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A test against the stratified additive hazards model*

Yanqin Feng†, Xin Yuan, and Shishun Zhao

Stratified data are commonly encountered in practice. An interesting problem for this type of data is to test the existence of stratum effect. This paper discusses hypothesis testing of stratum effect for interval-censored data with informative observation times under the stratified additive hazards model. We construct a test statistic for this test problem, and show that the test statistic is asymptotically distributed as a chi-squared distribution. Finite sample performance of the proposed method is assessed through an extensive simulation study, which indicates the procedure works well. A real data set from a hemophilia study is analyzed to illustrate the proposed method.

Keywords and phrases: Interval-censored, Informative censoring, Partial likelihood, Hypothesis test.

1. INTRODUCTION

Interval-censored failure time data arise frequently in practice when an exact failure time of interest is not available. This type of data is only observed to belong to some intervals rather than observed exactly. Many regression models have been used to study this type of data. For example, Finkelstein (1986), Goggins and Finkelstein (2000), Huang (1996), Pan (2000) and Sun et al. (2015) investigated the fitting of the proportional hazards model. Sun (1997) considered a logistic regression model. Zhang et al. (2009) studied the proportional odds model. Zhang et al. (2005a) and Feng et al. (2015a) studied a class of linear transformation models. Wang et al. (2010), Feng et al. (2015b), and Feng and Chen (2018) studied the additive hazards model. For many objective causes, stratified data are commonly encountered in practice. For instance, a medical study may have data from several centers, or results might be reported separately by gender, race, dose or age. At this time, the stratified models and the corresponding stratum effects are interesting and needed to be analyzed.

One question of interest when study subjects come from different strata is the testing of the stratum effect. To address this, Sun and Yang (2000) studied the stratum effect problem and developed a class of nonparametric test procedures for right-censored data under the framework of the proportional hazards model. Fan et al. (2019) considered the same problem for case I interval-censored failure time data under the framework of the additive hazards model. As we know, similar methods based on the additive hazards model have not yet been explored for case II interval-censored data. This paper studies test method for testing stratum effect under the additive hazards model when one observes case II interval-censored data.

Case II interval-censoring is a mixture of left-, interval-, and right-censoring, and it is a common situation in periodical follow-up studies. Furthermore, the observation time may depend on the event time of interest, which often is referred to as informative censoring. For instance, patients with certain symptoms are more likely to visit the doctor than other patients. For the situation, the observation processes are related to the failure time process. We usually refer the observed data as interval-censored data with information (Zhang et al. 2005b). It is more complicated to test the stratum effects based on case II informatively interval-censored data. We could carry out a more powerful statistical analysis from the stratified model only when the stratum effects give a significant result. The additive hazards model is one of the most commonly used regression models and many inference procedures for this model have been discussed (Sun 2006). Compared with the proportional hazards model, the additive hazards model focuses on the additive effect or excess risks. We applied this model to discuss the test of stratum effects in this paper and more comments on this will be given afterwards.

The remainder of the paper is organized as follows. We will begin in Section 2 with introducing some notations, models, the test problem to be considered, and an estimation procedure for regression parameters. In Section 3, we propose a testing procedure and study its asymptotic properties. In Section 4, we give some results obtained from an extensive simulation study conducted for the evaluation of the finite sample performance of the proposed test procedure. Section 5 applies the proposed test method to a real data set from a hemophilia study. Some discussion and concluding remarks are given in Section 6.

2. NOTATIONS AND MODELS

In this section, we discuss the stratified additive hazards model for case II interval-censored data. We focus on testing

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†Corresponding author.

the existence of the stratum effect. For this, consider a failure time study that involves n independent subjects from K strata. Let T_{ki} denote the failure time of interest corresponding to the i-th subject in the k-th stratum, where $i = 1, \ldots, n_k; k = 1, \ldots, K$ and $n_1 + \cdots + n_K = n$. For stratified interval censored data, the observed information can be written as

$$\{Z_{ki}, U_{ki}, V_{ki}, \delta_{1i}^k, \delta_{2i}^k\} \quad \text{for} \quad i = 1, \ldots, n_k;\ k = 1, \ldots, K,$$

where $Z_{ki}(t)$ denotes a p-dimensional covariate vector for subject i in the k-th stratum, which may depend on time t, U_{ki} and V_{ki} are the observation times and $\delta_{1i}^k = I(T_{ki} < U_{ki})$ and $\delta_{2i}^k = I(U_{ki} \leq T_{ki} < V_{ki})$ are the censoring indicators for event time T_{ki}. To model the covariate effect, we assumed that T_{ki} follows the stratified additive hazards model

$$\lambda_{ki}^T(t|\, Z_{ki}(s), b_{1ki}, s \leq t) \;=\; \lambda_{0k}(t) \;+\; \beta_0' Z_{ki}(t) + b_{1ki}. \tag{1}$$

In the additive hazards model (1), $\lambda_{0k}(t)$ is the unknown baseline hazard function. For simplicity, the covariate effects β_0 are assumed to be identical for all T_{ki}. Our goal is to test the hypothesis

$$H_0 : \lambda_{01}(t) = \cdots = \lambda_{0K}(t).$$

Under informative censoring condition, we need to assume that the distributions of U_{ki}'s and V_{ki}'s depend on the survival time T_{ki}'s given the covariates. In order to model the dependence, following Wang et al. (2010), for $i = 1, \ldots, n_k$, and $k = 1, \ldots, K$, we assumed that the hazard functions of U_{ki} and V_{ki} have the forms of

$$\lambda_{ki}^U(t|Z_{ki}(s), b_{2ki}, s \leq t) \;=\; \lambda_{1k}(t)\, \exp(\gamma_0'\, Z_{ki}(t) + b_{2ki}), \tag{2}$$

and

$$\begin{aligned} &\lambda_{ki}^V(t|U_{ki} = u_{ki}, Z_{ki}(s), b_{3ki}, s \leq t) \\ &= I(t > U_{ki})\, \lambda_{2k}(t)\, \exp(\gamma_0' Z_{ki}(t) + b_{3ki}). \end{aligned} \tag{3}$$

In the above, $\lambda_{1k}(t)$ and $\lambda_{2k}(t)$ denote some unknown baseline hazard functions for U_{ki} and V_{ki}. The γ_0 is the vector of unknown regression parameters associated with the censoring times U_{ki} and V_{ki}. It is also assumed to be identical for all U_{ki} and V_{ki}. Here it is assumed that the random effects $\boldsymbol{b}_{ki} = (b_{1ki}, b_{2ki}, b_{3ki})', i = 1, \ldots, n_k; k = 1, \ldots, K$ are independent and identically distributed with mean zero and the covariance structure is subject to $\mathrm{cov}(b_{jki}, b_{lki}) = \sigma_{jl}$ for $j, l \in \{1, 2, 3\}$. The marginal dependence between T_{ki} and (U_{ki}, V_{ki}) is due to the fact that the unobserved b_{1ki}, b_{2ki} and b_{3ki} are dependent. For the rest part of this paper, we assumed that given $\boldsymbol{b}_{ki}$'s and the covariates, T_{ki}'s, U_{ki}'s and V_{ki}'s are independent.

The motivation of choosing the additive hazards model to fit the failure time T_{ki} is that, if the hazard function of T_{ki} conditional on the latent variable b_{1ki} has additive format, then it can be shown that the marginal hazard function of T_{ki} with respect to b_{1ki} also has the similar additive format as below,

$$\lambda_{ki}(t|Z_{ki}(s), s \leq t) \;=\; \lambda_{0k}^*(t) + \beta_0' Z_{ki}(t), \tag{4}$$

where

$$\lambda_{0k}^*(t) \;=\; \frac{d\,\Gamma_{0k}^*(t)}{d\,t}$$
$$\text{with} \;\; \Gamma_{0k}^*(t) \;=\; \int_0^t \lambda_{0k}(s) ds \;-\; \log[E(e^{(-tb_{1ki})})].$$

Also combining the conditional independence between T_{ki}'s, U_{ki}'s and V_{ki}'s, it can be shown that the hazard functions of $N_{ki}^{(1)}(t)$ and $N_{ki}^{(2)}(t)$ defined below satisfy the well-known Cox proportional hazards model (Cox 1972). The unobservable latent variables are all included in the nuisance parameters, which do not need to be estimated in this method. Therefore, this nice feature of additive hazards model could largely simplify the parameter estimation procedure as well as its asymptotic distribution derivation.

In order to estimate the regression parameter vectors, we start with defining some notations. Let $\delta_{3i}^k = 1 - \delta_{1i}^k - \delta_{2i}^k$, which indicates whether subject i in the k-th stratum is right censored or not. $N_{ki}^{(1)}(t) = (1 - \delta_{1i}^k) I(U_{ki} \leq t)$, $N_{ki}^{(2)}(t) = \delta_{3i}^k I(V_{ki} \leq t)$ if $t \geq U_{ki}$ and 0 if $t < U_{ki}$ are the counting processes for the event time T_{ki}. $\tilde{N}_{ki}^{(1)}(t) = I(U_{ki} \leq t)$ and $\tilde{N}_{ki}^{(2)}(t) = I(V_{ki} \leq t)$ are the counting processes for the observation times. $Y_{ki}^{(1)}(t) = I(U_{ki} \geq t)$ and $Y_{ki}^{(2)}(t) = I(V_{ki} \geq t)$ are two risk processes. According to the definitions, some straightforward computations yield that the counting processes $N_{ki}^{(1)}(t)$ and $N_{ki}^{(2)}(t)$ have intensity functions

$$\begin{aligned} &E_b\left[e^{b_{2ki} - tb_{1ki}}\right] e^{-\int_0^t \lambda_{0k}(s)ds} \lambda_{1k}(t) e^{-\beta_0' Z_{ki}^*(t) + \gamma_0' Z_{ki}(t)} \\ &:= \lambda_{1k}^*(t) e^{-\beta_0' Z_{ki}^*(t) + \gamma_0' Z_{ki}(t)}, \end{aligned} \tag{5}$$

and

$$I(t > U_{ki}) \lambda_{2k}^*(t) e^{-\beta_0' Z_{ki}^*(t) + \gamma_0' Z_{ki}(t)}, \tag{6}$$

where

$$\lambda_{2k}^*(t) = E_b\left[e^{b_{3ki} - tb_{1ki}}\right] e^{-\int_0^t \lambda_{0k}(s)ds} \lambda_{2k}(t),$$

and 'E_b' is the expectation with respect to the random effect $\boldsymbol{b}$. The intensity functions of $\tilde{N}_{ki}^{(1)}(t)$ and $\tilde{N}_{ki}^{(2)}(t)$ are

$$\begin{aligned} \lambda_{ki}^{(1)}(t|Z_i(s), s \leq t) &= e^{\gamma_0' Z_{ki}(t)} E_b[e^{b_{2ki}}] \lambda_{1k}(t) \\ &:= \tilde{\lambda}_{1k}(t) e^{\gamma_0' Z_{ki}(t)}, \end{aligned} \tag{7}$$

and

$$\begin{aligned} \lambda_{ki}^{(2)}(t|Z_i(s), s \leq t) &= I(U_{ki} < t) e^{\gamma_0' Z_{ki}(t)} E_b[e^{b_{3ki}}]\; \lambda_{2k}(t) \\ &:= \tilde{\lambda}_{2k}(t) I(U_{ki} < t) e^{\gamma_0' Z_{ki}(t)}. \end{aligned} \tag{8}$$

It can be seen that

$$M_{ki}^{(1)}(t) = N_{ki}^{(1)}(t) - \int_0^t Y_{ki}^{(1)}(s)\lambda_{1k}^*(s)e^{-\beta_0' Z_{ki}^*(s)+\gamma_0' Z_{ki}(s)}ds,$$

$$M_{ki}^{(2)}(t) = N_{ki}^{(2)}(t) - \int_0^t Y_{ki}^{(2)}(s)I(s > U_{ki})\lambda_{2k}^*(s)e^{-\beta_0' Z_{ki}^*(s)+\gamma_0' Z_{ki}(s)}ds,$$

$$\tilde{M}_{ki}^{(1)}(t) = \tilde{N}_{ki}^{(1)}(t) - \int_0^t Y_{ki}^{(1)}(s)\tilde{\lambda}_{1k}(s)e^{\gamma_0' Z_{ki}(s)}ds,$$

$$\tilde{M}_{ki}^{(2)}(t) = \tilde{N}_{ki}^{(2)}(t) - \int_0^t Y_{ki}^{(2)}(s)I(s > U_{ki})\tilde{\lambda}_{2k}(s)e^{\gamma_0' Z_{ki}(s)}ds$$

are martingales.

It can be seen that all the equations (5)–(8) satisfy the Cox proportional hazards models. Motivated by the estimating equation procedure proposed in Wang et al. (2010), in order to estimate the unknown parameters included in the models above, we can consider the partial likelihood function $L_1(\beta,\gamma) = L_1^1(\beta,\gamma)L_1^2(\beta,\gamma)$, where

$$L_1^1(\beta,\gamma) = \prod_{k=1}^{K}\prod_{i=1}^{n_k}\left[\frac{e^{-\beta' Z_{ki}^*(U_{ki})+\gamma' Z_{ki}(U_{ki})}}{\sum_{t=1}^{K}\sum_{j=1}^{n_t} I(U_{tj} \geq U_{ki})e^{-\beta' Z_{tj}^*(U_{ki})+\gamma' Z_{tj}(U_{ki})}}\right]^{1-\delta_{1i}^k},$$

$$L_1^2(\beta,\gamma) = \prod_{k=1}^{K}\prod_{i=1}^{n_k}\left[\frac{e^{-\beta' Z_{ki}^*(V_{ki})+\gamma' Z_{ki}(V_{ki})}}{\sum_{t=1}^{K}\sum_{j=1}^{n_t} I(V_{tj} \geq V_{ki} > U_{tj})e^{-\beta' Z_{tj}^*(V_{ki})+\gamma' Z_{tj}(V_{ki})}}\right]^{\delta_{3i}^k}.$$

Note that the function $L_1(\beta,\gamma)$ utilizes only U_{ki}'s and V_{ki}'s with non zero δ_{3i}^k's. This fact motivates us to improve the efficiency of estimates if all U_{ki}'s and V_{ki}'s information can be combined. Therefore we consider the following partial likelihood function

$$L_2(\gamma) = \prod_{k=1}^{K}\prod_{i=1}^{n_k}\frac{e^{\gamma' Z_{ki}(U_{ki})}}{\sum_{t=1}^{K}\sum_{j=1}^{n_t} I(U_{tj} \geq U_{ki})e^{\gamma' Z_{tj}(U_{ki})}} \cdot \frac{e^{\gamma' Z_{ki}(V_{ki})}}{\sum_{t=1}^{K}\sum_{j=1}^{n_t} I(V_{tj} \geq V_{ki} > U_{tj})e^{\gamma' Z_{tj}(V_{ki})}}.$$

We first estimate γ_0 by maximizing the function $L_2(\gamma)$ or solving the estimating equation $U_\gamma(\gamma) = 0$, where

$$U_\gamma(\gamma) = \frac{\partial \log L_2(\gamma)}{\partial\gamma} = \sum_{k=1}^{K}\sum_{i=1}^{n_k}\left(\int_0^\tau \left(Z_{ki}(t) - \bar{Z}_{1,\gamma}(t,\gamma)\right) d\tilde{N}_{ki}^{(1)}(t) + \int_0^\tau \left(Z_{ki}(t) - \bar{Z}_{2,\gamma}(t,\gamma)\right) d\tilde{N}_{ki}^{(2)}(t)\right).$$

We denote the resulting estimator by $\hat{\gamma}$. Next we plug $\hat{\gamma}$ into $L_1(\beta,\gamma)$ and get the estimator $\hat{\beta}$ by maximizing $L_1(\beta,\hat{\gamma})$ or solving the estimating equation $U_\beta(\beta,\hat{\gamma}) = 0$, where

$$U_\beta(\beta,\gamma) = \frac{\partial \log L_1(\beta,\gamma)}{\partial\beta} = -\sum_{k=1}^{K}\sum_{i=1}^{n_k}\left[\int_0^\tau \left[Z_{ki}^*(t) - \bar{Z}_{1,\beta}^*(t,\beta,\gamma)\right] dN_{ki}^{(1)}(t) + \int_0^\tau \left[Z_{ki}^*(t) - \bar{Z}_{2,\beta}^*(t,\beta,\gamma)\right] dN_{ki}^{(2)}(t)\right],$$

τ is the longest follow-up time, and

$$\bar{Z}_{1,\gamma}(t,\gamma) = \frac{S_{1,\gamma}^1(t,\gamma)}{S_{1,\gamma}^0(t,\gamma)},\quad \bar{Z}_{2,\gamma}(t,\gamma) = \frac{S_{2,\gamma}^1(t,\gamma)}{S_{2,\gamma}^0(t,\gamma)},$$

$$\bar{Z}_{1,\beta}^*(t,\beta,\gamma) = \frac{S_{1,\beta}^1(t,\beta,\gamma)}{S_{1,\beta}^0(t,\beta,\gamma)},\quad \bar{Z}_{2,\beta}^*(t,\beta,\gamma) = \frac{S_{2,\beta}^1(t,\beta,\gamma)}{S_{2,\beta}^0(t,\beta,\gamma)},$$

with

$$S_{1,\gamma}^j(t,\gamma) = \frac{1}{n}\sum_{k=1}^{K}\sum_{i=1}^{n_k}(Z_{ki}(t))^{\otimes j}Y_{ki}^{(1)}(t)e^{\gamma' Z_{ki}(t)},$$

$$S_{2,\gamma}^j(t,\gamma) = \frac{1}{n}\sum_{k=1}^{K}\sum_{i=1}^{n_k}(Z_{ki}(t))^{\otimes j}Y_{ki}^{(2)}(t)I(t > U_{ki})e^{\gamma' Z_{ki}(t)},$$

$$S_{1,\beta}^j(t,\beta,\gamma) = \frac{1}{n}\sum_{k=1}^{K}\sum_{i=1}^{n_k}(Z_{ki}^*(t))^{\otimes j}Y_{ki}^{(1)}(t)e^{-\beta' Z_{ki}^*(t)+\gamma' Z_{ki}(t)},$$

$$S_{2,\beta}^j(t,\beta,\gamma) = \frac{1}{n}\sum_{k=1}^{K}\sum_{i=1}^{n_k}(Z_{ki}^*(t))^{\otimes j}Y_{ki}^{(2)}(t) \cdot I(t > U_{ki})e^{-\beta' Z_{ki}^*(t)+\gamma' Z_{ki}(t)}$$

for $j = 0, 1$, and $Z^{\otimes 0} = 1, Z^{\otimes 1} = Z$. Using the similar arguments in Wang et al. (2010), it can be shown that $\hat{\gamma}$ is a consistent estimate of γ_0, and $\hat{\beta}$ is a consistent estimate of β_0 under H_0.

On the other hand, it can be seen that Cox proportional hazards model structures are also satisfied for the whole group under H_0. For $j = 1, 2$, it is natural to estimate $\Lambda_{jk}(t) = \int_0^t \lambda_{jk}^*(s)ds$ as follows

$$\hat{\Lambda}_{1k}(t,\beta,\gamma) = \int_0^t \frac{\sum_{i=1}^{n_k} dN_{ki}^{(1)}(s)}{\sum_{i=1}^{n_k} Y_{ki}^{(1)}(s)e^{-\beta' Z_{ki}^*(s)+\gamma' Z_{ki}(s)}},$$

$$\hat{\Lambda}_{2k}(t,\beta,\gamma) = \int_0^t \frac{\sum_{i=1}^{n_k} dN_{ki}^{(2)}(s)}{\sum_{i=1}^{n_k} Y_{ki}^{(2)}(s)I(s > U_{ki})e^{-\beta' Z_{ki}^*(s)+\gamma' Z_{ki}(s)}}.$$

Let $\lambda_j^*(t)$ denote the common underlying hazard function under H_0. The common function $\Lambda_j(t) = \int_0^t \lambda_j^*(s)ds$ can be estimated by

$$\hat{\Lambda}_1(t,\beta,\gamma) = \int_0^t \frac{\sum_{k=1}^K \sum_{i=1}^{n_k} dN_{ki}^{(1)}(s)}{\sum_{k=1}^{K}\sum_{i=1}^{n_k} Y_{ki}^{(1)}(s) e^{-\beta' Z_{ki}^*(s)+\gamma' Z_{ki}(s)}},$$

$$\hat{\Lambda}_2(t,\beta,\gamma) = \int_0^t \frac{\sum_{k=1}^K \sum_{i=1}^{n_k} dN_{ki}^{(2)}(s)}{\sum_{k=1}^{K}\sum_{i=1}^{n_k} Y_{ki}^{(2)}(s) I(s > U_{ki}) e^{-\beta' Z_{ki}^*(s)+\gamma' Z_{ki}(s)}}.$$

For testing of no stratification effect, we first introduce the vector function $W(\beta,\gamma) = (W_1(\tau,\beta,\gamma),\ldots, W_K(\tau,\beta,\gamma))'$, where

$$\begin{aligned} W_k(t,\beta,\gamma) &= \sum_{i=1}^{n_k} \int_0^t Y_{ki}^{(1)}(s) e^{-\beta' Z_{ki}^*(s)+\gamma' Z_{ki}(s)} d\left(\hat{\Lambda}_{1k}(s,\beta,\gamma)\right. \\ &\left. -\hat{\Lambda}_1(s,\beta,\gamma)\right) + \sum_{i=1}^{n_k} \int_0^t Y_{ki}^{(2)}(s) I(s > U_{ki}) \cdot \\ & e^{-\beta' Z_{ki}^*(s)+\gamma' Z_{ki}(s)} d\left(\hat{\Lambda}_{2k}(s,\beta,\gamma) - \hat{\Lambda}_2(s,\beta,\gamma)\right). \end{aligned}$$

The statistics $W(\hat{\beta},\hat{\gamma})$ represent the estimates of survival differences among strata adjusted for covariate effects. In the next section, we will propose a test for the existence of stratum effect based on $W(\hat{\beta},\hat{\gamma})$ and study its asymptotic distribution under H_0.

3. TEST METHOD FOR NO STRATIFICATION EFFECT

In order to test H_0, we first establish the limiting distribution of $W(\hat{\beta},\hat{\gamma})$ under H_0. We start from the following Taylor series expansions

$$\begin{aligned} \frac{1}{\sqrt{n}} U_\gamma(\gamma_0) &= -\frac{1}{\sqrt{n}}(U_\gamma(\hat{\gamma}) - U_\gamma(\gamma_0)) \\ &= \left(-\frac{1}{n}\frac{\partial U_\gamma(\gamma^*)}{\partial\gamma}\right)\sqrt{n}(\hat{\gamma}-\gamma_0), \\ \frac{1}{\sqrt{n}} U_\beta(\beta_0,\hat{\gamma}) &= -\frac{1}{\sqrt{n}}\left(U_\beta(\hat{\beta},\hat{\gamma}) - U_\beta(\beta_0,\hat{\gamma})\right) \\ &= -\frac{1}{n}\frac{\partial U_\beta(\beta^*,\hat{\gamma})}{\partial\beta}\sqrt{n}(\hat{\beta}-\beta_0), \\ \frac{1}{\sqrt{n}} U_\beta(\beta_0,\hat{\gamma}) &= \frac{1}{\sqrt{n}} U_\beta(\beta_0,\gamma_0) + \frac{1}{n}\frac{\partial U_\beta(\beta_0,\gamma_*)}{\partial\gamma}\sqrt{n}(\hat{\gamma}-\gamma_0), \end{aligned}$$

and

$$\begin{aligned} &\frac{1}{\sqrt{n}} W_k(\hat{\beta},\hat{\gamma}) \\ &= \frac{1}{\sqrt{n}} W_k(\beta_0,\gamma_0) + \frac{1}{n}\left(\frac{\partial W_k(\beta_*,\tilde{\gamma})}{\partial\beta}\right)\sqrt{n}(\hat{\beta}-\beta_0) \\ &+ \frac{1}{n}\left(\frac{\partial W_k(\beta_*,\tilde{\gamma})}{\partial\gamma}\right)\sqrt{n}(\hat{\gamma}-\gamma_0), \end{aligned}$$

where both β^* and β_* lie on the line segment between $\hat{\beta}$ and β_0, γ^*,γ_* and $\tilde{\gamma}$ are all in the line segment between $\hat{\gamma}$ and γ_0. Combining the consistency of $(\hat{\beta}',\hat{\gamma}')'$ and the equations above, we can obtain that

$$\begin{aligned} &\frac{1}{\sqrt{n}} W(\hat{\beta},\hat{\gamma}) \\ &= \frac{1}{\sqrt{n}} W(\beta_0,\gamma_0) + \frac{1}{n}\frac{\partial W(\beta_*,\tilde{\gamma})}{\partial\gamma}\left(-\frac{1}{n}\frac{\partial U_\gamma(\gamma^*)}{\partial\gamma}\right)^{-1} \\ &\cdot \frac{1}{\sqrt{n}} U_\gamma(\gamma_0) + \frac{1}{n}\frac{\partial W(\beta_*,\tilde{\gamma})}{\partial\beta}\left(-\frac{1}{n}\frac{\partial U_\beta(\beta^*,\hat{\gamma})}{\partial\beta}\right)^{-1} \\ &\cdot \frac{1}{\sqrt{n}} U_\beta(\beta_0,\hat{\gamma}) \\ &= \frac{1}{\sqrt{n}} W(\beta_0,\gamma_0) + \frac{1}{\sqrt{n}} W_\gamma(\beta_0,\gamma_0) B^{-1}(\gamma_0) U_\gamma(\gamma_0) \\ &+ \frac{1}{\sqrt{n}} W_\beta(\beta_0,\gamma_0) A_\beta^{-1}(\beta_0,\gamma_0) U_\beta(\beta_0,\hat{\gamma}) + o_p(1) \\ &:= \frac{1}{\sqrt{n}} W(\beta_0,\gamma_0) + \frac{1}{\sqrt{n}} \mathcal{B}(\beta_0,\gamma_0,\hat{\gamma}) + o_p(1), \end{aligned}$$

where $W_\gamma(\beta_0,\gamma_0), W_\beta(\beta_0,\gamma_0)$ and $A_\beta(\beta_0,\gamma_0)$ denote the limits of $n^{-1}\partial W(\beta,\gamma)/\partial\gamma, n^{-1}\partial W(\beta,\gamma)/\partial\beta$ and $n^{-1}\partial U_\beta(\beta,\gamma)/\partial\beta$ at $\beta=\beta_0$ and $\gamma=\gamma_0$, respectively.

To give the asymptotic properties, we assume the following regularity conditions are satisfied: (1) $Z_{ki}(t)$ is bounded. (2) $P\{Y_{ki}^{(j)}(t) = 1, 0 \le t \le \tau\} > 0$ for $k = 1,\ldots,K$; $i = 1,\ldots,n_k$; $j = 1,2$. Moreover, we suppose that $\lim_{n\to\infty} = \rho_k > 0$ for $k = 1,\ldots,K$; $j = 0,1$; and $m = 1,2$, and assume that $n_k^{-1}\sum_{i=1}^{n_k} Y_{ki}^{(1}(t) I(t > U_{ki}) e^{-\beta_0' Z_{ki}^*(t)+\gamma_0' Z_{ki}(t)}$, $n_k^{-1}\sum_{i=1}^{n_k} Y_{ki}^{(2)}(t) e^{-\beta_0' Z_{ki}^*(t)+\gamma_0' Z_{ki}(t)}$, $S_{m,\beta}^j(t,\beta_0,\gamma_0)$ and $S_{m,\gamma}^j(t,\gamma_0)$ uniformly converge to $\xi_k(t), \eta_k(t)$, $\kappa_m^j(t)$ and $\pi_m^j(t)$, respectively.

Under these assumptions, the following theorem gives the main result in this paper.

Theorem 3.1. *Under H_0 and the regularity conditions given above, as $n\to\infty$, $n^{-1/2}W(\hat{\beta},\hat{\gamma})$ converges in distribution to a zero-mean normal random vector, and the covariance matrix can be consistently estimated by $\hat{\Sigma}(\hat{\beta},\hat{\gamma})$ given in the Appendix.*

The proof of this theorem is sketched in the Appendix. It is easy to see that $\sum_{k=1}^K W_k(\hat{\beta},\hat{\gamma}) = 0$, this means that the components of the random vector $W(\hat{\beta},\hat{\gamma})$ have a strict linear relationship. Combining the Slutsky theorem, we suggest using statistic $T(\hat{\beta},\hat{\gamma}) := n^{-1}W(\hat{\beta},\hat{\gamma})'\hat{\Sigma}^-(\hat{\beta},\hat{\gamma})W(\hat{\beta},\hat{\gamma})$ to test the null hypothesis H_0, where $\hat{\Sigma}^-$ denotes the generalized inverse of $\hat{\Sigma}$. Under H_0, $T(\hat{\beta},\hat{\gamma})$ has the asymptotical χ^2-distribution with $K-1$ degrees of freedom.

4. SIMULATION STUDY

In this section, we conducted some simulation studies to evaluate the finite-sample properties of the test procedure

Table 1. Empirical sizes

			$Z \sim B(1, 0.5)$		$Z \sim N(0, 1)$		$Z \sim U(0, 1)$	
			$n_1 = n_2 =$		$n_1 = n_2 =$		$n_1 = n_2 =$	
(β_0, γ_0)	(λ_U, λ_V)	$(\lambda_{01}(t), \lambda_{02}(t))$	100	200	100	200	100	200
$(0, 0)$	$(2, 4)$	(1,1)	0.052	0.053	0.045	0.055	0.061	0.055
		(2,2)	0.042	0.049	0.058	0.044	0.054	0.048
		(3,3)	0.044	0.043	0.057	0.046	0.044	0.050
		(4,4)	0.056	0.042	0.051	0.049	0.048	0.047
		(t,t)	0.047	0.052	0.064	0.055	0.060	0.056
$(0, 0.5)$		(1,1)	0.053	0.046	0.061	0.047	0.054	0.051
		(2,2)	0.048	0.051	0.057	0.047	0.053	0.054
		(3,3)	0.042	0.049	0.060	0.045	0.055	0.046
		(4,4)	0.052	0.048	0.053	0.049	0.048	0.056
		(t,t)	0.047	0.051	0.062	0.052	0.057	0.052
$(0.5, 0)$		(1,1)	0.064	0.052	0.053	0.054	0.056	0.053
		(2,2)	0.046	0.045	0.056	0.046	0.047	0.045
		(3,3)	0.052	0.048	0.051	0.055	0.052	0.053
		(4,4)	0.041	0.055	0.052	0.051	0.059	0.046
		(t,t)	0.052	0.053	0.062	0.053	0.063	0.059
$(0.5, 0.5)$		(1,1)	0.058	0.058	0.058	0.056	0.063	0.058
		(2,2)	0.056	0.045	0.057	0.059	0.059	0.052
		(3,3)	0.058	0.057	0.062	0.053	0.064	0.055
		(4,4)	0.054	0.043	0.045	0.049	0.047	0.047
		(t,t)	0.054	0.048	0.059	0.053	0.057	0.045

proposed in the previous sections. For simplicity, we only considered two-stratum situation with $p = 1$ and assumed that the two sample strata had the same sample sizes. In this study, we generated the latent random variables b_{1ki}, b_{2ki} and b_{3ki} from a multivariate normal distribution with zero means, 0.1 standard deviations, and the correlation coefficients between b_{1ki} and b_{2ki}, b_{2ki} and b_{3ki}, and b_{1ki} and b_{3ki} are 0.8, 0.4 and 0.3, respectively.

The failure times T_{ki}'s, censoring times U_{ki}'s and V_{ki}'s were generated from models (1), (2) and (3), respectively. Specially, we generated the covariates Z_{ki}'s from the binomial distribution with the success probability of 0.5, the normal distribution $N(0, 1)$ or the uniform distribution $U(0, 1)$. We took $\lambda_{11}(t) = \lambda_{12}(t) := \lambda_U(t)$ and $\lambda_{21}(t) = \lambda_{22}(t) := \lambda_V(t)$. Here we considered the situation with the sample sizes of $n_1 = n_2 = 100$ or $n_1 = n_2 = 200$, and $(\beta_0, \gamma_0) = (0, 0), (0, 0.5), (0.5, 0)$ or $(0.5, 0.5)$. Tables 1 and 2 summarize the estimated sizes and powers of the proposed test procedure at level 0.05. The results given in the following tables are based on 1000 replications.

It can be seen from Table 1 that the proposed test procedure seems to give proper sizes and perform well for testing H_0 for all the set-ups considered here. One can see from Table 2 that the test procedure can also give good powers. It can also be seen from Table 2 that the power of the test procedure may depend on the underlying failure time processes. The smaller the difference between $\lambda_{01}(t)$ and $\lambda_{02}(t)$ is, the smaller the power becomes. All the estimated sizes and powers become better when the sample size increases.

In order to further see the performance of the chi-squared approximation to the null distribution of the test statistic $T(\hat{\beta}, \hat{\gamma})$, we examined the quantile-quantile (Q-Q) plots of $T(\hat{\beta}, \hat{\gamma})$ against the chi-squared random variable with 1 degree of freedom. For example, Figure 1 presents the Q-Q plots of $T(\hat{\beta}, \hat{\gamma})$ corresponding to the results given in Table 1 with $n_1 = n_2 = 100, Z \sim B(1, 0.5)$, and $(\beta_0, \gamma_0, \lambda_{01}(t), \lambda_{02}(t)) = (0, 0, 1, 1), (0, 0, 3, 3), (0.5.0.5, 1, 1), (0.5.0.5, 3, 3)$, respectively. Under the same set-ups of $(\beta_0, \gamma_0, \lambda_{01}(t), \lambda_{02}(t))$ and sample sizes as those used in Figure 1, Figures 2–3 give the Q-Q plots of $T(\hat{\beta}, \hat{\gamma})$ corresponding to $Z \sim N(0, 1)$ and $Z \sim U(0, 1)$, respectively. One can see from these Q-Q plots that the chi-squared approximation seems to be reasonable for $T(\hat{\beta}, \hat{\gamma})$ under H_0. We also investigated some other set-ups given in Table 1 and obtained similar results to these given above, we do not show them here.

5. AN APPLICATION

In this section, we applied the proposed method to analyze a real data set discussed in Data Set II of Sun (2006), which arises from a 16-center prospective study in the 1980s on people with hemophilia to investigate the risk of HIV-1 infection on these people. In the study, for patients' HIV-1 infection times, only interval-censored data are available. The patients were placed into two different groups based on the average annual dose of the blood they received. The

Table 2. Empirical powers

(β_0, γ_0)	$(\lambda_U(t), \lambda_V(t))$	$(\lambda_{01}(t), \lambda_{02}(t))$	$Z \sim B(1, 0.5)$ $n_1 = n_2 =$ 100	200	$Z \sim N(0, 1)$ $n_1 = n_2 =$ 100	200	$Z \sim U(0, 1)$ $n_1 = n_2 =$ 100	200
$(0, 0)$	$(2, 4)$	(2,4)	0.720	0.951	0.721	0.952	0.705	0.962
		(4,2)	0.750	0.954	0.737	0.955	0.728	0.960
		(2,3)	0.321	0.579	0.327	0.561	0.341	0.560
		(3,2)	0.335	0.555	0.322	0.574	0.327	0.580
		(1,3)	0.972	1	0.963	0.999	0.972	0.999
		(3,1)	0.968	1	0.957	0.998	0.953	1
		(1,t)	0.599	0.846	0.578	0.856	0.593	0.841
		(t,1)	0.574	0.853	0.577	0.853	0.575	0.863
$(0, 0.5)$		(2,4)	0.697	0.934	0.683	0.923	0.716	0.948
		(4,2)	0.707	0.941	0.675	0.932	0.718	0.956
		(2,3)	0.296	0.521	0.280	0.510	0.320	0.552
		(3,2)	0.276	0.514	0.290	0.530	0.313	0.504
		(1,3)	0.953	0.999	0.949	0.999	0.924	0.999
		(3,1)	0.923	0.998	0.951	1	0.942	0.999
		(1,t)	0.549	0.813	0.519	0.796	0.544	0.840
		(t,1)	0.559	0.835	0.521	0.801	0.567	0.839
$(0.5, 0)$		(2,4)	0.657	0.937	0.740	0.971	0.660	0.923
		(4,2)	0.673	0.907	0.750	0.954	0.666	0.917
		(2,3)	0.293	0.514	0.325	0.617	0.277	0.487
		(3,2)	0.301	0.503	0.351	0.620	0.276	0.482
		(1,3)	0.936	0.998	0.963	1	0.914	0.997
		(3,1)	0.926	0.999	0.970	1	0.942	0.996
		(1,t)	0.488	0.782	0.518	0.791	0.488	0.778
		(t,1)	0.478	0.800	0.534	0.811	0.540	0.790
$(0.5, 0.5)$		(2,4)	0.637	0.911	0.714	0.949	0.668	0.921
		(4,2)	0.654	0.917	0.732	0.955	0.650	0.914
		(2,3)	0.260	0.481	0.343	0.548	0.296	0.467
		(3,2)	0.287	0.462	0.329	0.572	0.269	0.482
		(1,3)	0.905	0.998	0.984	1	0.897	0.993
		(3,1)	0.911	0.997	0.971	1	0.899	0.997
		(1,t)	0.497	0.760	0.456	0.708	0.500	0.742
		(t,1)	0.475	0.763	0.468	0.773	0.508	0.744

data set includes the observations on 368 patients, 236 of them received no-factor VIII concentrate and 132 of them received low-dose factor VIII concentrate. One objective of this study is to compare the HIV-infection risks between the patients who received no factor VIII concentrate and those who received low dose factor VIII concentrate for their treatment. For this, we divided the patients into two strata, define $Z_{ki} = 0$ for the patients in the no does group and 1 otherwise.

Note that in the previous discussion, we have assumed that the observation for each subject is characterized by two variables U_{ki} and V_{ki}, and assumed that $T_{ki} < U_{ki}$ or $U_{ki} \leq T_{ki} < V_{ki}$ or $T_{ki} \geq V_{ki}$. But in this real data set, interval-censored data are given in the format $[L_{ki}, R_{ki}]$, and T_{ki} always belongs to $[L_{ki}, R_{ki}]$. To apply the proposed procedure, it is needed to do some data adjustment. Here we considered three data adjustment methods, which have been used by Feng et al. (2017). The first one referred to Method I is that for an interval-censored observation, it is natural to set $U_{ki} = L_{ki}$ and $V_{ki} = R_{ki}$; for a left-censored observation, we set $U_{ki} = R_{ki}$ and $V_{ki} = \tau$, while for a right-censored observation, a natural way is to set U_{ki} to be the smallest observation time and $V_{ki} = L_{ki}$. The second one referred to Method II is that for a left-censored observation, we set $U_{ki} = R_{ki}$ and V_{ki} being U_{ki} plus the median of all the observation times, while for right-censored and interval-censored observations, we will use the same adjustments as with Method I. The final one referred to Method III is that the adjustment will be the same as with Method I for left-censored and interval-censored observations, while for a right-censored observation, we will define $V_{ki} = L_{ki}$ and U_{ki} to be the smallest observation time if L_{ki} is not equal to the largest observation time and to be the median of all the observation times otherwise. The appropriateness

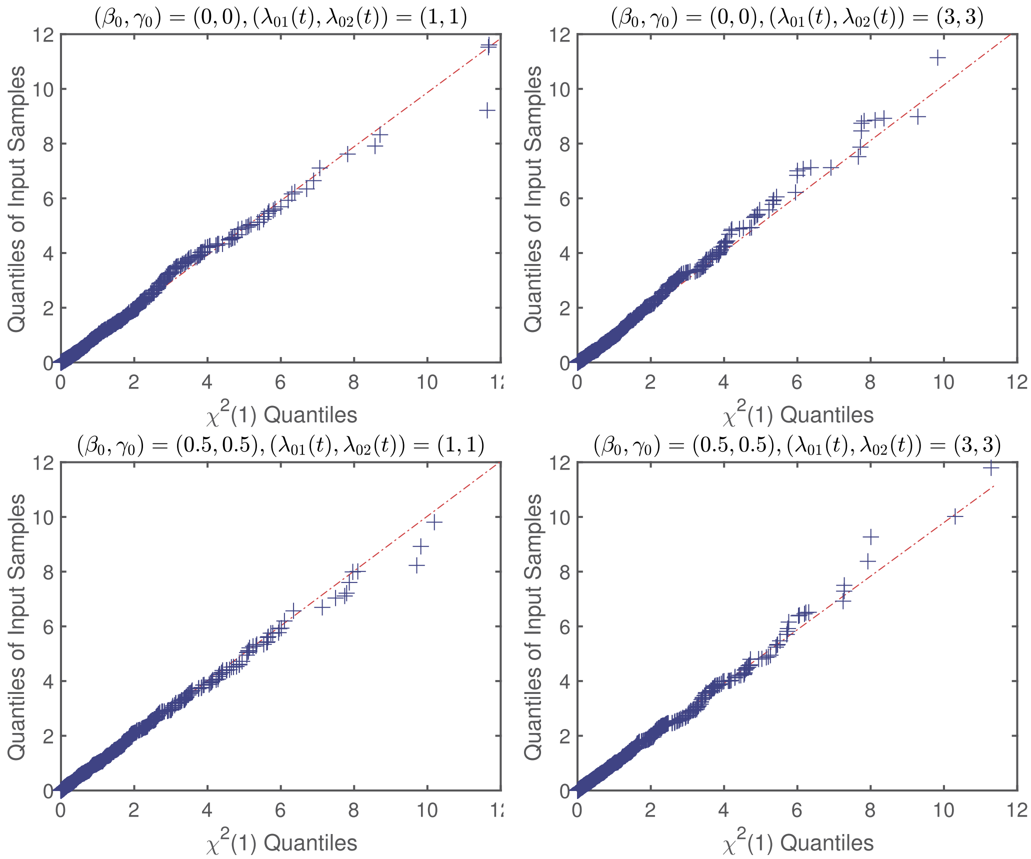

Figure 1. QQ-plots for $T(\hat{\beta}, \hat{\gamma})$ under $Z \sim B(1, 0.5)$.

of the models (2)–(3) for these adjusted data have been validated by Feng et al. (2017). Chen et al. (2020) used model (1) to fit the interval-censored failure time data considered here.

We apply the proposed test method to these three sets of data obtained by adjustment methods I, II and III respectively. The values of the test statistics for testing no stratification effect are 5.9298, 11.9378 and 5.1134, and the corresponding p-values are 0.0149, 0.0004 and 0.0237, respectively. One can see that all three data adjustment methods gave similar results. They all indicate that the patients receiving the factor VIII blood concentrate had significantly higher HIV-1 infection risk than those receiving no factor VIII concentrate, which agrees with the analysis result given by Sun et al. (2015).

6. CONCLUDING REMARKS

As discussed above, many methods have been developed for regression analysis of interval-censored data under various models. However, it seems that there does not exist an established method for testing of stratum effect under case II interval-censored data and the additive hazards model. This paper studied the testing of the stratum effect based on the stratified additive hazards and case II interval-censored data with informative observation times. A test statistic was proposed and the asymptotic chi-squared distribution of this statistic was established. The numerical study results indicate that the proposed test procedure works well for the practical situations.

This proposed procedure can be easily implemented since it does not involve any complicated nonparametric estimation of the distribution of the failure time. In particular, the determination of the proposed estimate $\hat{\beta}$ and $\hat{\gamma}$ can be easily carried out by some software packages. For example, we can use two Matlab functions 'fsolve' or 'fminsearch' to find $\hat{\beta}$ and $\hat{\gamma}$.

There exist several other further research directions related to the problem discussed here. First, this paper has assumed that the failure times of interest follow the additive hazards model (1). Sometimes one may prefer to consider some other models such as the linear transformation model or others. That is to say, one may want to develop some testing procedures similar to that given above for some other models. Second, in the previous preceding sections, we have assumed that all the covariates are observed exactly. The proposed method given above can be developed to the case where some covariates are missing. Third, there may ex-

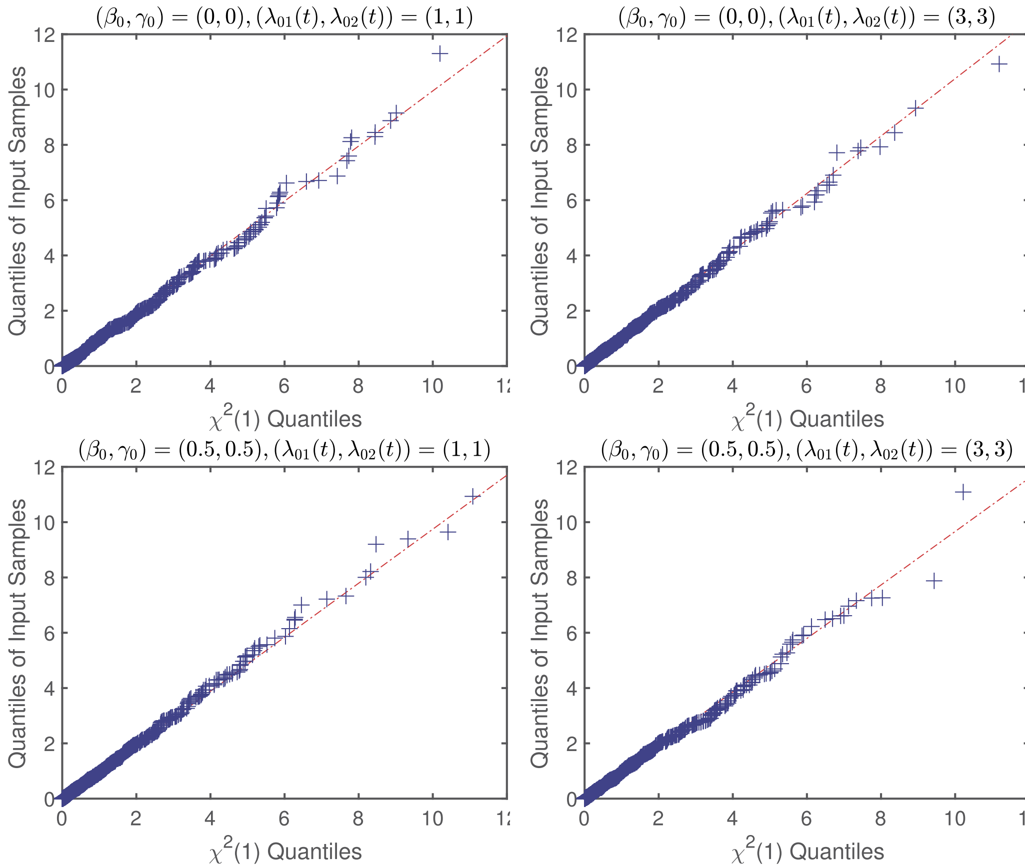

Figure 2. QQ-plots for $T(\hat{\beta}, \hat{\gamma})$ under $Z \sim N(0, 1)$.

ist some types of truncation in practice, it would be useful to develop similar test procedures that allow the existence of the truncations in addition to censoring. Finally, it would be useful to develop similar methods to clustered interval-censored data.

APPENDIX A

We consider a sequence of queueing systems indexed by n. It is assumed that each system is composed of J stations, indexed by 1 through J, and K customer classes, indexed by 1 through K. Each customer class has a fixed route through the network of stations. Customers in class k, $k = 1, \ldots, K$, arrive to the system according to a renewal process, independently of the arrivals of the other customer classes. These customers move through the network, never visiting a station more than once, until they eventually exit the system.

A.1 Proof for the limit theory of the test statistic

Proof. Let $\Delta_{kj} = 1$ if $j = k$, and 0 otherwise. Under H_0, some algebraic computations yield that

$$W_k(\beta_0, \gamma_0) = \sum_{j=1}^{K}\sum_{i=1}^{n_j}\int_0^\tau\left(\Delta_{kj} - \frac{\sum_{i=1}^{n_k} Y_{ki}^{(1)}(t)e^{-\beta_0' Z_{ki}^*(t)+\gamma_0' Z_{ki}(t)}}{\sum_{j=1}^{K}\sum_{i=1}^{n_j} Y_{ji}^{(1)}(t)e^{-\beta_0' Z_{ji}^*(t)+\gamma_0' Z_{ji}(t)}}\right) dM_{ji}^{(1)}(t)$$
$$+ \sum_{j=1}^{K}\sum_{i=1}^{n_j}\int_0^\tau\Bigg(\Delta_{kj} - \frac{\sum_{i=1}^{n_k} Y_{ki}^{(2)}(t)I(t > U_{ki})e^{-\beta_0' Z_{ki}^*(t)+\gamma_0' Z_{ki}(t)}}{\sum_{j=1}^{K}\sum_{i=1}^{n_j} Y_{ji}^{(2)}(t)I(t > U_{ji})e^{-\beta_0' Z_{ji}^*(t)+\gamma_0' Z_{ji}(t)}}\Bigg) dM_{ji}^{(2)}(t)$$
$$= \sum_{j=1}^{K}\sum_{i=1}^{n_j}\left\{\int_0^\tau\left[\Delta_{kj} - \frac{\rho_k \xi_k(t)}{\kappa_1^0(t)}\right] dM_{ji}^{(1)}(t) + \int_0^\tau\left[\Delta_{kj} - \frac{\rho_k \eta_k(t)}{\kappa_2^0(t)}\right] dM_{ji}^{(2)}(t)\right\} + o_p(1).$$

Denote $\xi_\rho(t) = (\rho_1\xi_1(t), \ldots, \rho_K\xi_K(t))', \eta_\rho(t) = (\rho_1\eta_1(t), \ldots, \rho_K\eta_K(t))'$, and $\Delta_j = (\Delta_{j1}, \ldots, \Delta_{jK})'$, we obtain that

(9)
$$\frac{1}{\sqrt{n}}W(\beta_0, \gamma_0) = \frac{1}{\sqrt{n}}\sum_{j=1}^{K}\sum_{i=1}^{n_j}\int_0^\tau\left[\int_0^\tau\left[\Delta_j - \frac{\xi_\rho(t)}{\kappa_1^0(t)}\right] dM_{ji}^{(1)}(t) + \int_0^\tau\left[\Delta_j - \frac{\eta_\rho(t)}{\kappa_2^0(t)}\right] dM_{ji}^{(2)}(t)\right] + o_p(1)$$
$$:= \frac{1}{\sqrt{n}}\sum_{j=1}^{K}\sum_{i=1}^{n_j}[c_{ji}^1(\beta_0, \gamma_0) + c_{ji}^2(\beta_0, \gamma_0)] + o_p(1).$$

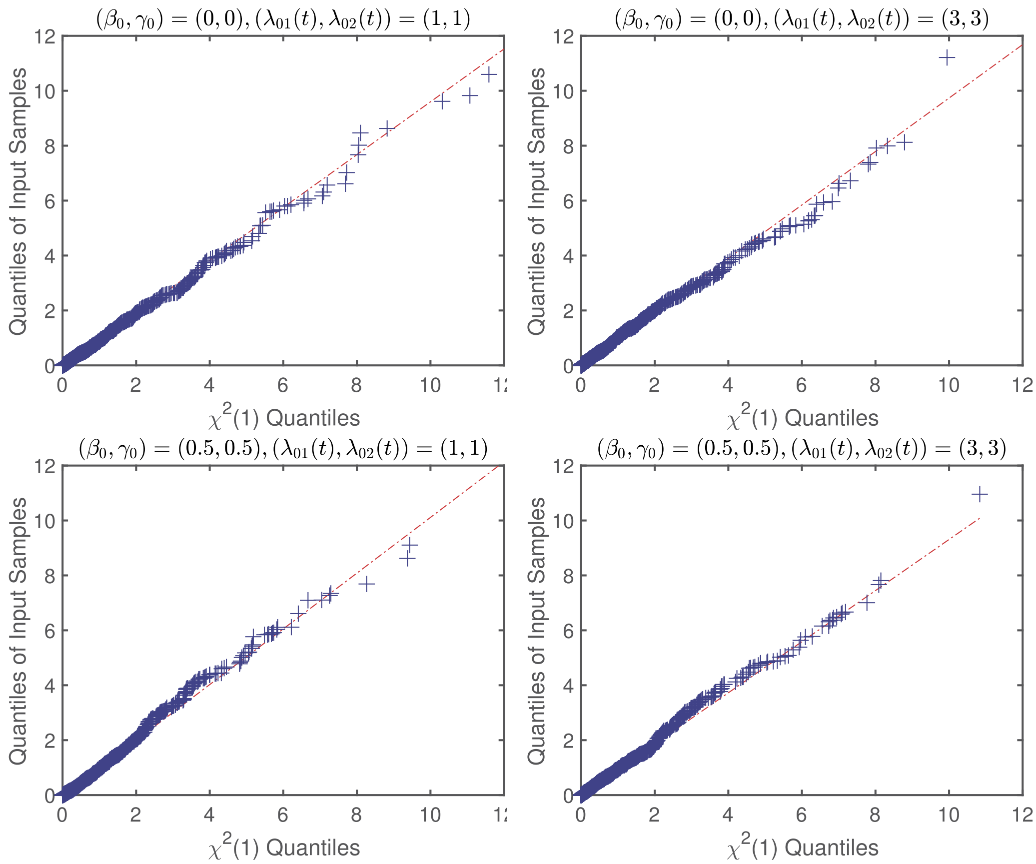

Figure 3. QQ-plots for $T(\hat{\beta},\hat{\gamma})$ under $Z\sim U(1,0.5)$.

Note that $n^{-1/2}\hat{U}_\gamma(\gamma_0)$ and $n^{-1/2}\hat{U}_\beta(\beta_0,\gamma_0)$ can be rewritten as

$$\begin{aligned}
&\frac{1}{\sqrt{n}}U_\gamma(\gamma_0)\\
&=\frac{1}{\sqrt{n}}\sum_{k=1}^{K}\sum_{i=1}^{n_k}\left(\int_0^\tau\left(Z_{ki}(t)-\bar{Z}_{1,\gamma}(t,\gamma_0)\right)d\tilde{M}_{ki}^{(1)}(t)\right.\\
&\left.+\int_0^\tau\left(Z_{ki}(t)-\bar{Z}_{2,\gamma}(t,\gamma_0)\right)d\tilde{M}_{ki}^{(2)}(t)\right)\\
&=\frac{1}{\sqrt{n}}\sum_{k=1}^{K}\sum_{i=1}^{n_k}\left[\int_0^\tau\left(Z_{ki}(t)-\frac{\pi_1^1(t)}{\pi_1^0(t)}\right)d\tilde{M}_{ki}^{(1)}(t)\right.\\
&\left.+\int_0^\tau\left(Z_{ki}(t)-\frac{\pi_2^1(t)}{\pi_2^0(t)}\right)d\tilde{M}_{ki}^{(2)}(t)\right]+o_p(1)\\
&:=\frac{1}{\sqrt{n}}\sum_{k=1}^{K}\sum_{i=1}^{n_k}[a_{ki}^1(\gamma_0)+a_{ki}^2(\gamma_0)]+o_p(1),
\end{aligned}$$

and

$$\begin{aligned}
&\frac{1}{\sqrt{n}}U_\beta(\beta_0,\gamma_0)\\
&=\frac{-1}{\sqrt{n}}\sum_{k=1}^{K}\sum_{i=1}^{n_k}\left[\int_0^\tau\left[Z_{ki}(t)-\bar{Z}_{1,\beta}^*(t,\beta_0,\gamma_0)\right]dM_{ki}^{(1)}(t)\right.\\
&\left.+\int_0^\tau\left[Z_{ki}(t)-\bar{Z}_{2,\beta}^*(t,\beta_0,\gamma_0)\right]dM_{ki}^{(2)}(t)\right]\\
&=\frac{-1}{\sqrt{n}}\sum_{k=1}^{K}\sum_{i=1}^{n_k}\left[\int_0^\tau\left[Z_{ki}(t)-\frac{\kappa_1^1(t)}{\kappa_1^0(t)}\right]dM_{ki}^{(1)}(t)\right.\\
&\left.+\int_0^\tau\left[Z_{ki}(t)-\frac{\kappa_2^1(t)}{\kappa_2^0(t)}\right]dM_{ki}^{(2)}(t)\right]+o_p(1)\\
&:=\frac{1}{\sqrt{n}}\sum_{k=1}^{K}\sum_{i=1}^{n_k}[b_{ki}^1(\beta_0,\gamma_0)+b_{ki}^2(\beta_0,\gamma_0)]+o_p(1).
\end{aligned}$$

Using the Taylor expansion, $n^{-1/2}\hat{U}_\beta(\beta_0,\hat{\gamma})$ can be rewritten as

$$\begin{aligned}
&\frac{1}{\sqrt{n}}U_\beta(\beta_0,\hat{\gamma})\\
&=\frac{1}{\sqrt{n}}U_\beta(\beta_0,\gamma_0)+\frac{1}{n}\frac{\partial U_\beta(\beta_0,\gamma_*)}{\partial\gamma}\\
&\cdot\left(-\frac{1}{n}\frac{\partial U_\gamma(\gamma^*)}{\partial\gamma}\right)^{-1}\frac{1}{\sqrt{n}}U_\gamma(\gamma_0)\\
&=\frac{1}{\sqrt{n}}\sum_{k=1}^{K}\sum_{i=1}^{n_k}\left\{b_{ki}^1(\beta_0,\gamma_0)+b_{ki}^2(\beta_0,\gamma_0)\right.\\
&\left.+A_\gamma(\beta_0,\gamma_0)B^{-1}(\gamma_0)[a_{ki}^1(\gamma_0)+a_{ki}^2(\gamma_0)]\right\}+o_p(1)
\end{aligned}$$

$$:= \frac{1}{\sqrt{n}} \sum_{k=1}^{K} \sum_{i=1}^{n_k} D_{ki}(\beta_0, \gamma_0) + o_p(1),$$

where $A_\gamma(\beta_0, \gamma_0), B(\gamma_0)$ denote the limits of $n^{-1}\partial U_\beta(\beta_0, \gamma)/\partial\gamma$ and $-n^{-1}\partial U_\gamma(\gamma)/\partial\gamma$ at $\gamma = \gamma_0$, respectively. Thus $n^{-1/2}\mathcal{B}(\beta_0, \gamma_0, \hat{\gamma})$ can be rewritten as

$$(10) \quad \frac{1}{\sqrt{n}} \sum_{j=1}^{K} \sum_{i=1}^{n_j} W_\gamma(\beta_0, \gamma_0) B^{-1}(\gamma_0)[a^1_{ji}(\gamma_0) + a^2_{ji}(\gamma_0)] + W_\beta(\beta_0, \gamma_0) A^{-1}_\beta(\beta_0, \gamma_0) D_{ji}(\beta_0, \gamma_0) + o_p(1).$$

Combining (7) and (8), we obtain that $n^{-1/2}W(\hat{\beta}, \hat{\gamma})$ is approximately equal to

$$\frac{1}{\sqrt{n}} \sum_{j=1}^{K} \sum_{i=1}^{n_j} \Big\{ [c^1_{ji}(\beta_0, \gamma_0) + c^2_{ji}(\beta_0, \gamma_0)] + W_\gamma(\beta_0, \gamma_0) B^{-1}(\gamma_0)[a^1_{ji}(\gamma_0) + a^2_{ji}(\gamma_0)] + W_\beta(\beta_0, \gamma_0) A^{-1}_\beta(\beta_0, \gamma_0) D_{ji}(\beta_0, \gamma_0) \Big\}$$
$$:= \frac{1}{\sqrt{n}} \sum_{j=1}^{K} \sum_{i=1}^{n_j} \Gamma_{ji}(\beta_0, \gamma_0).$$

Note that $a^1_{ki}(\gamma_0), a^2_{ki}(\gamma_0), b^1_{ki}(\beta_0, \gamma_0), b^2_{ki}(\beta_0, \gamma_0), c^1_{ki}(\beta_0, \gamma_0)$ and $c^2_{ki}(\beta_0, \gamma_0)$ are all martingales with mean zeros. It thus follows from the multivariate Central Limit Theorem that $n^{-1/2}W(\hat{\beta}, \hat{\gamma})$ converges in distribution to a zero-mean normal random vector with the covariance matrix can be consistently estimated by

$$\hat{\Sigma}(\hat{\beta}, \hat{\gamma}) := \frac{1}{n} \sum_{j=1}^{K} \sum_{i=1}^{n_j} \hat{\Gamma}_{ji}(\hat{\beta}, \hat{\gamma}) \hat{\Gamma}'_{ji}(\hat{\beta}, \hat{\gamma}),$$

where

$$\hat{\Gamma}'_{ji}(\hat{\beta}, \hat{\gamma}) = \hat{c}^1_{ji}(\hat{\beta}, \hat{\gamma}) + \hat{c}^2_{ji}(\hat{\beta}, \hat{\gamma}) + W_\gamma(\hat{\beta}, \hat{\gamma}) \hat{B}^{-1}(\hat{\gamma})[\hat{a}^1_{ji}(\hat{\gamma}) + \hat{a}^2_{ji}(\hat{\gamma})] + W_\beta(\hat{\beta}, \hat{\gamma}) \hat{A}^{-1}_\beta(\hat{\beta}, \hat{\gamma}) \hat{D}_{ji}(\hat{\beta}, \hat{\gamma}).$$

Hence, the statistic $T(\hat{\beta}, \hat{\gamma}) = n^{-1}W(\hat{\beta}, \hat{\gamma})'\hat{\Sigma}^-(\hat{\beta}, \hat{\gamma})W(\hat{\beta}, \hat{\gamma})$ has the asymptotically chi-squared distribution with $K-1$ degrees of freedom. □

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Yanqin Feng
School of Mathematics and Statistics
Wuhan University
Wuhan
China
Computational Science Hubei Key Laboratory
Wuhan University
Wuhan 430072
China
E-mail address: yanqf2008@aliyun.com

Xin Yuan
School of Mathematics and Statistics
Wuhan University
Wuhan
China
E-mail address: 624371799@qq.com

Shishun Zhao
Center for Applied Statistical Research and College of Mathematics
Jilin University
Changchun
China
E-mail address: zhaoss@jlu.edu.cn
url: http://www.foo.com