.0849 months for every 1 ml/min/1.73m² increase in eGFR levels. Hence both models suggested that eGFR has a significant effect on time-to-graft failure. Moreover, we applied a cure rate model on this dataset to assess the predictive ability of eGFR on cure and hazard rates. The cure rate model had a survival model of the form $S(t) = \pi + (1 - \pi)S^*(t)$ where π is the cure rate and $S^*(t)$ is the survival function that generates survival probabilities for non-cured. The effect of eGFR on the cure rate and the survival of the non-cures was assessed assuming exponential model for survival and was found to be significantly associated with both. The parameter estimate of eGFR corresponding to the cure rate was 0.44 (P-value ≤ 0.0001) and to the hazard among the non-cures was -0.014 (P-value = 0.0037). This result reinforces once again that eGFR is associated with renal failure.

The proposed logistic non-constant hazard censoring model was applied on this cohort of patients with eGFR being the outcome of interest measured on a logarithmic scale to achieve normality. Various covariates that are known to affect renal function after renal transplantation were incorporated in the model in a univariate and multivariable manner and their corresponding slope estimates were generated. Covariates of interest included gender, race, age, and matching between donors and recipients on race and gender.

Our estimated slopes generated under the univariate analysis for the various covariates are presented in Table 1. Our results suggest that being a female recipient increases the eGFR levels by 1.25 ml/min/1.73m² compared to males. Hence female recipients appear to have better kidney function since the higher the eGFR the better the kidney function. Caucasian recipients also appear to have better kidney function in comparison to African-Americans with an increase of 2.25 ml/min/1.73m² in eGFR levels. Moreover, the younger the recipient the higher the eGFR levels the better the kidney function. Specifically a recipient who is one year younger appears to have an increase by 1.01 ml/min/1.73m² in eGFR levels; moreover, recipients who are below the age of 35 years have an increased eGFR level of 1.2 ml/min/1.73m² compared to those who are 35 years old and above. Our results were all of statistical significance (P-value < 0.05) and were primarily relevant to the recipients' characteristics. The donors' characteristics are also shown to be significantly impacting the eGFR levels of the recipients and hence their kidney function and likelihood to graft rejection. For instance, recipients of kidneys from Caucasian donors appear to have increased level of eGFR by about 1.7 ml/min/1.73m² compared to those whose donors were African-Americans. The same was observed for male donors wherein an increase by about 2.61 ml/min/1.73m² in eGFR levels was observed for recipients of kidneys from male donors versus female donors. Last but not least the donors' vital status also appear to influence eGFR levels with an observed increase of eGFR levels by about 1.24 ml/min/1.73m² for recipients of kidneys from alive donors versus deceased donors. Again the donors characteristic are shown to be significantly impacting the eGFR levels and kidney function for their respective recipients (P-values < 0.05). To sum up, recipients and donors characteristics are significantly affecting eGFR levels and therefore the censoring process and graft-rejection drop out hazard appear

to be directly affected by these determinants. The degree of matching between recipients and donors determined by factors such as having donors and recipients of same gender and race is shown to significantly impact the eGFR levels. In this context recipients of kidneys from the same race have increased eGFR levels of 2.56 ml/min/1.73m² compared to those who received kidneys from donors of different races. Female recipients of kidneys from female donors and male recipients of kidneys from male donors appeared to experience an increase in their eGFR levels (1.15 and 2.36 ml/min/1.73m² respectively) compared to those with opposite gender. Caucasians experience a significant increase in eGFR levels of 1.22 ml/min/1.73m² when they receive kidneys from donors of the same race. Nonetheless, the opposite was observed for African-Americans who appear to have a decrease of 1.49 ml/min/1.73m² in their eGFR levels when they receive kidneys from African-American donors. Hence, Caucasian donors are shown to have better kidney function outcome on their recipients irrespective of their race. All these characteristics are significantly affecting the changes in eGFR levels (P-value < 0.05) indicating that the dropout hazard is also determined by the degree of matching between donors and recipients. As for the multivariable analysis we assessed the effects of recipients gender, race, age below 35 years versus above this cutoff point, and donors' vital signs collectively in one model, donors race and gender in a different model, and degree of matching determined by having same race and gender between donors and recipients in a separate model. These determinants should not all be considered together in the same model since intuitively such a collective inclusion of correlated determinants will result in collinearity. Accordingly we included within the same model factors that do not exhibit any collinearity and this resulted in the three models described earlier. Our multivariable analysis suggested that recipients' gender, race, age and donors vital signs are all significantly associated with eGFR levels (P-values < 0.0001) with an increase of 1.1 ml/min/1.73m² for females recipients compared to males

$(\hat{\theta}_{Female_Recipients}=0.075, SE=0.015)$, similar increase for Caucasian recipients versus non-Caucasians $(\hat{\theta}_{Caucasian_Recipients}=0.078, SE=0.014)$ and alive donors compared to deceased $(\hat{\theta}_{Alive_Donors}=0.090, SE=0.018)$. Similarly, an increase of 1.25 ml/min/1.73m² was shown for recipients who are younger than the age of 35 years compared to those of that age or

older $(\hat{\theta}_{Recipients_Age<35\ years}=0.221, SE=0.019)$. Hence being a Caucasian female with age less than 35 years and recipient of kidney from an alive donor are protective factors for kidney function. In the second model, the generated estimates demonstrated that male and Caucasian donors were both significantly associated with eGFR levels (P-values < 0.0001) with an observed respective increase of 1.25 ml/min/1.73m²

$(\hat{\theta}_{Male_Donors}=0.221, SE=0.017)$ for male donors and 2 ml/min/1.73m²

$(\hat{\theta}_{Caucasian_Donors}=0.655, SE=0.047)$ for Caucasian donors. Accordingly, recipients of kidneys from a Caucasian male donor appear to have a better kidney function compared to other recipients whose donors are non-Caucasian females. Results of the third multivariable model suggested that recipients of kidneys from donors of same gender and race exhibit an increase in eGFR levels of 1.4 and 1.2 ml/min/1.73m² respectively compared to those recipients whose donors were of different gender and race

$$\left(\hat{\theta}_{Same_Gender}=0.349, SE=0.022; \hat{\theta}_{Same_Race}=0.164, SE=0.017; P-value<0.0001\right).$$

Hence recipients of kidneys from donors of the same gender and race appeared to have better kidney function than those whose donors are of different gender and race. For comparative purposes, we have also analyzed the renal transplant data using the naïve OLS multivariable approach similarly to the multivariable application of our proposed model on this cohort of patients. A significant difference in the results between the two approaches was noted. Specifically, unlike the results of our model, under OLS only male donors appeared to be significantly associated with eGFR while all other determinants considered earlier did not have any significant association. This discrepancy in the results is anticipated since in contrast to our proposed model, the naïve model does not account for the inter-observation correlation pertaining to the same subject and does not model the dropout process. Hence, it discards the longitudinal nature of the data and the informative dropout problem and results in inaccurate inferences (Schluchter 1992). The OLS slope estimates are reported as Supplementary Data.

The accuracy of the estimates generated under the logistic non-constant hazard censoring model was comprehensively evaluated in the simulation study described in the following section.

4. Simulation Study

A simulation study was conducted to assess the accuracy of the estimates generated under the proposed model in comparison to less complex models such as the logistic non-constant hazard without covariates in which we assume that $\beta_r \sim \text{Normal}(\beta, \sigma_\beta^2)$; and that of constant hazard with covariates described in Jaffa et al. (2012). Furthermore, a comparison was also carried out between the estimates generated under this model and the ones generated using the bootstrap technique as well as those generated using mixed models. The bootstrap technique was employed using resampling on the same individual in order to account for the correlation among the observations. Datasets each of size 200 were simulated and 2000 repetitions were conducted using parameter values generated from the renal transplant application and described in Tables 2 and 3. The accuracy of the estimates was assessed using bias, mean squared errors for the population slopes that we denote as MSE(a) and mean squared errors for the individual slopes referred to as MSE(b). Precisely MSE(a) and MSE(b) were computed respectively as follows:

$$MSE(a) = \frac{1}{r} \sum_{s=1}^r (\hat{\beta}_s - \beta)^2 \quad (9)$$

$$\text{and } MSE(b) = \frac{1}{nr} \sum_{s=1}^r \sum_{i=1}^n (\hat{\beta}_{is} - \beta_{is})^2 \quad (10)$$

Different levels of censoring ranging from non-informative with $\gamma_1 = 0$, low-level censoring with $\gamma_1 = 2.3$, mid-level censoring with $\gamma_1 = 4.3$ and high level censoring with $\gamma_1 = 6.2$ were all incorporated in the simulation study to assess the performance of the different approaches at the various levels of censoring.

In this simulation study we also aimed at assessing the robustness of the non-constant hazard model to the violation of the non-constant hazard assumption. In this regard, we conducted a sensitivity analysis wherein the model with the constant hazard and covariate effect was assumed to be the correct model and data were simulated under this new assumption. The robustness of the non-constant hazard model was then assessed using the newly simulated data to determine the impact of violating the non-constant hazard assumption on the model's performance. Bias and MSEs that are associated with the non-constant and constant hazard models using the newly simulated datasets are listed in Table 2 columns 6 and 7 respectively.

Moreover, a sensitivity analysis that investigates the scenarios of Gaussian errors versus Non-Gaussian errors with lognormal distribution was also conducted in our simulation study. The purpose of this sensitivity analysis is to ascertain whether violation of the normality assumption affects the performance of the proposed model and to identify the approach that is less robust to such violation. The results of our study are presented in Tables 2 and 3 respectively.

In the Gaussian errors setting (Table 2) when the dataset were simulated under the non-constant hazard model we realize that this model (Table 2, column 1) had the smallest bias and MSEs across all levels of censoring in comparison to all other approaches. For instance, compared to the model with constant hazard and covariates (Table 2, column 2), the proposed model exhibited an average reduction in bias, MSEa and MSEb of 50, 71, and 10 percent respectively. Moreover, the proposed model had an average decrease in bias, MSEa and MSEb of 70, 75, and 17 percent respectively compared to the model with non-constant hazard and no covariates (Table 2, column 3). An average decrease in bias, and MSEa of 92 and 86 percent were observed under the proposed model in comparison to mixed models. Similarly, an average decrease of 91 and 80 percent were exhibited by the proposed model versus the bootstrap approach.

Our sensitivity analysis indicated that when the non-constant hazard assumption was violated and data in reality exhibited a constant hazard dropout pattern, an increase in bias and MSE was detected under the non-constant hazard model compared to the constant hazard one. Specifically, the estimates generated under the non-constant hazard model (Table 2, column 6) had an increase of 1.3 to 4.1 fold in bias, 3 to 4.4 fold in MSEa, and 1.3 fold in MSEb compared to the estimates of the constant hazard model (Table 2, column 7). In addition, the estimates of the non-constant hazard model generated when datasets were simulated under the constant hazard assumption (Table 2, column 6) had higher bias and MSEs compared to those generated under the correct assumption of non-constant hazard datasets and model (Table 2, column 1). Specifically, the detected increase was 1.5 to 3.4 fold in bias, 3 to 4 fold in MSEa, and 1.2 fold in MSEb. Results of this sensitivity analysis confirm that inaccurate modeling and assumptions of the dropout hazard result in some loss of accuracy in the estimates.

Under the Non-Gaussian errors (Table 3), all approaches were minimally impacted with a minor increase in bias and MSEs compared to when the normality assumption was satisfied. The proposed model continued to have better performance compared to all other approaches. In this context the proposed model had a decreased bias of 54%, and MSEs of 42% in comparison to the other models of constant hazard with covariates, and non-constant hazard without covariates. Compared to the mixed model and bootstrap approach our model had an average decrease in bias and MSEa of 88 and 82% respectively. Accordingly, accounting for non-constant hazard and covariates in the same model results in valid estimates with minimal bias and MSEs at the different levels of censoring and under normal and non-normal data.

To assess the accuracy of eGFR as a predictor for graft rejection a simulation study with 2000 replications was conducted using the hierarchical random-intercepts and random-intercepts and slopes models. Our simulation results indicated that the bias and MSE for the slope estimate for time-to-graft failure associated with eGFR were minimal (0.000916 and 0.000213 respectively). As for the hierarchical random-intercepts-slopes model, the associated bias and MSE were 0.0014 and 0.00057. Results from both models suggested that eGFR is an accurate and unbiased predictor for time-to-graft failure.

5. Discussion

In this study we propose a new approach to estimate individual and population slopes that are adjusted for informative dropout. We assumed the survival logistic model with non-constant dropout hazard and incorporated covariate effects on the censoring process. This setting is widely encountered in clinical situations where the hazard of developing certain complications is high at the initial phase following intervention but this risk subsides with time. Moreover, censoring in most cases is not just a function of time but is also influenced by other factors. A typical example of this clinical setting is organ transplantation where the risk of graft rejection determined by a decline in eGFR to negligible levels is relatively high following transplantation then reduces with time. Moreover, eGFR levels and accordingly hazard of graft rejection are always determined by the patients' characteristics and the degree of matching between donors and recipients. The eGFR formula is based on age, gender, and race and the model describes the effect of these same covariates on the eGFR pattern. While identifiability has not been an issue computationally, this fact should be kept in mind in the interpretation of the covariate effects. Even though this work focuses on renal failure as a censoring event, the scope of the model is more general as it describes both the effect of risk factors on eGFR and its relationship with the renal failure event.

It is worthy to highlight here that the censoring process could also be easily simplified into constant hazard. This simplification can be accomplished using a geometric model or other distributions that are suitable for the clinical problem being investigated (Jaffa, Lipsitz and Woolson, 2011).

Our simulation results suggested superiority of the proposed model over the bootstrap technique, the mixed models and other models with non-constant hazard and no covariates as well as that with constant hazard and covariates. Sensitivity analysis was conducted on

the proposed model with non-constant hazard wherein we simulated data under the assumption of constant hazard and then applied these datasets on the proposed model with non-constant hazard. Our new results suggested that mis-specification of the dropout hazard results in an increase in bias and MSEs. Accordingly precise specification of the dropout hazard increases the accuracy of the estimates. Moreover, our simulation results also showed the robustness of the models to the violation of normality assumption which is in line with what has been suggested in earlier studies that examined the robustness of the mixed models with non-Gaussian errors (Jacqmin-Gadda et al 2006, Zhang and Davidian 2001). Although it adjusts for informative censoring, our model also demonstrated that it can generate accurate results compared to the mixed model and bootstrap approach when censoring is non-informative. The rationale behind this superiority in performance is due to the over-parameterization in the model specification when censoring is non-informative. Another potential source of non-normality could be the slope itself. It is intuitive here to note that whether the violation of normality assumption originated from the errors or the slope, similar conclusions will be reached. In this context we conducted a simulation study whereby we considered non-Gaussian slopes with lognormal distribution at a level of censoring of 6.2. This simulation study generated similar results in terms of bias and mean squared errors in comparison to the non-Gaussian lognormal error model (bias=-0.00985, MSEa=0.000782 and MSEb=0.0239).

In summary, we are proposing here a novel approach based on a joint modeling of the slopes and the censoring process that are all incorporated in the same likelihood function the maximization of which is feasible and efficiently implementable. This was consistently demonstrated by its successful convergence that resulted in accurate estimates of the slopes under different contexts and settings. Future direction for this research work is adding another level of complexity by extending this model to multivariate settings with correlated longitudinal outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

This work was supported by National Institutes of Health Grants HL077192 and HL087986

Appendix A: Algorithm for empirical Bayes estimates using Gaussian Quadrature

Assume that we have an observed vector of data y_i for each i subjects, $i=1, \dots, s$. Let be the u_i vectors of latent random-effect. Assume that y_i and u_i are linked by a model that leads to the joint probability density function

$$p(y_i | X_i, \phi, u_i) q(u_i | \xi)$$

where X_i is a matrix of observed explanatory variables and ϕ and ξ are vectors of unknown parameters. Let $\theta = [\phi, \xi]$ and assume that it is of dimension n . A quadrature method approximates a given integral by a weighted sum over predefined abscissas for the random effects. Adaptive Gaussian quadrature for the integral over u_i centers the integral at the empirical Bayes estimates of u_i defined as the vector $\hat{u}_i$ that minimizes $-\log[p(y_i | X_i, \phi, u_i) q(u_i | \xi)]$ with ϕ and ξ set equal to their current estimates. The final Hessian matrix from this optimization can be used to scale the quadrature abscissas. Let $(z_j, w_j, j=1, \dots, p)$ denote the standard Gauss-Hermite abscissas and weights which can be obtained from Golub and Welsch (1969). The adaptive Gaussian quadrature integral approximation will have the following form:

$$\int p(y_i | X_i, \phi, u_i) q(u_i | \xi) du_i \approx 2^{r/2} |\Gamma(X_i, \theta)|^{-1/2} \sum_{j_1=1}^p \dots \sum_{j_r=1}^p \left[p(y_i | X_i, \phi, a_{j_1, \dots, j_r}) q(a_{j_1, \dots, j_r} | \xi) \prod_{k=1}^r w_{j_k} \exp z_{j_k}^2 \right]$$

Where r is the dimension of u_i , $\Gamma(X_i, \theta)$ is the Hessian matrix from the empirical Bayes minimization, $z_{j_1, \dots, j_r}$ is a vector with elements $(z_{j_1}, \dots, z_{j_r})$ and

$$a_{j_1, \dots, j_r} = \hat{u}_i + 2^{1/2} \Gamma(X_i, \theta)^{-1/2} z_{j_1, \dots, j_r}$$

The number of quadrature points p is adaptively selected by evaluating the log-likelihood function at the starting values of the parameters until two successive evaluations have a relative difference that is less than a specific defined value. We also tried the nonadaptive Gaussian quadrature whereby the grid of abscissas is centered on zero rather than $\hat{u}_i$ and very close estimates to the adaptive version were obtained.

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Table 1

Estimated univariate population slope* corresponding to the covariates: 1) patient's gender, 2) patient's race, 3) patient's age, 4) patients age in years 5) donor's race, 6) donor's gender, 7) donor's vital status (alive/deceased), 8) same donor-patient race vs. different donor-patient race, 9) male donor-patient vs. male donor-female patient 10) female donor-patient vs. female donor-male patient, 11) Caucasian donors-Caucasian patients vs. Caucasian donors-African-American patients, and 12) African-American Donors and patients vs. African-American donors-Caucasian patients.

Recipients/donors characteristics	N [‡]	$\hat{\theta}_1^*$	SE	P-value
Female Recipients	46	0.223	0.0195	<0.0001
Caucasian Recipients	47	0.812	0.014	<0.0001
Recipients age < 35years	32	0.154	0.0265	<0.0001
Recipients age (in years)	110	-0.006	0.0003	<0.0001
Caucasian Donors	80	0.478	0.0298	<0.0001
Male Donors	72	0.956	0.0103	<0.0001
Alive Donors	21	0.287	0.0274	0.0001
Same Race Donors- Recipients	62	0.938	0.0531	<0.0001
Male Donors-Male Recipients	41	0.857	0.0592	<0.0001
Female Donors-Female Recipients	15	0.143	0.042	0.0016
Caucasian Donors-Caucasian Recipients	42	0.197	0.008	<0.0001
African-American Donors and Recipients	19	-0.399	0.008	<0.0001

N[‡] indicates the number of subjects in the corresponding category.

Table 2

Binary covariate with $\pi=0.5$ and datasets were simulated with Gaussian errors assuming:

		a) Non-Constant Hazard					b) Constant Hazard [±]	
		Non-Constant Hazard with Covariates	Constant Hazard with Covariates	Non-Constant Hazard without Covariates	Mixed	Bootstrap	Non-Constant Hazard with Covariates	Constant Hazard with Covariates
$\gamma_1=0$	Bias	-0.006347	-0.0089157	-0.012922	-0.055106	-0.049683	-0.009515	-0.006571
	MSEa	0.0008305	0.0024722	0.00303	0.005138	0.003498	0.0027766	0.0008148
	MSEb	0.019667	0.021647	0.02406	---	---	0.0237	0.019269
$\gamma_1=2.3$	Bias	-0.005318	-0.007303	-0.013854	-0.05559	-0.050535	-0.007417	-0.005901
	MSEa	0.0006239	0.002557	0.0027056	0.0053262	0.003096	0.002313	0.000618
	MSEb	0.020721	0.022701	0.025114	---	---	0.0242661	0.01965
$\gamma_1=4.3$	Bias	-0.0024471	-0.0081487	-0.012605	-0.056009	-0.050457	-0.0082274	-0.0020197
	MSEa	0.00077705	0.0025493	0.0031217	0.0045466	0.003154	0.0022620	0.000769
	MSEb	0.02188	0.02397	0.025898	---	---	0.025206	0.019802
$\gamma_1=6.2$	Bias	-0.002929	-0.007929	-0.01623	-0.0565	-0.0506	-0.0085138	-0.003084
	MSEa	0.00074016	0.002562	0.003198	0.005938	0.0043311	0.0030519	0.0006964
	MSEb	0.022135	0.02505	0.026442	---	---	0.0269295	0.023057

$\gamma_{01}=-5.413$, $\gamma_{02}=-4.9799$, $\gamma_{03}=-4.6499$, $\gamma_{04}=-3.3212$, $\gamma_{05}=-3.7862$, $\sigma\beta=0.07$, $\beta_0=-0.0517$, $\beta_1=0.0517$, $\sigma_e=0.346$, $\alpha_0=3.238^{\pm}$, $\beta_0=-0.005$, $\beta_1=0.052$, $\gamma_0=-3.46$

Table 3

Binary covariate with $\pi=0.5$ and datasets were simulated assuming non-constant hazard with Non-Gaussian errors

		Non-Constant Hazard with Covariates	Constant Hazard with Covariates	Non-Constant Hazard without Covariates	Mixed	Bootstrap
$\gamma_1=0$	Bias	-0.008878	-0.0123	-0.019229	-0.055217	-0.049792
	MSEa	0.000907	0.00248	0.00305	0.005583	0.004035
	MSEb	0.020682	0.022768	0.025469	---	---
$\gamma_1=2.3$	Bias	-0.005874	-0.00977	-0.015155	-0.055622	-0.050972
	MSEa	0.000768	0.002602	0.003092	0.00613	0.0040862
	MSEb	0.021541	0.024098	0.026576	---	---
$\gamma_1=4.3$	Bias	-0.004879	-0.011243	-0.016739	-0.056112	-0.05069
	MSEa	0.0007807	0.002573	0.003139	0.006696	0.0038556
	MSEb	0.02274	0.02522	0.027162	---	---
$\gamma_1=6.2$	Bias	-0.0054989	-0.011129	-0.017221	-0.056590	-0.050827
	MSEa	0.001326	0.002562	0.003205	0.0062807	0.005344
	MSEb	0.024065	0.028642	0.030057	---	---

$\gamma_{01}=-5.413$, $\gamma_{02}=-4.9799$, $\gamma_{03}=-4.6499$, $\gamma_{04}=-3.3212$, $\gamma_{05}=-3.7862$, $\sigma\beta=0.07$, $\beta_0=-0.0517$, $\beta_1=0.0517$, $\sigma_e=0.346$, $\alpha_0=3.238$