SEMIPARAMETRIC TRANSFORMATION MODELS FOR COMPETING RISKS DATA WITH CURE FRACTION

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Abstract. We propose a new method for the analysis of competing risks data with long term survivors. The proposed method enables us to estimate the overall survival probability and cure fraction simultaneously. We formulate the effect of covariates on cumulative incidence functions using linear transformation models. Estimating equations based on counting process are developed to estimate regression coefficients. The asymptotic properties of the estimators are studied using martingale theory. An extensive Monte Carlo simulation study is carried out to assess the finite sample performance of the proposed estimators. Finally, we illustrate our method using a real data set.

Key words: Competing risks; Counting process; Cure rate model; Martingale.

1. Introduction

Competing risks emerge naturally in lifetime data analysis when the subjects under study are at risks for more than one cause of failure. For example, consider a study of patients suffering from heart disease. The patients may die due to other causes like an accident or other diseases, which may alter the probability of death due to heart disease. The cause specific hazard and cumulative incidence functions are commonly employed for the analysis of competing risks data. For a comprehensive review on this topic, one may refer to Crowder (1997), Kalbfleisch and Prentice (2002) and Lawless (2002).

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In lifetime studies, we generally assume that all subjects under study will experience the event of interest, if they are followed sufficiently long. However, in some situations, a non-negligible proportion of individuals may not experience the event of interest even after a long period of observation. For example, in many clinical trials, there exist a proportion of subjects who may not experience the event of interest. These patients cannot be treated as censored, and should be considered as cured individuals. In such a scenario, traditional methods for analyzing survival data have to be modified. Cure rate models have wide range of applications in many fields including medical and public health. In cure rate models, the entire population is considered as a mixture of two groups of patients, susceptible (non-cured) and non-susceptible (cured). In clinical trials of cancer studies, the proportion of cured individuals is an important factor in estimating survival probabilities. Hence, it is of interest to develop models which incorporate cure fraction.

The mixture cure rate model (MCM) proposed by Boag (1949) has been popular in the analysis of survival data with long term survivors. Some important works in this area include Farewell (1982), Taylor (1995), Peng and Dear (2000) Sy and Taylor (2000) and Zhang and Peng (2007) among others. The books by Maller and Zhou (1996) and Ibrahim, Chen and Sinha (2002) served as excellent references on this topic.

Competing risks data with cure fraction arises when the susceptible group is exposed to different risks of failure. For example, consider the data obtained from a clinical trial on HIV infection and AIDS of 329 homosexual men from Amsterdam, reported in Geskus (2015). During the course of period from HIV infection (NSI phenotype) to death, the virus may be switched to SI phenotype or AIDS; which are mutually exclusive events and both affect the subsequent disease progression differently. Accordingly it is important to observe which infection has occurred first. The presence or absence of the CCR5-Δ32 deletion in one or both chromosomes is considered as the covariate in the study. An interesting characteristic of the data is that time of occurrence of these events vary from 0.112 years (approximately 41 days) to 13.936 years (approximately
5090 days). We also found that after 12.4 years (4526 days), there are only 3 events observed (one due to AIDS and two due to SI), whereas around 14.5% of the total lifetimes reported are larger than 12.4 years. This scenario indicates the presence of cured individuals in the data (Maller and Zhao, 1996). Hence, it is required to analyse the data using cure rate model with competing risks. In Section 5, we use this data to illustrate the applicability of the proposed method.

Modelling and analysis of competing risks data with cure fraction is considered by several authors in literature. A Bayesian method that unifies the mixture cure and competing risks approach is developed by Basu and Tiwari (2010). Choi and Huang (2014) considered a finite mixture model for analysing competing risks with cure fraction. Choi, Huang, and Cromier (2015) proposed a semiparametric mixture model to analyse competing risks data with cure fraction using a multinomial logistic model. A semiparametric accelerated failure time model for the cause-specific survival function that is combined through a multinomial logistic model within the cure-mixture modeling framework is developed by Choi, Zhu and Huang (2018). The vertical modeling approach is extended to analyse competing risks data with cure fraction by Nicolaie, Taylor and Legrand (2019). Recently, Wang, Zhang and Tang (2020) have proposed a semiparametric estimation procedure for the accelerated failure time mixture cure model in the presence of competing risks. However, in all the aforementioned and other related works, one needs to estimate the probability of failure due to each cause in the presence of covariates, in order to estimate the overall survival function.

Motivated by this, we propose a new semi-parametric regression model to analyse competing risks data with cured individuals. We use a mixture model approach to analyse the competing risks data with cure fraction. We specify cumulative incidence functions of the competing risks data using linear transformation model. Unlike the traditional approach discussed earlier, the novelty of our approach is that we can estimate the overall survival function without estimating the cure fraction separately. This
achievement is in the line of promotion time cure model discussed by Tsodikov (2002) in the non-competing risks scenario.

The rest of the article is organized as follows. In Section 2, we propose a semiparametric regression model for the analysis of competing risks data with cure fraction. In Section 3, we develop counting process based estimating equations to find the estimators of regression coefficients. The asymptotic properties of the estimators are also studied. An extensive Monte Carlo simulation study is carried out to assess the finite sample performance of the proposed estimators. Computational algorithms along with the results of the simulation study are presented in Section 4. In Section 5, we illustrate the application of the proposed method using a real data set obtained from a study of HIV and AIDS infection. Finally, in Section 6, we summarise major conclusions of the study along with discussion on some open problems.

2. Model and methods

We propose a new method to analyse competing risks data with cure fraction. Consider a general competing risks setup with $K$ distinct failure types. Let $(T, J)$ be the observed data, where $T$ denotes the time to failure and $J \in \{0, 1, \ldots, K\}$ be the corresponding cause of failure. We use $J = 0$ to denote a subject who is insusceptible to any type of failures. The mixture modeling approach has been popular in the analysis of lifetime data with long term survivors. In the presence of cure fraction, mixture model of competing risks data assumes that the failure time $T$ can be decomposed as

$$T = \sum_{k=1}^{K} T_k.I(J = k) + \infty.I(J = 0),$$

where $T_k$ denote the latent failure times due to cause $k$, $k = 1, \ldots, K$ and $I$ denotes the indicator function.

Let $Z$ be $p$-dimensional covariates, possibly time variant. We assume that the censoring random variable $C$ is independent of $T$, conditional on the covariates $Z$. Denote $\pi_k(Z) = P(J = k|Z)$ as the probability of experiencing the event from cause
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$k, k = 1, \ldots, K$ and $\pi_0(Z)$ as the cure fraction. Clearly, $\pi_0(Z) = 1 - \sum_{k=1}^{K} \pi_k(Z)$. Mixture cure rate model assumes that the overall conditional survival function of $T$ given $Z$ has the representation given by

$$S(t|Z) = P(T > t|Z) = \pi_0(Z) + \sum_{k=1}^{K} \pi_k(Z)S_k(t|Z),$$

where $S_k(t|Z) = P(T_k > t|J = k, Z)$ and $\beta = \{\beta_1 \ldots \beta_k\}$ denote the full set of parameters. To estimate $S(t|Z)$ specified in (1), we need to model the effect of covariates on $\pi_k(Z)$ and $S_k(t|Z)$ separately (Patilea and Keilegom, 2017). Under the finite-mixture model, apart from estimating $S_k(t|Z)$, practitioners usually model $\pi_k(Z)$ using logistic regression (Farewell, 1982). This makes the implementation of the method complex and computationally challenging. Motivated by this, we propose a new method to analyse the competing risks data with long term survivors.

We consider a semi-parametric transformation model for cumulative incidence functions, which is the probability of failure from any one cause in the presence of other risks over a certain time period. The cumulative incidence function conditional on $Z$ denoted by $F_k(t|Z)$ is given by

$$F_k(t|Z) = P(T \leq t, J = k|Z), \ k = 1, \ldots, K.$$  

It is the cumulative probability of failure from the $j$-th cause of failure in the presence of the remaining causes of failure, conditional on the covariates. Now, we express $S(t|Z)$ given in (1) in terms of $F_k(t|Z)$. For $k = 1, 2, \ldots, K$, consider

$$F_k(t|Z) = P(T \leq t, J = k|Z)$$

$$= P(T \leq t|J = k, Z)P(J = k|Z)$$

$$= (1 - P(T > t|J = k, Z))P(J = k|Z)$$

$$= \pi_k(Z)(1 - S_k(t|Z)).$$

(2)
The representation given in (2) allows us to model the conditional cumulative incidence function through \( \pi_k(Z) \). We use linear transformation models to specify each cumulative incidence function \( F_k(t|Z) \) without using \( \pi_k(Z) \). Thus, using (2), we rewrite \( S(t|Z) \) given in (1) as

\[
S(t|Z) = 1 - \sum_{k=1}^{K} F_k(t|Z).
\] (3)

In the proposed method, we formulate the conditional cumulative function \( F_k(t|Z) \) specified in (3), through a class of linear transformation models proposed by (Mao and Lin, 2017)

\[
g_k \{ F_k(t|Z) \} = h_k(t) + Z'\beta_k, \quad k = 1, 2, \ldots, K,
\] (4)

where \( g_k \) is a known increasing cause specific link function, \( h_k(t) \) is an unknown non-decreasing function and \( \beta_k \) is a set of \( p \)-dimensional regression coefficients. We assume \( h_k(0) = -\infty \). The proportional hazards (PH) model and proportional odds (PO) model are special cases of (4) when \( g_k(x) \) takes the form \( \log(-\log(1-x)) \) and \( \log(x/(1-x)) \), respectively. For more details on linear transformation model one can refer to Doksum (1987), Chen, Jin and Ying (2002), Zeng and Lin (2006) and Mao and Lin (2017). The LT model in (4) can be represented as

\[
h_k(T) = -Z'\beta_k + \epsilon_k, \quad k = 1, 2, \ldots, K,
\] (5)

where \( \epsilon_k \) is a random error with a known distribution \( F_{\epsilon_k}(x) = P(\epsilon_k \leq x) = g_{\epsilon_k}^{-1}(x) \) and is independent of the covariate \( Z \). The model in (5) reduces to PH and PO model, when \( \epsilon_k \) has standard extreme value and standard logistic distribution, respectively. For further details of this equivalent form, see Fine, Ying and Wei (1998), Zhang, Sun, Zhao and Sun (2005) and Guo and Zeng (2014). Define conditional cause specific hazard rate function as

\[
\lambda_k(t|Z) = \lim_{\delta t \to 0} \frac{1}{\delta t} Pr \left( t \leq T < t + \delta t, J = k | T \geq t, Z \right).
\]
Clearly, $F_k(t|Z) = 1 - \exp(-\Lambda_k(t|Z))$, where $\Lambda_k(t|Z) = \int_0^t \lambda_k(s|Z) ds$. We use the form given in (5), while developing the estimating equations based on Martingale. Hence, inference on $F_k(t|Z)$ follows from the simple relationship $F_k(t|Z) = 1 - \exp(-\Lambda_k(t|Z))$.

From (4), we have

$$F_k(t|Z) = g_k^{-1}(h_k(t) + Z'\beta_k), \quad k = 1, 2, \ldots, K.$$  \hfill (6)

Thus using (3), the survival function of $T$ given $Z$ is given by

$$S(t|Z) = 1 - \sum_{k=1}^K g_k^{-1}(h_k(t) + Z'\beta_k).$$  \hfill (7)

In view of (11) given in Section 3, we can easily see that as $t \to \infty$, $S(t|Z)$ become $\pi_0(Z)$, the cure fraction. From the representation (7), it is obvious that we can find the overall survival function of $T$ without estimating the cure fraction. For finding overall survival function $S(t|Z)$, we need to estimate $h_k(.)$ and $\beta_k$ in (7). The estimation of $h_k(t)$ and $\beta_k$ are discussed in the next section.

3. Estimating equation and asymptotic properties

Let $T$ and $C$ be the failure time and the censoring time random variables, respectively. Let $\bar{T} = \min(T, C)$, then we observe $\bar{T}$ and $\delta$ where $\delta = I(T < C)$ with $I$ as the indicator function. Let $J$ be a discrete random variable with support $\{0, 1, \ldots, K\}$. We assume that the failure of a subject is due to any of the causes $\{1, 2, \ldots, K\}$ and we use the notation $J = 0$ to denote the subject which are insusceptible to any of the $K$ causes. Let $Z$ be $p$-dimensional covariate vector. The observed data $(\bar{T}_i, \delta_i, \delta_i J_i, Z_i)$, $i = 1, 2, \ldots, n$, is the independent copies of the vector $(\bar{T}, \delta, \delta J, Z)$. Let $\lambda_k(t)$ and $\Lambda_k(t)$, $k = 1, \ldots, K$ be the cause specific hazard function and cause specific cumulative hazard function conditional on $Z$ corresponding to $k$-th cause.

To estimate $\beta_k$ and $h_k(.)$, $k = 1, \ldots, K$ we propose the estimating equations based on counting process. Let $N_{ik}(t) = \delta_i I(\bar{T}_i \leq t, J = k)$ be the counting process associated
with failure time of $i$-th subject due to cause $k$, $k = 1, \ldots, K$ and $i = 1, 2, \ldots, n$. Let $N_k(t) = \sum_{i=1}^{n} N_{ik}(t)$ be the number of failures due to cause $k$ by time $t$. Then $N(t) = \sum_{k=1}^{K} N_k(t)$ is the total number of events experienced by time $t$. Define at-risk process $Y_i(t) = I(\tilde{T}_i > t)$ and $Y(t) = \sum_{i=1}^{n} Y_i(t)$. It can be easily verified that $N_{ik}(t), i = 1, \ldots, n$ and $k = 1, \ldots, K$ are local sub-martingales with respect to appropriate filtration (Andersen et al., 1993). By Doob-Meyer decomposition, martingale process associated with $N_{ik}(t)$ is given by (Andersen et al., 1993)

$$M_{ik}(t) = N_{ik}(t) - \int_{0}^{t} Y_i(u) dA_{\epsilon_k}(u|Z), i = 1, \ldots, n, k = 1, 2, \ldots, K,$$

where $A_{\epsilon_k}$ is the cumulative cause-specific hazard functions of $\epsilon_k$. Using linear transformation model specified in (5), we have

$$M_{ik}(t) = N_{ik}(t) - \int_{0}^{t} Y_i(u) dA_{\epsilon_k}(h_k(u) + Z'_i \beta_k).$$

(8)

By definition, $M_{ik}(t)$ is a mean zero martingale process with respect to appropriate filtration (Andersen and Gill, 1982). We now propose the following estimating equations to obtain the estimators of $\beta_k$ and $h_k(\cdot)$, $k = 1, 2, \ldots, K$,

$$U_{\beta_k}(\beta_k, h_k) = \sum_{i=1}^{n} \int_{0}^{\infty} Z_i \left[ dN_{ik}(u) - Y_i(u) dA_{\epsilon_k}(h_k(u) + Z'_i \beta_k) \right] = 0,$$

(9)

and

$$U_{h_k}(\beta_k, h_k) = \sum_{i=1}^{n} \left[ dN_{ik}(t) - Y_i(t) dA_{\epsilon_k}(h_k(t) + Z'_i \beta_k) \right] = 0, t \geq 0.$$

(10)

Solving the above equations iteratively we obtain the estimators of $\beta_k$ and $h_k(\cdot)$, $k = 1, 2, \ldots, K$. The estimating equations in (9) and (10) reduce to the estimating equations given by Chen et al. (2002) when $k = 1$.

When the estimators of $\beta_k$ and $h_k(t)$ are obtained, one can estimate the overall survival function without estimating cure probability. However, our newly proposed method enables us to estimate the cured probability from the proposed model itself. We use (6) to estimate the cure fraction. From the definition of cumulative incidence
function we have (Lawless, 2002),
\[ P(J = k|Z) = F_k(\infty, J = k|Z) = g_k^{-1}(h_k(\infty) + Z'\beta_k). \]

Hence, the cure probability can be obtained using the relation
\[ \pi_0(Z) = 1 - \sum_{k=1}^{K} g_k^{-1}(h_k(\infty) + Z'\beta_k). \]  
(11)

Thus the cure fraction is estimated by
\[ \hat{\pi}_0(Z) = 1 - \sum_{k=1}^{K} g_k^{-1}(\hat{h}_k(\infty) + Z'\hat{\beta}_k). \]  
(12)

In practice, \( h_k(\infty) \) can be estimated by \( \max(\hat{h}_k(t)) \). We now provide the asymptotic distribution of the \( \hat{\beta}_k \). To find the distribution of \( \hat{\beta}_k \), first we show that each \( \hat{h}_k(t) \) is a consistent estimator of \( h_k(t) \). Then we use the estimating equation in (9) to find the asymptotic distribution of \( \hat{\beta}_k \). We assume the following regularity conditions to prove the asymptotic properties.

D1. The covariates \( Z \) are bounded in probability.
D2. The true value of the parameters \( \beta_k, k = 1, \ldots, K \) lies in a compact set of \( \mathbb{R}^p \)
D3. Define \( \tau = \inf\{t : P(\hat{T} > t) = 0\} \).
D4. The derivatives of \( \lambda_{ek}(\cdot), k = 1, \ldots, K \) exists and continuous.
D5. The martingales defined in equation (8) satisfies the regularity conditions as in Fleming and Harrington (1991).

The conditions D1 – D4 are standard regularity conditions used in survival analysis. The assumption D5 is used to establish martingale central limit theorem.

The following additional notations are needed for deriving asymptotic distribution.

For any \( s < t \in (0, \tau] \), define
\[ B_k(t, s) = \exp\left( \int_s^t \frac{E[\partial \lambda_{ek}/\partial t(\hat{Z}'\beta_k + h_k(u))Y(u)]}{E[\lambda_{ek}(\hat{Z}'\beta_k + h_k(u))Y(u)]}dh_k(u) \right). \]
For $k = 1, \ldots, K$, define $\mu_k(t) = \frac{C_{zk}(t)}{C_{dk}(t)}$ where

$$C_{zk}(t) = E[\lambda_{\epsilon_k}(Z'\beta_k + h_k(t))Y(t)B_k(t, T)]$$

and

$$C_{dk}(t) = E[\lambda_{\epsilon_k}(Z'\beta_k + h_k(t))Y(t)].$$

The asymptotic properties of $\hat{\beta}_k$ and $\hat{h}_k(t)$ are established in the following theorems.

**Theorem 1.** Under the regularity conditions $D_1 - D_4$, for $k = 1, \ldots, K$, $\hat{\beta}_k$ and $\hat{h}_k(t)$ are strongly consistent. That is

$$\|\hat{\beta}_k - \beta_k\| + \sup_{t \in [0, \tau]} \sum_{k=1}^{K} |\hat{h}_k(t) - h_k(t)| \to 0,$$

almost surely, where $\|\cdot\|$ denotes the Euclidean norm.

**Theorem 2.** Under the regularity conditions $D_1 - D_5$, for $k = 1, \ldots, K$, as $n \to \infty$, $\sqrt{n}(\hat{\beta}_k - \beta_k)$ converges in distribution to multivariate normal with zero mean vector and variance-covariance matrix $\Sigma_k$ where $\Sigma_k = \Sigma_{1k}^{-1}\Sigma_{0k}(\Sigma_{1k}^{-1})'$ with

$$\Sigma_{0k} = \int_0^\tau E\{(Z - \mu_k(t))(Z - \mu_k(t))'Y(t)d\lambda_{\epsilon_k}[Z'\beta_k + h_k(t)]\}$$

and

$$\Sigma_{1k} = \int_0^\tau E\{(Z - \mu_k(t))(Z'\partial\lambda_{\epsilon_k}/\partial t\{Z'\beta_k + h_k(t)\})Y(t)\}dh_k(t).$$

Proofs of Theorem 1 and Theorem 2 are given in Appendix.

4. **Computational Algorithm and Simulations**

The estimators $\hat{\beta}_k$ and $\hat{h}_k(t)$ are obtained as the solutions of the equations (9) and (10). The value of $\hat{h}_k(t)$ are estimated at observed failure time due to cause $k$. For computational simplicity we express the set of equations (10) in an alternative form. Let $t_{k1}, t_{k2}, \ldots, t_{km}$ be the observed failure times due to the cause $k$, $k = 1, 2, \ldots, K$. 

For $k = 1, \ldots, K$, define $\mu_k(t) = \frac{C_{zk}(t)}{C_{dk}(t)}$ where

$$C_{zk}(t) = E[\lambda_{\epsilon_k}(Z'\beta_k + h_k(t))Y(t)B_k(t, T)]$$

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Then (10) can be rewritten as

\[ \sum_{i=1}^{n} Y_i(t_{k1}) \Lambda_{\epsilon_k}(Z_i' \beta_k + h_k(t_{k1})) = 1, \quad (15) \]

\[ \sum_{i=1}^{n} Y_i(t_{kj})(\Lambda_{\epsilon_k}(h_k(t_{kj}) + Z_i' \beta_k) - \Lambda_{\epsilon_k}(h(t_{kj}-) + Z_i' \beta_k)) = 1, \quad j = 2, 3, \ldots, m. \quad (16) \]

Thus, we have the following iterative algorithms for computing \( \hat{\beta}_k \) and \( \hat{h}_k(t) \).

Step 1. Choose an initial value \( \beta_k^{(0)} \) for \( \beta_k \), \( k = 1, \ldots, K \). Obtain an estimator \( \hat{h}_k(t) \) for \( h_k(t) \) by solving the equations (15) and (16).

Step 2. Find \( \hat{\beta}_k \) by solving the equations (9) using \( \hat{h}_k(t) \) obtained in Step 2.

Step 3. Set \( \beta_k^{(0)} = \hat{\beta}_k \) (the estimator obtained in the previous step) and repeat the Steps 1-3 until the convergence of \( \hat{\beta}_k \).

We conduct an extensive Monte Carlo simulation study to assess the finite sample performance of the proposed estimators. In simulation, we consider two models where the cause specific hazard function is specified by \( \lambda_{\epsilon_k}(t) = e^{r_1 + r_2 t} \), \( r = 0, 1 \), \( k = 1, 2 \) and \( h_k(T) = \log T_k \). Here, \( r = 0, 1 \) corresponds to the proportional hazards and the proportional odds model, respectively.

The covariate \( Z_1 \) is generated from Bernoulli distribution with probability of success equal to 0.5. When \( r = 0 \), we generate \( T \) using the model expression \( -\log(U) \exp(-Z_1 b_k) \), where \( U \) is \( U(0, 1) \) random variable. Also, when \( r = 1 \), we simulate \( T \) using the expression \( ((1-U)/U) \exp(-Z_1 b_k) \). In both the cases, we choose the values of the regression parameters as \( (\beta_1, \beta_2) = (2, 2), (2, 3), (3, 2) \) and \( (3, 3) \). Censoring random variable \( C \) is simulated from \( U(0, c) \) distribution where \( c \) is chosen so that the sample contain desired percentage of censored observations, ie. \( P(T > C) = q, 0 \leq q < 1 \). We consider two different censoring scenarios with \( q = 0.2, 0.4 \). We simulate observations with different samples sizes \( n = 100, 200, 500 \) and simulation is repeated ten thousand times. The simulation is carried out using R program.

The regression parameters are estimated using the iterative algorithm given in the beginning of this section. The absolute bias and MSE (Mean Square Error) of the
estimators of regression coefficients obtained under PH and PO models for different parameter settings are reported in Tables 1 and 2. From Tables 1 and 2, we observe that the absolute bias of the estimators of regression coefficients approaches zero as sample size increases. In all cases, the MSE also decreases as sample size increases. We also note that the absolute bias and MSE of the estimators increase with the censoring percentage.
The absolute bias and the MSE of the estimates of $h_j(\cdot)$ for $j = 1, 2$ are estimated at three different time points $t = 1, 2, 3$. The results are reported in Tables 3-6. In Tables 3 and 4, we present absolute bias and MSE of the estimators of $h_j(\cdot)$ for $j = 1, 2$ and for parameter combinations $(\beta_1, \beta_2) = (2, 2)$ and $(3, 2)$ under PH model. Under PO model, absolute bias and MSE of the estimators of $h_j(\cdot)$ for $j = 1, 2$ and for parameter combinations $(\beta_1, \beta_2) = (2, 3)$ and $(3, 3)$ are given in Tables 5 and 6. We obtain similar results for other parameter combinations also under both PH and PO model and we report the results of two scenario. We observe that, the absolute bias and MSE of the estimators of $h_j(\cdot)$ for $j = 1, 2$ decrease with increase in sample size.

**Table 3.** Absolute bias and MSE of the estimators of $h_1(\cdot)$ and $h_2(\cdot)$ under PH model at various time points for $\beta_1 = 2, \beta_2 = 2$

| Censoring(%) | n   | Bias  | MSE  | Bias  | MSE  | Bias  | MSE  |
|--------------|-----|-------|------|-------|------|-------|------|
|              |     | $t_1 = 1$ |      | $t_2 = 2$ |      | $t_3 = 3$ |      |
| $h_1(\cdot)$ |     |       |      |       |      |       |      |
| 20           | 100 | 0.1334 | 0.0229 | 0.1482 | 0.0279 | 0.1046 | 0.0172 |
|              | 200 | 0.0119 | 0.0103 | 0.0552 | 0.0152 | 0.0378 | 0.0142 |
|              | 500 | 0.0032 | 0.0021 | 0.0138 | 0.0025 | 0.0056 | 0.0024 |
| 40           | 100 | 0.0661 | 0.0110 | 0.1008 | 0.0230 | 0.0840 | 0.0206 |
|              | 200 | 0.0266 | 0.0096 | 0.0502 | 0.0086 | 0.0601 | 0.0101 |
|              | 500 | 0.0024 | 0.0028 | 0.0049 | 0.0025 | 0.0012 | 0.0026 |
| $h_2(\cdot)$ |     |       |      |       |      |       |      |
| 20           | 100 | 0.0721 | 0.0206 | 0.0858 | 0.0194 | 0.1062 | 0.0271 |
|              | 200 | 0.0553 | 0.0101 | 0.0643 | 0.0125 | 0.0944 | 0.0199 |
|              | 500 | 0.0034 | 0.0028 | 0.0452 | 0.0106 | 0.0885 | 0.0112 |
| 40           | 100 | 0.2594 | 0.0879 | 0.2479 | 0.0853 | 0.2187 | 0.0727 |
|              | 200 | 0.2594 | 0.0879 | 0.2479 | 0.0853 | 0.2187 | 0.0727 |
|              | 500 | 0.0260 | 0.0045 | 0.0279 | 0.0053 | 0.0166 | 0.0050 |

Next, we obtain the coverage probability and average width of the confidence interval of the regression parameters for different parameter combinations considered above. The results for PH and PO models are given in Tables 7 and 8, respectively. We observe that, the coverage probability approaches 0.95 and the average width of the interval decreases as $n$ increases for both PH and PO models.

Finally, we compare theoretical asymptotic variance and Monte Carlo variance of the estimators of $\beta_1$ and $\beta_2$ for different parameter combinations under PH model. In PH
Table 4. Absolute bias and MSE of the estimators of $h_1(.)$ and $h_2(.)$ under PH model at various time points for $\beta_1 = 3, \beta_2 = 2$

| Censoring(%) | n   | Bias $t_1 = 1$ | MSE $t_1 = 1$ | Bias $t_2 = 2$ | MSE $t_2 = 2$ | Bias $t_3 = 3$ | MSE $t_3 = 3$ |
|--------------|-----|----------------|---------------|----------------|---------------|----------------|---------------|
| 20           | 100 | 0.0590        | 0.0148        | 0.0765         | 0.0170        | 0.0811         | 0.0190        |
|              | 200 | 0.0324        | 0.0071        | 0.0172         | 0.0092        | 0.0364         | 0.0101        |
|              | 500 | 0.0124        | 0.0063        | 0.0028         | 0.0083        | 0.0107         | 0.0088        |
| 40           | 100 | 0.1293        | 0.0241        | 0.1785         | 0.0479        | 0.1922         | 0.0565        |
|              | 200 | 0.0634        | 0.0192        | 0.1747         | 0.0394        | 0.1767         | 0.0405        |
|              | 500 | 0.0148        | 0.0032        | 0.0287         | 0.0043        | 0.0350         | 0.0048        |

Table 5. Absolute bias and MSE of the estimators of $h_1(.)$ and $h_2(.)$ under PO model at various time points for $\beta_1 = 2, \beta_2 = 3$

| Censoring(%) | n   | Bias $t_1 = 1$ | MSE $t_1 = 1$ | Bias $t_2 = 2$ | MSE $t_2 = 2$ | Bias $t_3 = 3$ | MSE $t_3 = 3$ |
|--------------|-----|----------------|---------------|----------------|---------------|----------------|---------------|
| 20           | 100 | 0.0611        | 0.0140        | 0.0454         | 0.0124        | 0.0367         | 0.0140        |
|              | 200 | 0.0249        | 0.0051        | 0.0264         | 0.0065        | 0.0325         | 0.0061        |
|              | 500 | 0.0144        | 0.0026        | 0.0034         | 0.0044        | 0.0027         | 0.0038        |
| 40           | 100 | 0.0253        | 0.0117        | 0.0562         | 0.0163        | 0.0480         | 0.0141        |
|              | 200 | 0.0176        | 0.0057        | 0.0392         | 0.0064        | 0.0186         | 0.0090        |
|              | 500 | 0.0079        | 0.0022        | 0.0067         | 0.0040        | 0.0172         | 0.0029        |

model, we obtain the variance-covariance matrix specified in (13) and (14) as

$$\Sigma_{0k} = \Sigma_{1k} = Var\left(\int_{0}^{\infty} (Z - \mu_k(t))dM_k(t)\right), \ k = 1, 2,$$

where $\mu_k(t) = E(Z|\tilde{T}, \delta = 1)$. Hence $\Sigma_k = \Sigma_{0k}^{-1}$. For more details see Chen, Jin and Zhang (2002). Comparison results are given in Table 9. We observe that the estimators
Table 6. Absolute bias and MSE of the estimators of $h_1(.)$ and $h_2(.)$ under PO model at various time points for $\beta_1 = 3, \beta_2 = 3$.

| Censoring(%) | n   | Bias $t_1 = 1$ | MSE $t_1 = 1$ | Bias $t_2 = 2$ | MSE $t_2 = 2$ | Bias $t_3 = 3$ | MSE $t_3 = 3$ |
|-------------|-----|----------------|---------------|----------------|---------------|----------------|---------------|
| 20          | 100 | 0.0809        | 0.0206        | 0.1048         | 0.0184        | 0.0185         | 0.0185        |
|             | 200 | 0.0720        | 0.0080        | 0.0354         | 0.0143        | 0.0215         | 0.0109        |
|             | 500 | 0.0138        | 0.0069        | 0.0100         | 0.0082        | 0.0100         | 0.0086        |
| 40          | 100 | 0.1567        | 0.0400        | 0.1172         | 0.0321        | 0.1077         | 0.0295        |
|             | 200 | 0.0136        | 0.0074        | 0.0398         | 0.0104        | 0.0639         | 0.0109        |
|             | 500 | 0.0099        | 0.0031        | 0.0384         | 0.0050        | 0.0414         | 0.0078        |

Table 7. Coverage probability and average width of the confidence interval of the estimates of $\beta_1$ and $\beta_2$ under PH model.

| Censoring(%) | n   | CP $\beta_1 = 2$ | AW $\beta_1 = 2$ | CP $\beta_2 = 2$ | AW $\beta_2 = 2$ | CP $\beta_1 = 2$ | AW $\beta_2 = 3$ | CP $\beta_1 = 3$ | AW $\beta_2 = 3$ |
|-------------|-----|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 20          | 100 | 0.9507          | 0.5628          | 0.9529          | 0.6710          | 0.9529          | 0.5606          | 0.9524          | 0.7391          |
|             | 200 | 0.9504          | 0.3918          | 0.9528          | 0.4564          | 0.9528          | 0.3886          | 0.9506          | 0.5125          |
|             | 500 | 0.9497          | 0.2443          | 0.9487          | 0.2882          | 0.9499          | 0.2457          | 0.9495          | 0.3258          |
| 40          | 100 | 0.9529          | 0.5751          | 0.9539          | 0.7796          | 0.9530          | 0.5763          | 0.9547          | 0.8544          |
|             | 200 | 0.9526          | 0.4012          | 0.9522          | 0.5385          | 0.9487          | 0.4055          | 0.9505          | 0.5911          |
|             | 500 | 0.9509          | 0.2547          | 0.9512          | 0.3440          | 0.9494          | 0.2518          | 0.9498          | 0.3703          |

of theoretical variance (EAV) and the estimators of Monte Carlo variance (MCV), agree each other.
Table 8. Coverage probability and average width of the confidence interval of the estimates of $\beta_1$ and $\beta_2$ under PO model

| Censoring(%) | n  | CP  | AW  | CP  | AW  | CP  | AW  | CP  | AW  |
|-------------|----|-----|-----|-----|-----|-----|-----|-----|-----|
|              | 100| 0.9523 | 0.5546 | 0.9523 | 0.6599 | 0.9520 | 0.5567 | 0.9542 | 0.7385 |
|              | 20 | 0.9507 | 0.3917 | 0.9521 | 0.4621 | 0.9515 | 0.3863 | 0.9520 | 0.5182 |
|              | 500| 0.9499 | 0.2460 | 0.9491 | 0.9491 | 0.9511 | 0.2474 | 0.9506 | 0.3226 |
|              | 100| 0.9491 | 0.5766 | 0.9561 | 0.7904 | 0.9527 | 0.5800 | 0.9539 | 0.8649 |
|              | 20 | 0.9493 | 0.4063 | 0.9519 | 0.5472 | 0.9514 | 0.4096 | 0.9524 | 0.5888 |
|              | 500| 0.9508 | 0.2540 | 0.9485 | 0.3394 | 0.9512 | 0.2540 | 0.9508 | 0.3657 |
|              | 100| 0.9541 | 0.6232 | 0.9528 | 0.6604 | 0.9530 | 0.6318 | 0.9524 | 0.7407 |
|              | 20 | 0.9538 | 0.4372 | 0.9509 | 0.4625 | 0.9474 | 0.4353 | 0.9525 | 0.5133 |
|              | 500| 0.9508 | 0.2742 | 0.9496 | 0.2888 | 0.9505 | 0.2788 | 0.9484 | 0.3195 |
|              | 100| 0.9522 | 0.6453 | 0.9537 | 0.7964 | 0.9491 | 0.6463 | 0.9537 | 0.8690 |
|              | 20 | 0.9521 | 0.4516 | 0.9518 | 0.5503 | 0.9508 | 0.4500 | 0.9530 | 0.5926 |
|              | 500| 0.9504 | 0.2865 | 0.9507 | 0.3388 | 0.9508 | 0.2844 | 0.9511 | 0.3713 |

Table 9. Theoretical asymptotic variance and Monte Carlo variance of the estimates of $\beta_1$ and $\beta_2$ under PH model

| Censoring(%) | n  | EAV  | MCV  | EAV  | MCV  | EAV  | MCV  | EAV  | MCV  |
|-------------|----|------|------|------|------|------|------|------|------|
|              | 100| 0.0200 | 0.0206 | 0.0221 | 0.0273 | 0.0200 | 0.0204 | 0.0200 | 0.0356 |
|              | 20 | 0.0100 | 0.0100 | 0.0100 | 0.0136 | 0.0100 | 0.0098 | 0.0100 | 0.0171 |
|              | 500| 0.0040 | 0.0039 | 0.0040 | 0.0054 | 0.0040 | 0.0039 | 0.0040 | 0.0069 |
|              | 100| 0.0200 | 0.0215 | 0.0201 | 0.0395 | 0.0200 | 0.0216 | 0.0201 | 0.0475 |
|              | 20 | 0.0100 | 0.0105 | 0.0100 | 0.0189 | 0.0100 | 0.0107 | 0.0100 | 0.0227 |
|              | 500| 0.0040 | 0.0042 | 0.0040 | 0.0077 | 0.0040 | 0.0041 | 0.0040 | 0.0089 |
|              | 100| 0.0200 | 0.0251 | 0.0200 | 0.0280 | 0.0200 | 0.0252 | 0.0200 | 0.0357 |
|              | 20 | 0.0100 | 0.0126 | 0.0100 | 0.0141 | 0.0100 | 0.0126 | 0.0100 | 0.0172 |
|              | 500| 0.0040 | 0.0051 | 0.0040 | 0.0055 | 0.0040 | 0.0049 | 0.0040 | 0.0068 |
|              | 100| 0.0200 | 0.0274 | 0.0201 | 0.0424 | 0.0200 | 0.0277 | 0.0201 | 0.0498 |
|              | 20 | 0.0100 | 0.0133 | 0.0100 | 0.0196 | 0.0100 | 0.0137 | 0.0100 | 0.0234 |
|              | 500| 0.0345 | 0.0053 | 0.0040 | 0.0077 | 0.0040 | 0.0054 | 0.0040 | 0.0090 |

5. An example

In this section, we apply our proposed method to the data obtained from a clinical trial on HIV infection and AIDS of 329 homosexual men from Amsterdam. The data is available in R package ‘mstate’ and is exclusively studied by Geskus (2015). During the course from HIV infection from non-syncytium-inducing (NSI) phenotype to death, intermediate events may occur that have an impact on subsequent disease progression.
One such event is a switch of the HIV virus to the syncytium inducing (SI) phenotype and the other is the progression to AIDS. Since neither of the events is final and changes the probability of relapse/ survival of a patient, it is of interest to know whether AIDS or SI is the first event to occur. As mentioned in the introductory section, the data may contain cured individuals. Accordingly, we use this data to illustrate our newly proposed method. We use the estimating equation \[ \hat{\beta} = \frac{\sum_{i=1}^{n} d_i Y_i}{\sum_{i=1}^{n} n_i} \] for finding the estimators of regression coefficients. We estimate cumulative incidence functions for patients with AIDS and SI using proportional hazard (PH) model and proportional odds (PO) models.

The presence or absence of the CCR5-Δ32 deletion in one or both chromosomes affect the progression to AIDS or SI significantly, it is considered as one covariate in this study. We also consider the age of the patient at the time of infection of HIV as another covariate. Individuals without the deletion of one of the chromosomes are referred to as WW (wild type allele on both chromosomes) and those who have the deletion are considered as having a mutation and referred to as WM (mutant allele on one chromosome). We removed 5 records due to missingness of covariate value CCR5-Δ32. Out of 324 patients, the first event to occur was AIDS for 113 patients and SI was occurred as the first event to 107 patients. The remaining 104 patients are observed to be event free in the study period. For 259 patients the covariate value is ‘WW’ and for the remaining 65 patients it is ‘WM’. An interesting characteristic of the data is that time to occurrence of the event varies from 0.112 years (approximately 41 days) to 13.936 years (approximately 5090 days). We also see that after 12.4 years (4526 days) there are only 3 event times observed one due to AIDS and two with the cause SI, whereas around 14.5% of the total lifetimes are larger than 12.4 years. Presence of large number of right censored observations indicates the possible presence of cured individuals in the population. This fact motivates us to analyse the data using the proposed method. To ensure the presence of cured individuals in the population, we plot Kaplan Meier curve of the complete data in Figure 1. From Figure 1, we can see that the minimum survival probability is around 0.2, and then the curve experiences a
sudden fall. This is due to the fact that the largest time is an observed lifetime. To differentiate between the behavior of causes AIDS and SI over time, we also plot the baseline cumulative incidence functions in Figure 2.

![Kaplan Meier Plot](image)

**Figure 1.** Kaplan Meier curve of the complete data

The regression coefficients are estimated using the estimating equation under PH and PO model assumption. We use the R package ‘TransModel’ to estimate the regression coefficients. The estimated regression coefficients with corresponding standard errors are reported in Table 10. To understand how the covariate values affect the lifetimes due to different causes, we plot the cumulative incidence functions due to AIDS and SI separately. To plot the graphs, we categorize the covariate age as less than or equal to 34.5 years (median age) and greater than 34.5 years. We plot the graphs of cumulative incidence functions of AIDS patients, for various categories according to the covariate values in Figure 3 and the same for SI patients in Figure 4. Cure fraction is estimated using Eq. (12). The value of cure fraction obtained using PH 0.1655. This
estimated value of cure fraction also supports the claim that the data consist of cured individuals as evident from the Kaplan Meier curve. As mentioned earlier, here it is not required to model the $\pi(Z)$’s separately to find the overall cure fraction. To compare our estimator of the cure rate with the existing methods, we fit a logistic regression model (Farewell, 1982) for the data by ignoring causes and then estimate the cure rate.
We made the lifetime as binary variable by taking 12.4 years as cutoff. The estimate of the cure rate is obtained as 0.2961. This might be an over estimate of the cure rate as evident from the discussion above.

![Graphs showing CIF for different categories](image)

**Figure 3.** CIF of patients with AIDS under PH model in different categories

6. Concluding Remarks

Cure rate models become popular due to its applications in various fields. In the present study, we proposed a semi-parametric model for the analysis of competing risks data with cure fraction. We developed estimators of cumulative incidence functions using linear transformation models. Unlike the traditional approach, it does not require to find the estimator of the cure fraction to compute the overall survival function, which leads to a simple procedure. The regression parameters are estimated using martingale based estimating equations. The asymptotic distribution of the estimators was shown
to be Gaussian. The finite sample performance of the estimators of $\beta_k$ and $h_k(\cdot)$ at different time points, are evaluated in terms of bias and MSE, through a Monte Carlo simulation study. We also find the coverage probability and the average width of the regression estimators. A real data obtained from a study of HIV and AIDS infection was analysed using the proposed method. The newly developed method has a good impact due to the model flexibility and computational advantages.

In the present study, we considered right censored data. Different types of censoring schemes such as current status censoring, double censoring and interval censoring are common in survival studies. The proposed method can be extended to these set up by suitably constructing martingale based estimating equations. The works in this direction will be reported elsewhere. The model selection is an important concern in the analysis of competing risks data with cure fraction when the cumulative incidence functions are specified through linear transformation. A criterion for model selection
can be developed using martingale based residuals. This problem has to be addressed separately.

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Appendix A.

A.1. Proof of Theorem 1: The estimators of $F_k(t|Z)$ are obtained from equation (6) by replacing $\beta_k$ and $h_k(t)$ with its estimators. Then we obtain

$$\widehat{F}_k(t|Z) = g_k^{-1}(\widehat{h}_k(t) + Z^T\widehat{\beta}_k), \quad k = 1, \ldots, K.$$  

In cure rate model, we know that $\lim_{t\to\infty} S(t|Z) = a_0 > 0$. Hence in view of the relation specified in equation (3), we have $\lim inf \left\{ 1 - \sum_{k=1}^K \widehat{F}_k(t|Z) \right\} > 0$. The estimators $\widehat{\beta}_k$ and $\widehat{h}_k(t)$ are obtained by solving the equations (9), (15) and (16). Now using the assumption $h_k(0) = -\infty$ and that $h_k(t)$ is non-decreasing function, from these three equations it follows that, $\widehat{\Lambda}_{\epsilon_k}(\tau) < \infty$, where $\tau$ is defined in Assumption D3. Therefore, the consistency of the estimators $\widehat{\beta}_k$ and $\widehat{\Lambda}_{\epsilon_k}(t)$ follows from Theorem 1 of Mao and Lin (2017). By Step A1 of Chen et al. (2002, p.665), we have consistency of $\widehat{h}_k(t)$, which completes the proof of the Theorem 1.

A.2. Proof of Theorem 2: We use martingale central limit theorem to establish the asymptotic normality of $\widehat{\beta}_k$, $k = 1, \ldots, K$.

First we represents $U(\widehat{\beta}_k, \widehat{h}_k(t))$ as

$$U(\widehat{\beta}_k, \widehat{h}_k(t)) = U(\widehat{\beta}_k, \widehat{h}_k(t)) + (\widehat{\beta}_k - \beta_k) \frac{\partial}{\partial \beta_k} U(\beta_k, \widehat{h}_k(t)).$$

Since $\widehat{\beta}_k$ and $\widehat{h}_k(t)$ are the solutions of equations (9) and (10) we have $U(\widehat{\beta}_k, \widehat{h}_k(t)) = 0$. Now we can write

$$\sqrt{n}(\widehat{\beta}_k - \beta_k) = \left( \frac{1}{n} \frac{\partial}{\partial \beta_k} U(\beta_k, \widehat{h}_k(t)) \right)^{-1} \frac{1}{\sqrt{n}} U(\beta_k, \widehat{h}_k(t)).$$  \hspace{1cm} (17)
To establish the asymptotic normality of $\sqrt{n} (\hat{\beta}_k - \beta_k)$, first we show that, as $n \to \infty$, 
$(\frac{1}{n} \frac{\partial}{\partial \beta_k} U (\beta_k, \hat{h}_k(t)))^{-1}$ converges in probability to $\Sigma_{1k}$ given in Eq. (14) and $\frac{1}{\sqrt{n}} U (\beta_k, \hat{h}_k(t))$ converges in distribution to Gaussian. Then the asymptotic normality of $\sqrt{n}(\hat{\beta}_k - \beta_k)$ follows from equation (17) by applying Slutsky’s theorem.

Using similar argument of Step A3 of Chen et al. (2002), we have

$$
\frac{1}{n} \frac{\partial}{\partial \beta_k} U (\beta_k, \hat{h}_k(t)) = \Sigma_{1k} + o_p(1),
$$

where $\Sigma_{1k}$ is specified in Eq. (14). In view of the martingale representation given in [8], using the Step A4 of Chen et al. (2002), we have

$$
\frac{1}{\sqrt{n}} U (\beta_k, \hat{h}_k(t)) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \int_{0}^{\tau} (Z - \mu_k(t)) dM_{i}(t) + o_p(1).
$$

Using martingale central limit theorem, as $n \to \infty$, $\frac{1}{\sqrt{n}} U (\beta_k, \hat{h}_k(t))$ converges in distribution to multivariate normal with mean vector zero and variance-covariance matrix $\Sigma_{0k}$, where $\Sigma_{0k}$ is the limit of the predictable variation process. Using the martingale representation given in [8], the predictable variation process is given by

$$
\Sigma_{0k}^{*} = \frac{1}{n} \sum_{i=1}^{n} \int_{0}^{\tau} (Z - \mu_k(t))(Z - \mu_k(t))' Y(t) d\Lambda_{\epsilon_{ik}}(Z' \beta_k + h_k(t)).
$$

By law of large numbers, as $n \to \infty$, $\Sigma_{0k}^{*}$ converges in probability to $\Sigma_{0k}$, where $\Sigma_{0k}$ is specified in Eq. (13). In view of the representations (17) and (18) by applying Slutsky’s theorem, as $n \to \infty$, $\sqrt{n}(\hat{\beta}_k - \beta_k)$ converges in distribution to multivariate normal with zero mean vector and variance-covariance matrix $\Sigma_{k} = \Sigma_{1k}^{-1} \Sigma_{0k} (\Sigma_{1k}^{-1})'$. This completes the proof of the Theorem 2.