Chapter Three
Proportional Hazards Model for Gap Time Distributions of Recurrent Events

3.1. Introduction

As mentioned earlier, in many survival studies, the investigators are more interested in the analysis of gap time than the total time. In these studies, investigators are often interested in the distribution of gap times and how this distribution depends on important predictor variables. The analysis of gap time data is usually done by assuming proportional hazards model for marginal hazard functions. In the present study, we deal with the regression problem for gap time of recurrent events in which the marginal and conditional hazard functions depend on certain covariates. Since the covariates under study have different effect on marginal and conditional hazard functions, proposed model will be more useful to study the dependence of gap times on covariates.

In Section 3.2, we consider bivariate proportional hazards model for gap times. Estimation of parameter vector and baseline hazard functions is discussed in Section 3.3. Asymptotic properties of estimators are also studied. In Section 3.4, we carried out a simulation study to investigate the finite sample properties of the estimators and their robustness. In Section 3.5, we apply the new model to a real life data. Finally, we conclude our study in Section 3.6.

3.2. The Model

Suppose that an individual may experience $k$ consecutive events at times $X_1 < X_2 < \ldots < X_k$ which are measured from the start of the follow up. We are interested in gap times $T_1 = X_1$, $T_2 = X_2 - X_1$ and $T_k = X_k - X_{k-1}$. We assume that

The results in this Chapter have been communicated as entitled "Proportional Hazards Model for Gap Time Distributions of Recurrence Events" (see Sankaran and Sreeja (2008)).
the follow up time is subject to independent right censoring by $C$ which implied that $(X_1, X_2, \ldots, X_k)$ are independent of $C$. On the other hand, the gap time $T_i$ is subject to right censoring by $C \sim X_{i-1}$, $i = 2, 3, \ldots, k$, which is naturally correlated with $T_i$ unless $T_i$ is independent of $X_{i-1}$. We now consider the regression problem in which the marginal and conditional hazard functions of $(T_1, T_2, \ldots, T_k)$ depend on certain covariates. We confine our study for $k = 2$. The extension to higher dimensions is direct.

Suppose that $S_i(t_i) = P[T_i > t_i]$ is the marginal recurrence survival function of $T_i$, $i = 1, 2$. Let $S(t_1, t_2) = P[T_1 > t_1, T_2 > t_2]$ be the joint recurrence survival function of $T_1$ and $T_2$. Our objective is to estimate $S(t_1, t_2)$ in the presence of covariates. For this, one possible method is to consider marginal hazard functions of $T_1$ and $T_2$ and then apply ideas from generalized estimating function to calculate an appropriate combination of the two marginal estimates. This can be done in the case of homogeneity of the two regression coefficients. Another technique, one could use, is to model $T_i$ and then consider the conditional distribution of $T_2$ given $T_i = t_i$. From Wang and Wells (1998), the survival function $S(t_1, t_2)$ is given by

$$S(t_1, t_2) = - \int P[T_2 > t_2 \mid T_1 = t_1] S_1(u)du = - \int \prod_{u > t_1} (1 - \lambda^*(u, t_2)) S_1(u)du$$

(3.1)

where $\lambda^*(t_1, t_2)$ is the hazard function of $T_2$ given $T_1 = t_1$. When $X$ is continuous, estimating $\lambda^*(t_1, t_2)$ requires special smoothing techniques and can be very complicated when the dependent censoring condition is taken into account (see Wang and Wells, 1998).

In the following, we consider a simple method for the analysis using marginal hazard function of $T_1$ and conditional hazard function of $T_2$ given $T_1 \geq t_1$.

Let $\lambda_i(t)$ be the hazard function of $T_i$, which is defined as

$$\lambda_i(t) = \lim_{\Delta t_i \to 0} \frac{1}{\Delta t_i} P[t_i \leq T_i < t_i + \Delta t_i \mid T_i \geq t_i].$$

(3.2)
\( \lambda_i(t_i) \) is nothing but the instantaneous rate of occurrence of the first event at time \( t_i \) given that he was alive at the time \( T_i \geq t_i \).

Since \( T_2 \) depends directly on \( T_1 \), we consider the conditional hazard function of \( T_2 \) given \( T_1 \geq t_1 \), which is defined as

\[
\lambda_2(t_1, t_2) = \lim_{\Delta t_2 \to 0} \frac{1}{\Delta t_2} P[t_2 < t_2 + \Delta t_2 | T_1 \geq t_1, T_2 \geq t_2].
\] (3.3)

The meaning of \( \lambda_2(t_1, t_2) \) is instantaneous rate of occurrence of the second event at time \( t_2 \) given that \( T_1 \geq t_1 \) and \( T_2 \geq t_2 \).

The cumulative hazard functions respectively are denoted by \( \Lambda_1(t_1) \) and \( \Lambda_2(t_1, t_2) \) where,

\[
\Lambda_1(t_1) = \int_0^{t_1} \lambda_1(u) \, du
\] (3.4)

and

\[
\Lambda_2(t_1, t_2) = \int_0^{t_2} \lambda_2(t_1, u) \, du
\] (3.5)

The survival function can be written as

\[
S(t_1, t_2) = \exp[- \Lambda_1(t_1) - \Lambda_2(t_1, t_2)]
\] (3.6)

Now we define proportional hazards model for \((T_1, T_2)\) as

\[
\lambda_1(t_1 | \tilde{z}) = \lambda_{10}(t_1) e^{\beta_1' \tilde{z}}
\] (3.7)

and

\[
\lambda_2(t_1, t_2 | \tilde{z}) = \lambda_{20}(t_1, t_2) e^{\beta_2' \tilde{z}}
\] (3.8)

where \( \tilde{z} = (z_1, z_2, \ldots, z_r)' \) is a vector of covariates, \( \beta_1' \) and \( \beta_2' \) are \( r \)-component parameter vectors, independent of both \( t_1 \) and \( t_2 \) and \( \lambda_{10}(t_1) \) and \( \lambda_{20}(t_1, t_2) \) are baseline hazard functions. The model (3.7) means that the ratio \( \frac{\lambda_1(t_1 | \tilde{z}^{(1)})}{\lambda_1(t_1 | \tilde{z}^{(2)})} \) of the hazard functions of two individuals with covariate vectors \( \tilde{z}^{(1)} \) and \( \tilde{z}^{(2)} \) does not vary with \( t_1 \) and the model (3.8) means that the ratio \( \frac{\lambda_2(t_1, t_2 | \tilde{z}^{(1)})}{\lambda_2(t_1, t_2 | \tilde{z}^{(2)})} \) of the hazard
functions of two individuals with covariate vectors $z^{(1)}$ and $z^{(2)}$ does not vary with both $t_1$ and $t_2$.

From (3.7), it follows that the marginal hazard functions of $T_i$ for two-individuals are proportional to one another. The model (3.8) implies that the ratio of conditional hazard functions of $T_2$ given $T_i \geq t_1$ for two individuals are independent of both $t_1$ and $t_2$.

In many situations, one may be interested in the joint survival function $S(t_1,t_2 \mid z)$ of gap times. Using (3.6), (3.7) and (3.8), the survival function can be obtained as

$$S(t_1,t_2 \mid z) = \exp[-\Lambda_{10}(t_1)e^{\beta_1 z} - \Lambda_{20}(t_1,t_2)e^{\beta_2 z}]$$

(3.9)

3.3. Inference Procedures

Suppose now that there are $n$ independent subjects in the study so that $(T_{1i},T_{2i},C_i,z_i), \ i=1,2,...,n$ are $n$ independent replicates of $(T_1,T_2,C,z)$ where $T_i = X_i$ and $T_2 = X_2 - X_1$. In the presence of censoring, the observable data consists of $(\tilde{X}_{1i},\tilde{X}_{2i},\delta_{1i},\delta_{2i},z_i)$, where $\tilde{X}_{1i} = \min(T_{1i},C_i), \delta_{1i} = I(T_{1i} < C_i), \tilde{X}_{2i} = \min(T_{2i},C_i - T_{1i}), \delta_{2i} = I(T_{2i} < C_i - T_{1i})$ and $z_i$ is the covariate vector for $i=1,2,...,n$ and $j=1,2$ with $I(.)$ as indicator function. First, we consider the estimation of regression parameters $\beta_1$ and $\beta_2$.

The counting process $N_i(t_i) = \{N_{1i}(t_i), t_i \geq 0\}$ given at time $t_i$ by $N_i(t_i) = I(\tilde{X}_{1i} \leq t_i, \delta_i = 1)$ where $\tilde{X}_1 = \min(T_i,C)$ and $\delta_i = I(T_i < C)$. For fixed $t_i$, we also define a counting process $\{N_{2i}(t_1,t_2), t_1 \geq 0, t_2 \geq 0\}$, given at time $t_2$ by

$N_2(t_1,t_2) = I(\tilde{X}_{1i} \geq t_1, \tilde{X}_{2i} \leq t_2, \delta_2 = 1)$ where $\tilde{X}_2 = \min(T_2,C - T_1)$ and $\delta_2 = I(T_2 < C - T_1)$. Then we have, for $i=1,2,...,n$,

$$N_{1i}(t_i) = I(\tilde{X}_{1i} \leq t_i)\delta_{1i}$$

(3.10)

and

$$N_{2i}(t_1,t_2) = I(\tilde{X}_{1i} \geq t_1, \tilde{X}_{2i} \leq t_2)\delta_{2i}.$$  

(3.11)

Consider the at-risk processes $Y_i(t_i) = \{Y_{1i}(t_i), t_i \geq 0\}$ and
\[ Y_2(t_1, t_2) = \{ Y_2(t_1, t_2), t_1 \geq 0, t_2 \geq 0 \}, \text{ where} \]

\[ Y_{ii}(t_1) = I(X_{ii} \geq t_1) \quad (3.12) \]

and

\[ Y_{ii}(t_1, t_2) = I(X_{ii} \geq t_1, X_{ii} \geq t_2). \quad (3.13) \]

Then we can write

\[ E \left[ N_{ii}(dt_1) \mid \mathbb{F}^{t_2} \right] = Y_{ii}(t_1) \wedge Y_{ii}(dt_1) \quad (3.14) \]

and for fixed \( t_1 \),

\[ E \left[ N_{ii}(t_1, dt_2) \mid \mathbb{F}^{t_1, t_2} \right] = Y_{ii}(t_1, t_2) \wedge Y_{ii}(t_1, dt_2) \quad (3.15) \]

where \( \mathbb{F}^{t_1} \) belong to the right-continuous filtration \( \{ \mathbb{F}^{t_1} : t_1 \geq 0 \} \) and for fixed \( t_1, \mathbb{F}^{t_1, t_2} \) belong to the right-continuous filtration \( \{ \mathbb{F}^{t_1, t_2} : t_1 \geq 0, t_2 \geq 0 \} \) with \( \mathbb{F}^{t_1} \) and \( \mathbb{F}^{t_1, t_2} \) are defined by

\[ \mathbb{F}^{t_1} = \sigma \{ N_{ii}(u), Y_{ii}(u+), \xi : 0 \leq u \leq t_1, i = 1, 2, \ldots, n \} \quad (3.16) \]

and

\[ \mathbb{F}^{t_1, t_2} = \sigma \{ N_{ii}(t_1, v), Y_{ii}(t_1, v+), \xi : 0 \leq v \leq t_2, i = 1, 2, \ldots, n \}. \quad (3.17) \]

Denoting \( M_{ii}(t_1) = N_{ii}(t_1) - \int_{0}^{t_1} Y_{ii}(s) \wedge Y_{ii}(ds) \)

(3.18)

and

\[ M_{ii}(t_1, t_2) = N_{ii}(t_1, t_2) - \int_{0}^{t_2} Y_{ii}(t_1, s) \wedge Y_{ii}(t_1, ds), i = 1, 2, \ldots, n, \quad (3.19) \]

\( M_{ii}(t_1) \) is zero mean \( \mathbb{F}^{t_1} \) martingale and for fixed \( t_1, M_{ii}(t_1, t_2) \) is zero mean \( \mathbb{F}^{t_1, t_2} \) martingale.

Then the score function of \( \beta_i \) is given by

\[ U(\beta_i) = \sum_{i=1}^{n} \delta_i \left[ \xi_i - \frac{S_1^{(1)}(\beta_i, t_{ii})}{S_1^{(0)}(\beta_i, t_{ii})} \right] \quad (3.20) \]

where,

\[ S_1^{(0)}(t_{ii}, \beta_i) = \sum_{i=1}^{n} Y_{ii}(t_{ii}) e^{\beta_i \xi_i} \]
and
\[ S_1^{(1)}(\beta, t_{ii}) = \sum_{i=1}^{n} Y_{ii}(t_{ii}) e^{\beta^T \tilde{z}_i \tilde{z}_i}. \]

The maximum likelihood estimator of \( \beta \) is the solution of the score function \( U(\beta) = 0 \).

To obtain the estimate of \( \beta_2 \) consider the score function
\[ U(\beta_2) = \sum_{i=1}^{n} \delta_{2i} \left[ \frac{S_2^{(1)}(t_{ii}, t_{2i}, \beta_2)}{S_2^{(0)}(t_{ii}, t_{2i}, \beta_2)} \right] \]
where,
\[ S_2^{(0)}(t_{ii}, t_{2i}, \beta_2) = \sum_{i=1}^{n} Y_{2i}(t_{ii}, t_{2i}) e^{\beta^T \tilde{z}_i \tilde{z}_i} \]
and
\[ S_2^{(1)}(t_{ii}, t_{2i}, \beta_2) = \sum_{i=1}^{n} Y_{2i}(t_{ii}, t_{2i}) e^{\beta^T \tilde{z}_i \tilde{z}_i}. \]

As in the univariate set up, we can obtain the estimate of \( \beta_2 \) by maximizing the score function (3.21).

Now we discuss the estimation of baseline cumulative hazard functions \( \Lambda_{10}(t_1) \) and \( \Lambda_{20}(t_1, t_2) \). From Lawless (2003), the estimator of \( \Lambda_{10}(t_1) \) is given by
\[ \hat{\Lambda}_{10}(t_1) = \int_0^{t_1} \frac{I(Y_i(s) > 0)}{S_1^{(0)}(s, \hat{\beta})} dN_i(s), \]
which can be written as
\[ \hat{\Lambda}_{10}(t_1) = \sum_{i: t_{ii} \leq t_1} \left( \frac{\delta_{1i}}{\sum_{l=1}^{n} Y_{il}(t_{li}) e^{\hat{\beta}^T \tilde{z}_l \tilde{z}_l}} \right) \]
Similarly, by using the counting process approach, the estimator of \( \Lambda_{20}(t_1, t_2) \) is obtained as
\[ \hat{\lambda}_{20}(t_1, t_2) = \int_0^{t_1} \frac{I(Y_2(t_1, s) > 0)}{S_2^{(0)}(t_1, s, \hat{\beta}_1)} dN_2(t_1, s) \]  
(3.24)

which reduces to

\[ \hat{\lambda}_{20}(t_1, t_2) = \sum_{i:t_{i_1} \leq t_2} \left[ \frac{\delta_{2i}}{\sum_{i=1}^{n_2} Y_{2i}(t_{i_1}, t_{2i}) e^{\hat{\beta}_2 z}} \right]. \]  
(3.25)

Now we discuss the asymptotic properties of \( \hat{\beta}_1 \) and \( \hat{\beta}_2 \). The asymptotic properties of \( \hat{\beta}_1 \) are well studied in literature (see Lawless, 2003, p.342). Precisely, \( \hat{\beta}_1 \) is asymptotically \( r \)-variate normal with the mean vector \( \beta_1 \) and covariance matrix

\[ A_1^{-1}(\beta_1) \]  

where

\[ A_1(\beta_1) = \frac{1}{n} \sum_{i=1}^{n_2} \delta_{2i} \left[ \frac{S_1^{(2)}(t_{i_1}, \beta_1)}{S_1^{(0)}(t_{i_1}, \beta_1)} \frac{S_1^{(1)}(t_{i_1}, \beta_1) S_1^{(1)}(t_{i_1}, \beta_1)'}{\left(S_1^{(0)}(t_{i_1}, \beta_1) \right)^2} \right]. \]  
(3.26)

with

\[ S_1^{(2)}(t_{i_1}, \beta_1) = \sum_{i=1}^{n} Y_{1i}(t_{i_1}) e^{\beta_1 z}. \]

For fixed \( t_1 \), the maximum likelihood estimator \( \hat{\beta}_2 \) is the solution of the score function \( U(\beta_2) = 0 \) and hence \( \hat{\beta}_2 \) is a consistent estimator for \( \beta_2 \). When \( t_1 \) is fixed, the score statistic \( U(\beta_2) \) is asymptotically \( r \)-variate normal with mean zero vector and with covariance matrix \( A_2(\beta_2) \) where,

\[ A_2(\beta_2) = \frac{1}{n_2} \sum_{i=1}^{n_2} \delta_{2i} \left[ \frac{S_2^{(2)}(t_{i_1}, t_{2i}, \beta_2)}{S_2^{(0)}(t_{i_1}, t_{2i}, \beta_2)} \frac{S_2^{(1)}(t_{i_1}, t_{2i}, \beta_2) S_2^{(1)}(t_{i_1}, t_{2i}, \beta_2)'}{\left(S_2^{(0)}(t_{i_1}, t_{2i}, \beta_2) \right)^2} \right]. \]  
(3.27)

with \( n_2 \) as the number of observed occurrence of the second event and

\[ S_2^{(2)}(t_{i_1}, t_{2i}, \beta_2) = \sum_{i=1}^{n_2} Y_{2i}(t_{i_1}, t_{2i}) e^{\beta_2 z}. \]
Thus \( \hat{\beta}_2 \) is asymptotically \( r \)-variate normal with mean vector \( \beta_2 \) and covariance matrix \( A_2^{-1}(\beta_2) \).

The asymptotic properties of \( \hat{\lambda}_{10}(t_1) \) are well discussed in literature (see Lawless, 2003, p. 353). Under the same set of regularity conditions, as required for the asymptotic normality of \( \hat{\beta}_2 \), the \( (\hat{\lambda}_{20}(t_1,t_2) - \lambda_{20}(t_1,t_2)) \) converges weakly to a mean zero Gaussian process. In particular, for fixed \( t_1 \), the variance of \( \hat{\lambda}_{20}(t_1,t_2) \) can be consistently estimated by

\[
\text{var}[\hat{\lambda}_{20}(t_1,t_2)] = \sum_{t_1, t_2} \frac{\delta_{2i}}{S_2^{(0)}(t_1, t_2, \hat{\beta}_2)^2} + \hat{W}_2(t_1,t_2) A_2(\hat{\beta}_2)^{-1} \hat{W}_2(t_1,t_2) \tag{3.28}
\]

where,

\[
\hat{W}_2(t_1,t_2) = \sum_{t_1, t_2} \frac{\delta_{2i}}{S_2^{(0)}(t_1, t_2, \hat{\beta}_2)} \frac{\bar{X}_2(t_1, t_2, \hat{\beta}_2)}{S_2^{(0)}(t_1, t_2, \hat{\beta}_2)}
\]

with

\[
\bar{X}_2(t_1, t_2, \hat{\beta}_2) = \frac{\sum_{i=1}^{n_1} Y_{2i}(t_1, t_2) e^{\hat{\beta}_2' \bar{z}_i}}{\sum_{i=1}^{n_1} Y_{2i}(t_1, t_2) e^{\hat{\beta}_2' \bar{z}_i}}.
\]

One may often be interested in estimating the survival function \( S(t_1, t_2 \mid \bar{z}_0) \) of gap times with a fixed covariate \( \bar{z}_0 \). From (3.9), a natural estimate for \( S(t_1, t_2 \mid \bar{z}_0) \) is given by

\[
\hat{S}(t_1, t_2 \mid \bar{z}) = \exp[-\hat{\lambda}_{10}(t_1)e^{\hat{\beta}_2' \bar{z}_0} - \hat{\lambda}_{20}(t_1, t_2)e^{\hat{\beta}_2' \bar{z}_0}]. \tag{3.29}
\]

For fixed \( t_1, t_2 \) and \( \bar{z}_0 \), \( \{\hat{\lambda}_{10}(t_1), \hat{\lambda}_{20}(t_1, t_2)\} \) asymptotically follows a bivariate normal distribution with covariance matrix

\[
W(t_1, t_2) = \begin{bmatrix} W_1(t_1) & W_{12}(t_1, t_2) \\ W_{12}(t_1, t_2) & W_2(t_1, t_2) \end{bmatrix} \tag{3.30}
\]

where
\[ W_1(t_1) = \sum_{i: t_i \leq t_1} \frac{\delta_{t_1} \tilde{X}_i(t_{i1}, \hat{\beta}_i)}{S_1^{(0)}(t_{i1}, \hat{\beta}_i)} \]

with

\[ \tilde{X}_i(t_{i1}, \hat{\beta}_i) = \frac{\sum_{t=1}^n Y_{il}(t_{i1}) e^{\hat{\beta}_i' \tilde{z}_i}}{\sum_{t=1}^n Y_{il}(t_{i1}) e^{\hat{\beta}_i' \tilde{z}_i}} \]

\[ W_2(t_1, t_2) = \sum_{i: t_{i1} \leq t_1 \leq t_{i2}} \frac{\delta_{t_2} \tilde{X}_i(t_{i1}, t_{i2}, \hat{\beta}_i)}{S_2^{(0)}(t_{i1}, t_{i2}, \hat{\beta}_i)} \]

and

\[ W_{12}(t_1, t_2) = E \left[ \int_0^{t_2} \int_0^t I(Y_1(s) > 0) \frac{I(Y_2(t_1, u) > 0)}{Y_2(t_1, u)} dN_1(s) dN_2(t_1, u) \right] \]

A straightforward application of functional delta method, then, establishes the asymptotic normality of \( \hat{S}(t_1, t_2 | z_0) \) with mean \( S(t_1, t_2 | z_0) \) and variance that can be estimated as follows.

From Andersen et al. (1993, p. 503), the covariance between \( \hat{\lambda}_{10}(t_1) \) is consistently estimated as

\[ C_1(t_1, \hat{\beta}_1) = -A_1^{-1}(\hat{\beta}_1) \int_0^{t_1} S_1^{(1)}(s, \hat{\beta}_1) \left( S_1^{(0)}(s, \hat{\beta}_1) \right)^{-2} dN_1(s) \]

where

\[ dN_1(t_i) = \sum_{i=1}^n dN_{i1}(t_i) \]

with

\[ dN_{i1}(t_i) = I(T_{i1} \in [t_i, t_i + \Delta t_i]; \delta_{i1} = 1) \]

On similar lines, we can also obtain the covariance between \( \hat{\lambda}_{20}(t_1, t_2) \), which can be consistently estimated by

\[ C_2(t_1, t_2, \hat{\beta}_2) = -A_2^{-1}(\hat{\beta}_2) \int_0^{t_2} S_2^{(1)}(t_1, s, \hat{\beta}_2) \left( S_2^{(0)}(t_1, s, \hat{\beta}_2) \right)^{-2} dN_2(t_1, s) \]
The delta method is then used to estimate the covariance matrix of $(\hat{\beta}_1, \hat{\beta}_2, \hat{\lambda}_{10}(t_1), \hat{\lambda}_{20}(t_1, t_2))$. But in practical situations an attractive approach to variance or confidence interval estimation is through resampling methods. The naive bootstrap procedure of resampling the observed data units $(X_{1i}, X_{2i}, \delta_{1i}, \delta_{2i}, z_{0i})$ with replacement will be satisfactory under fairly mild conditions (see Efron and Tibshirani, 1993).

**Remark 3.1.**

In the absence of covariates ($\beta_1 = 0, \beta_2 = 0$), the expressions (3.23) and (3.25) for cumulative hazard function will reduces to the non-parametric estimates of $\hat{\lambda}_1(t_1)$ and $\hat{\lambda}_2(t_1, t_2)$ given in Wang and Wells (1998).

### 3.4. Simulation Study

In this section, we carried out a simulation study to evaluate the performance of the aforementioned inference procedures. We consider a Gumbel’s (1960) bivariate exponential distribution with survival function

$$S(t_1, t_2) = \exp(-t_1 - t_2 - \gamma t_1 t_2), \quad t_1, t_2 > 0$$  \hspace{1cm} (3.33)

with hazard functions

$$\lambda_1(t_1) = 1 \quad \text{and} \quad \lambda_2(t_1, t_2) = (1 + \gamma t_1).$$  \hspace{1cm} (3.34)

Two covariates $z_1$ and $z_2$ are generated from uniform (0, 1) distribution. We generated observations from Gumbel’s bivariate exponential distribution for different values of $\gamma$ using algorithm given in Devroye (1986). Independent censoring times are generated from the uniform distribution (0, $b$), where the constant $b$ is taken in such a way that 30% of the observations are censored. We compute estimates for 1000 simulations and we then calculate average bias and variance of the estimates of $\beta_1 = (\beta_{11}, \beta_{12}), \beta_2 = (\beta_{21}, \beta_{22})$ and baseline cumulative hazard functions. The estimates are given in Table 3.1 to Table 3.3. As $n$ increases, both bias and variance of the estimates decreases.
### Table 3.1. Bias and variance of $\hat{\beta}_{11}$ and $\hat{\beta}_{12}$

<table>
<thead>
<tr>
<th>$\beta_{11}$</th>
<th>$\beta_{12}$</th>
<th>$\gamma$</th>
<th>n</th>
<th>Bias $\hat{\beta}_{11}$</th>
<th>Var $\hat{\beta}_{11}$</th>
<th>Bias $\hat{\beta}_{12}$</th>
<th>Var $\hat{\beta}_{12}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>-0.8</td>
<td>0.7</td>
<td>50</td>
<td>-0.0789</td>
<td>0.0716</td>
<td>-0.0819</td>
<td>0.0884</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>-0.0486</td>
<td>0.0711</td>
<td>-0.0398</td>
<td>0.0113</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.8</td>
<td>50</td>
<td>-0.0157</td>
<td>0.0671</td>
<td>-0.0807</td>
<td>0.0934</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>-0.0134</td>
<td>0.0525</td>
<td>-0.0754</td>
<td>0.0536</td>
</tr>
<tr>
<td>0.7</td>
<td>0.9</td>
<td>0.7</td>
<td>50</td>
<td>-0.0801</td>
<td>0.0579</td>
<td>-0.0433</td>
<td>0.0607</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>-0.0462</td>
<td>0.0444</td>
<td>-0.0102</td>
<td>0.0296</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.8</td>
<td>50</td>
<td>-0.0826</td>
<td>0.0618</td>
<td>-0.0499</td>
<td>0.0693</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>-0.0493</td>
<td>0.0329</td>
<td>-0.0104</td>
<td>0.0475</td>
</tr>
</tbody>
</table>

### Table 3.2. Bias and variance of $\hat{\beta}_{21}$ and $\hat{\beta}_{22}$

<table>
<thead>
<tr>
<th>$\beta_{21}$</th>
<th>$\beta_{22}$</th>
<th>$\gamma$</th>
<th>n</th>
<th>Bias $\hat{\beta}_{21}$</th>
<th>Var $\hat{\beta}_{21}$</th>
<th>Bias $\hat{\beta}_{22}$</th>
<th>Var $\hat{\beta}_{22}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1.3</td>
<td>0.7</td>
<td>50</td>
<td>0.0236</td>
<td>0.0282</td>
<td>0.0289</td>
<td>0.0575</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>0.0210</td>
<td>0.0185</td>
<td>0.0287</td>
<td>0.0181</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.8</td>
<td>50</td>
<td>0.0231</td>
<td>0.0297</td>
<td>0.0284</td>
<td>0.0368</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>0.0188</td>
<td>0.0118</td>
<td>0.0280</td>
<td>0.0157</td>
</tr>
<tr>
<td>1.2</td>
<td>0.8</td>
<td>0.7</td>
<td>50</td>
<td>0.0273</td>
<td>0.0313</td>
<td>0.0182</td>
<td>0.0339</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>0.0239</td>
<td>0.0183</td>
<td>0.0167</td>
<td>0.0275</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.8</td>
<td>50</td>
<td>0.0236</td>
<td>0.0281</td>
<td>0.0166</td>
<td>0.0162</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>0.0224</td>
<td>0.0101</td>
<td>0.0153</td>
<td>0.0129</td>
</tr>
</tbody>
</table>
Table 3.3. Bias and variance of estimates of the baseline cumulative hazard functions

<table>
<thead>
<tr>
<th>$\beta_{11}$</th>
<th>$\beta_{12}$</th>
<th>$\beta_{21}$</th>
<th>$\beta_{32}$</th>
<th>$(t_1,t_2)$</th>
<th>$\gamma$</th>
<th>$n$</th>
<th>Bias $\hat{\lambda}_{10}(t_1)$</th>
<th>Var $\hat{\lambda}_{10}(t_1)$</th>
<th>Bias $\hat{\lambda}_{20}(t_1,t_2)$</th>
<th>Var $\hat{\lambda}_{20}(t_1,t_2)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>0.8</td>
<td>1</td>
<td>1.3</td>
<td>(1,0.9)</td>
<td>0.7</td>
<td>50</td>
<td>0.0969</td>
<td>0.0691</td>
<td>-0.0685</td>
<td>0.0301</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
<td>250</td>
<td>0.0305</td>
<td>0.0101</td>
<td>-0.0275</td>
<td>0.0192</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
<td>50</td>
<td>0.0124</td>
<td>0.0289</td>
<td>-0.0636</td>
<td>0.0364</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
<td>250</td>
<td>0.0102</td>
<td>0.0184</td>
<td>-0.0543</td>
<td>0.0156</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.8,1.1)</td>
<td>0.7</td>
<td>50</td>
<td>0.0322</td>
<td>0.0554</td>
<td>-0.0515</td>
<td>0.0307</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
<td>250</td>
<td>0.0291</td>
<td>0.0161</td>
<td>-0.0448</td>
<td>0.0255</td>
</tr>
<tr>
<td>0.7</td>
<td>0.9</td>
<td>1.2</td>
<td>0.8</td>
<td>(1,0.9)</td>
<td>0.7</td>
<td>50</td>
<td>0.0723</td>
<td>0.0769</td>
<td>-0.0522</td>
<td>0.0589</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
<td>250</td>
<td>0.0687</td>
<td>0.0656</td>
<td>-0.0293</td>
<td>0.0208</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
<td>50</td>
<td>0.0694</td>
<td>0.0736</td>
<td>0.0039</td>
<td>0.0764</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
<td>250</td>
<td>0.0201</td>
<td>0.0438</td>
<td>0.0003</td>
<td>0.0658</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.8,1.1)</td>
<td>0.7</td>
<td>50</td>
<td>0.0586</td>
<td>0.0432</td>
<td>-0.0279</td>
<td>0.0542</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
<td>250</td>
<td>0.0524</td>
<td>0.0374</td>
<td>-0.0229</td>
<td>0.0129</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
<td>50</td>
<td>0.0308</td>
<td>0.0619</td>
<td>0.0126</td>
<td>0.0855</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
<td>250</td>
<td>0.0127</td>
<td>0.0388</td>
<td>0.0015</td>
<td>0.0782</td>
</tr>
</tbody>
</table>

3.5. Data Analysis

For the illustration of the procedure, we consider a data given in Lawless (2003, p.531). This data show on the recurrent times to infection at the point of insertion of the catheter for 38 persons undergoing kidney dialysis. Data for the first two occurrences of infection are given; either one or both may be censored, because catheters were sometimes removed for causes other than infection. The two covariates considered are sex (1 = male, 2 = female) and kidney disease type (0 = glomerulo nephritis, 1 = acute nephritis, 2 = polycystic kidney disease, 3 = other). $T_1$ and $T_2$ represents the first two occurrences of infection.

We compute the estimates of $\hat{\beta}_1 = (\hat{\beta}_{11}, \hat{\beta}_{12})$, $\hat{\beta}_2 = (\hat{\beta}_{21}, \hat{\beta}_{22})$ by the method given in Section 3.3. The estimates $\hat{\beta}_1$ and $\hat{\beta}_2$ are $\hat{\beta}_1 = (-1.5046, -0.2354)$, $\hat{\beta}_2 = (-0.5185, -0.1008)$. It follows that both $\hat{\beta}_1$ and $\hat{\beta}_2$ have negative values. Thus the covariates in the study have negative effect on the recurrence time of the individuals. We then compute the estimates of baseline cumulative hazard functions.
and survival functions. The estimates are given in Table 3.4. From Table 3.4, we can observe that $\hat{\lambda}_{10}(t_1)$ is increasing in $t_1$, as expected. However, both $\hat{\lambda}_{20}(t_1,t_2)$ and $\hat{S}(t_1,t_2 \mid z)$ are depends on $t_1$ and $t_2$. Figure 3.1 shows the estimates of the survival function.

**Table 3.4.** Estimates of baseline cumulative hazard functions and survival function

<table>
<thead>
<tr>
<th>$(t_1,t_2)$</th>
<th>$z$</th>
<th>$\hat{\lambda}_{10}(t_1)$</th>
<th>$\hat{\lambda}_{20}(t_1,t_2)$</th>
<th>$\hat{S}(t_1,t_2 \mid z)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2,25)</td>
<td>(1,0)</td>
<td>0.3825</td>
<td>0.4547</td>
<td>0.7007</td>
</tr>
<tr>
<td>(7,9)</td>
<td>(1,0)</td>
<td>1.2435</td>
<td>0.1630</td>
<td>0.6885</td>
</tr>
<tr>
<td>(7,333)</td>
<td>(2,1)</td>
<td>1.2435</td>
<td>7.5370</td>
<td>0.0851</td>
</tr>
<tr>
<td>(8,16)</td>
<td>(1,3)</td>
<td>1.7286</td>
<td>0.3486</td>
<td>0.7097</td>
</tr>
<tr>
<td>(12,40)</td>
<td>(1,1)</td>
<td>2.2409</td>
<td>1.3795</td>
<td>0.3211</td>
</tr>
<tr>
<td>(13,66)</td>
<td>(2,1)</td>
<td>2.8038</td>
<td>1.9359</td>
<td>0.4820</td>
</tr>
<tr>
<td>(15,154)</td>
<td>(1,0)</td>
<td>3.9549</td>
<td>2.7114</td>
<td>0.0827</td>
</tr>
<tr>
<td>(22,28)</td>
<td>(1,3)</td>
<td>5.3857</td>
<td>0.6930</td>
<td>0.4085</td>
</tr>
</tbody>
</table>

**Figure 3.1.** Estimates of bivariate survival function

55
3.6. Conclusion

In this chapter, we developed a bivariate proportional hazards model, using marginal and conditional hazard functions, for gap times of recurrent events. Since the covariates under study have different effect on marginal and conditional hazard functions, proposed model is more useful to study the dependence of gap times on covariates. The estimators of the parameters and the baseline cumulative hazard functions were developed. Asymptotic properties of estimators were studied. Then, we illustrated our procedure with a real life data, given in Lawless (2003).