Research Article

Additive Hazard Regression for the Analysis of Clustered Survival Data from Case-Cohort Studies

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Received 6 March 2020; Revised 11 June 2020; Accepted 23 June 2020; Published 16 July 2020

Academic Editor: Antonio Di Crescenzo

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The case-cohort design is an effective and economical method in large cohort studies, especially when the disease rate is low. Case-cohort design in most of the existing literature is mainly used to analyze the univariate failure time data. But in practice, multivariate failure time data are commonly encountered in biomedical research. In this paper, we will propose methods based on estimating equation method for case-cohort designs for clustered survival data. By introducing the event failure rate, three different weight functions are constructed. Then, three estimating equations and parameter estimators are presented. Furthermore, consistency and asymptotic normality of the proposed estimators are established. Finally, the simulation results show that the proposed estimation procedure has reasonable finite sample behaviors.

1. Introduction

In many failure time studies, there is a natural clustering of study subjects such that failure times within the same cluster may be correlated. One example of clinical trial is that the failure times of patients within a family may be correlated because they have common genetic characteristics and environmental factors. Another example is the time to onset of blindness in the left and right eyes of the patients with diabetic retinopathy. So, in this case, the focus is on the potential clustering in the data. Moreover, the data structure is that the observations from different clusters are independent, while observations within a cluster may be correlated. Interested readers can refer to the papers [1–4] and the references therein.

In epidemiological research, the collection of detailed follow-up information is costly and time consuming, especially when the incidence of disease is low. One may consider the case-cohort design, proposed by Prentice [5], which is widely used for the large cohort studies. It entails collecting covariate data for all subjects who experienced the event of interest in the full cohort and for a random sample from the entire cohort. It has the same goals in studying risk factor as collecting the full

data. Therefore, many studies about case-cohort data have been yielded. For example, it has been applied to the Cox proportional risk model [6], additive risk regression model [7], semiparametric transfer model [8], accelerated failure time model [9], and additive multiple risk regression model [10, 11].

However, there is little research on group failure time data under case-cohort design. For example, Lu and Shih [12] applied the proportional risk model to clustered failure time data under case cohort and proposed three design methods of case cohort to extract subcolumns. Under different sampling mechanisms, the estimation equations are established, and then the large sample nature of the obtained estimation is proved. Unfortunately, the risk set considered by Lu and Shih [12] only contains the individuals in the subcolumns. Furthermore, Zhang et al. [13] added the failure information out of the subcolumns to the proportional risk model and proposed three kinds of different estimation equations and parameter estimates. The numerical simulation results show that the proposed model is effective. Note that the above literature studied the clustered data from case cohort based on the marginal proportional hazard models. In some practical cases, the effect of

covariates may be additive. Then, the proportional risk model is no longer applicable. Therefore, in this paper, an additive risk model will be applied to clustered data in case-cohort design. Moreover, we will construct the weighted estimation equation, propose the estimation of regression parameters, and prove the asymptotic properties of the estimators.

The remainder of the paper is organized as follows. In Section 2, we describe the proposed estimation procedures. Then, we establish the consistency and asymptotic normality of the resulting estimator in Section 3. Numerical evidence in support of the theory is presented in Section 4. Finally in Section 5, some conclusions are drawn.

2. Model and Estimation Procedures

Suppose the full cohort consists of n independent clusters, and the i -th cluster ($i = 1, \dots, n$) has m_i correlated subjects. We assume that subjects within the same cluster are exchangeable. In advance of follow-up, a random sample of the entire cohort, called the subcohort, is selected. Covariate data are then collected from individuals in the subcohort as well as those observed to fail in the entire cohort. Now, we consider the following three designs to obtain the subcohort [13]:

Design A: randomly sample individuals from each cluster with Bernoulli sampling. In other words, each individual in each cluster has an independent fixed probability of being selected to the subcohort.

Design B: randomly sample clusters from the full cohort with Bernoulli sampling.

Design C: randomly sample clusters from the full cohort with Bernoulli sampling and then randomly sample subjects with Bernoulli sampling from the selected clusters.

Note that Design A and Design B are special cases of Design C.

Let T_{ij} and C_{ij} denote the potential failure time and the potent censoring time for the j -th subject in the i -th cluster, respectively. Let $Z_{ij}(t)$ represent a possibly time-dependent $p \times 1$ vector of covariates, restricted to be external. We assume that T_{ij} and C_{ij} are independent conditional on the given $Z_{ij}(\cdot)$. The observed time is $X_{ij} = \min(Y_{ij}, C_{ij})$. Let $\delta_{ij} = I(T_{ij} \leq C_{ij})$ be the indicator of failure, $N_{ij}(t) = I(X_{ij} \leq t, \delta_{ij} = 1)$, and $Y_{ij}(t) = I(X_{ij} \geq t)$.

Let H_i denote the indicator for the i -th subject being selected into the subcohort and H_{ij} denote the indicator for the j th subject in the i -th cluster being selected into the sample. Both H_i and H_{ij} are the independent Bernoulli variables, where $\mathcal{E}(H_i) = \gamma$, $\mathcal{E}(H_{ij}) = \theta$. Under Design A, $H_i = 1$, for $i = 1, \dots, n$. Under Design B, $H_{ij} = 1$, for $i = 1, \dots, n, j = 1, \dots, m_i$.

Suppose that the marginal hazard function $\lambda_{ij}(t)$ is associated with $Z_{ij}(t)$ as follows:

$$\lambda_{ij}\{t | Z_{ij}(t)\} = \lambda_0(t) + \beta_0^T Z_{ij}(t), \quad (1)$$

where $\lambda_0(\cdot)$ is an unspecified baseline hazard function and β_0 is a $p \times 1$ vector of regression parameters.

If the full cohort data are available, the estimate of the true regression parameter β_0 in (1) could be obtained by solving the following estimating function [14]:

$$U_H(\beta) = \sum_{i=1}^n \sum_{j=1}^{m_i} \int_0^\tau \{Z_{ij}(t) - \bar{Z}_H(t)\} \{dN_{ij}(t) - Y_{ij}(t)\beta^T Z_{ij}(t)dt\}, \quad (2)$$

where $\bar{Z}_H(t) = (\sum_{i=1}^n \sum_{j=1}^{m_i} Y_{ij}(t)Z_{ij}(t) / \sum_{i=1}^n \sum_{j=1}^{m_i} Y_{ij}(t))$.

Then, the estimator of β_0 in (1) can be estimated by $\hat{\beta}_H$, which is the solution to the estimating equations $U_H(\beta) = 0$. That is,

$$\hat{\beta}_H = \left[\sum_{i=1}^n \sum_{j=1}^{m_i} \int_0^\tau Y_{ij}(t) \{Z_{ij}(t) - \bar{Z}(t)\}^{\otimes 2} dt \right]^{-1} \cdot \left[\sum_{i=1}^n \sum_{j=1}^{m_i} \int_0^\tau \{Z_{ij}(t) - \bar{Z}(t)\} dN_{ij}(t) \right], \quad (3)$$

where $\tau < \infty$, $a^{\otimes 2} = aa^T$.

For clustered failure time data from case-cohort studies, we consider the observed-event probability, $\Pr(\delta_{ij} = 1)$, which we denote by p_0 [15]. We propose three procedures to estimate β_0 , which are the same designs proposed by Zhang et al. [13] except that we consider the additive hazard regression model. We then develop a weighted estimating equation as follows:

$$U(\beta, p) = \sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} \int_0^\tau \{Z_{ij}(t) - \bar{Z}(t)\} \{dN_{ij}(t) - Y_{ij}(t)\beta^T Z_{ij}(t)dt\}, \quad (4)$$

where $\bar{Z}(t) = (\sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} Y_{ij}(t)Z_{ij}(t) / \sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} Y_{ij}(t))$, $\rho_{ij} = (p/(N_1/N))\delta_{ij} + ((1-p)/(n_0/N))(1-\delta_{ij})H_iH_{ij}$ with $N = \sum_{i=1}^n m_i$, $N_1 = \sum_{i=1}^n \sum_{j=1}^{m_i} \delta_{ij}$, and $n_0 = \sum_{i=1}^n \sum_{j=1}^{m_i} (1-\delta_{ij})H_iH_{ij}$.

By solving the estimation equation $U(\beta, p_0) = 0$, we could obtain $\hat{\beta}$ to estimate β_0 :

$$\hat{\beta} = \left[\sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} \int_0^\tau \{Z_{ij}(t) - \bar{Z}(t)\}^{\otimes 2} dt \right]^{-1} \cdot \left[\sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} \int_0^\tau \{Z_{ij}(t) - \bar{Z}(t)\} dN_{ij}(t) \right]. \quad (5)$$

However, p_0 is usually not known in most situations. In case where the study cohort is well defined, we can use $\hat{p}_w$, the full cohort case proportion, to estimate p . When the study cohort is less well defined, $\hat{p}_s$, the subcohort case proportion, is a suitable alternative. The corresponding estimator of β_0 is written as $\hat{\beta}_w$ or $\hat{\beta}_s$.

The cumulative baseline hazard function, $\Lambda_0(t) = \int_0^t \lambda_0(u)du$, can be consistently estimated by

$$\hat{\Lambda}_0(t; \hat{\beta}, \hat{p}) = \int_0^t \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} \{dN_{ij}(u) - Y_{ij}(u)\beta^T Z_{ij}(u)du\}}{\sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} Y_{ij}(u)}. \quad (6)$$

In (4) and (6), either $\hat{p}_s$, $\hat{p}_w$, or p_0 could be used to replace the parameter $\hat{p}$.

3. Asymptotic Properties

To derive the asymptotic properties of the proposed estimates, we impose the following assumptions:

(C1) $(T_i, C_i, Z_i(\cdot): i = 1, \dots, n)$ are independently and identically distributed, where $T_i = (T_{i1}, \dots, T_{im_i})^T$, $C_i = (C_{i1}, \dots, C_{im_i})^T$, and $Z_i = (Z_{i1}(\cdot), \dots, Z_{im_i}(\cdot))^T$.

(C2) $\Pr\{Y_{ij}(\tau) > 0\} > 0$ and $\Lambda_0(\tau) < \infty$, for $i = 1, \dots, n$, $j = 1, \dots, m_i$.

(C3) The matrix $\mathcal{E}\{\mathbf{W}_1(\beta_0, p_0)^{\otimes 2}\}$ is positive definite where

$$\begin{aligned} \mathbf{W}_i(\beta, p) = & \sum_{j=1}^{m_i} \left\{ \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) + \frac{1 - \delta_{ij}}{\gamma\theta} (H_i H_{ij} - \gamma\theta) \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) \right\} \\ & + D_1(\beta) \left\{ \frac{G_{1i}(p) - G_{2i}(p)}{p} \right\} + D_2(\beta) \left\{ \frac{G_{1i}(p) - G_{3i}(p)}{\gamma\theta} \right\}. \end{aligned} \quad (7)$$

(C4) There exists a constant C_z such that $|Z_{ij}(0) + \int_0^\tau dZ_{ij}(u)| < C_z < \infty$ holds almost everywhere.

Theorem 1. Under the regularity conditions (C1)–(C4), $n^{-(1/2)}U(\beta_0, p_0)$ converges to a mean zero normal distribution with covariance $\Sigma(\beta_0, p_0) = \mathcal{E}\{\mathbf{W}_1(\beta_0, p_0)^{\otimes 2}\}$, with

$$\begin{aligned} \mathbf{W}_i(\beta, p) = & \sum_{j=1}^{m_i} \left\{ \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) + \frac{1 - \delta_{ij}}{\gamma\theta} (H_i H_{ij} - \gamma\theta) \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) \right\} \\ & + D_1(\beta) \left\{ \frac{G_{1i}(p) - G_{1i}(p)}{p} \right\} + D_2(\beta) \left\{ \frac{G_{1i}(p) - G_{3i}(p)}{\gamma\theta} \right\}, \\ D_1(\beta) = & \mathcal{E} \left\{ \sum_{j=1}^{m_1} \frac{\delta_{1j}}{\mu} \int_0^\tau \{Z_{1j}(t) - e(t)\} dM_{1j}(t) \right\}, \\ D_2(\beta) = & \mathcal{E} \left\{ \sum_{j=1}^{m_1} \frac{1}{\mu\gamma\theta} (1 - \delta_{1j}) H_1 H_{1j} \int_0^\tau \{Z_{1j}(t) - e(t)\} dM_{1j}(t) \right\}, \\ G_{1i}(p) = & n^{-1} \left(\sum_{i=1}^n m_i - \mu \right), \\ G_{2i}(p) = & n^{-1} \left(\sum_{j=1}^{m_i} \delta_{ij} - \mu p \right), \\ G_{3i}(p) = & n^{-1} \left\{ \sum_{j=1}^{m_i} (1 - \delta_{ij}) H_i H_{ij} - \mu\gamma\theta(1 - p) \right\}, \\ e(t) = & \frac{E\{Y_{11}(t)Z_{11}(t)\}}{E\{Z_{11}(t)\}}. \end{aligned} \quad (8)$$

Theorem 2. Under conditions (C1)–(C4), $\hat{\beta}_t$ converges in probability to β_0 , and each of $n^{1/2}(\hat{\beta}_t - \beta_0)$ converges in distribution to a mean zero normal distribution with covariance matrix.

Theorem 3. Under conditions (C1)–(C4), both $\hat{\beta}_s$ and $\hat{\beta}_w$ converge in probability to β_0 , and each of $n^{1/2}(\hat{\beta}_s - \beta_0)$ and $n^{1/2}(\hat{\beta}_w - \beta_0)$ converges in distribution to a zero mean normal with covariance matrices $A(\beta_0)^{-1}\Omega_s(\beta_0, p_0)A(\beta_0)^{-1}$

TABLE 1: Simulation results for the estimation of $\beta_0 = \log(0.5)$.

Design	κ	Method	$n = 100, n_s = 800$					$n = 100, n_s = 600$				
			Bias	SE	SEE	BSE	CP	Bias	SE	SEE	BSE	CP
A	0.5	SC	0.0010	0.0568	0.0574	0.0500	0.948	-0.0021	0.0677	0.0635	0.0678	0.944
		WC	-0.0026	0.0526	0.0576	0.0550	0.969	-0.0023	0.0603	0.0646	0.0630	0.966
		T	-0.0021	0.0533	0.0525	0.0496	0.953	-0.0015	0.0594	0.0597	0.0642	0.956
	2	SC	0.0015	0.0573	0.0569	0.0506	0.948	-0.0020	0.0668	0.0656	0.0672	0.942
		WC	-0.0031	0.0531	0.0571	0.0560	0.953	-0.0031	0.0625	0.0648	0.0602	0.953
		T	-0.0016	0.0529	0.0536	0.0562	0.942	-0.0010	0.0584	0.0603	0.0618	0.947
B	0.5	SC	-0.0035	0.0578	0.0569	0.0460	0.937	-0.0012	0.0683	0.0644	0.0766	0.920
		WC	0.0023	0.0593	0.0612	0.0609	0.943	0.0004	0.0642	0.0640	0.0635	0.938
		T	-0.0030	0.0534	0.0511	0.0605	0.934	-0.0039	0.0629	0.0613	0.0614	0.936
	2	SC	-0.0012	0.0568	0.0573	0.0589	0.941	-0.0009	0.0679	0.0654	0.0685	0.920
		WC	0.0027	0.0578	0.0581	0.0513	0.939	0.0015	0.0653	0.0637	0.0591	0.938
		T	-0.0019	0.0534	0.0526	0.0480	0.940	-0.0026	0.0629	0.0613	0.0557	0.936
C	0.5	SC	-0.0009	0.0576	0.0570	0.0551	0.948	-0.0019	0.0685	0.0642	0.0651	0.929
		WC	-0.0032	0.0543	0.0571	0.0571	0.958	-0.0039	0.0605	0.0650	0.0632	0.963
		T	-0.0015	0.0540	0.0518	0.0481	0.941	-0.0047	0.0605	0.0591	0.0679	0.948
	2	SC	-0.0021	0.0576	0.0570	0.0515	0.948	-0.0024	0.0679	0.0653	0.0614	0.934
		WC	-0.0017	0.0547	0.0562	0.0565	0.942	-0.0026	0.0614	0.0647	0.0644	0.956
		T	-0.0010	0.0549	0.0523	0.0510	0.937	-0.0038	0.0587	0.0604	0.0613	0.943

Estimate of β_0 from five methods: SC = estimating p_0 using the subcohort $\hat{p}_s$; WC=estimating p_0 using the whole cohort, $\hat{p}_w$; T = using true value, p_0 .

and $A(\beta_0)^{-1}\Omega_w(\beta_0, p_0)A(\beta_0)^{-1}$, respectively, where for $a = s$ or w , $\Omega_a(\beta) = \mathcal{E}\{\psi_1(\beta, p_0)^{\otimes 2}\}$, $\psi_i(\beta, p) = W_i(\beta, p) + B(\beta)Q_i^a(p)$, $\Omega_a(\beta) = \mathcal{E}\{\psi_1(\beta, p_0)^{\otimes 2}\}$, $\psi_i(\beta, p) = W_i(\beta, p) + B(\beta)Q_i^a(p)$, $Q_i^s(p) = (1/\mu\gamma\theta)\sum_{j=1}^{m_i}H_iH_{ij}(\delta_{ij} - p)$, $Q_i^w(p) = (1/\mu)\sum_{j=1}^{m_i}(\delta_{ij} - p)$, $B(\beta) = \int_0^\tau \eta_{ij}Y_{ij}(t)\{Z_{ij}(t) - \bar{Z}(t)\}^{\otimes 2} dt$, and $\eta_{ij} = (1/(N_1/N))\delta_{ij} - (1/(n_0/N))(1 - \delta_{ij})H_iH_{ij}$.

Theorem 4. Under the regularity conditions (C1)–(C4), for each $k = 1, \dots, n$, $\hat{\Lambda}_0(\beta, \hat{p}, t)$ converges in probability to $\Lambda_0(t)$ uniformly in $t \in [0, \tau]$. In addition, $n^{1/2}\{\hat{\Lambda}_0(\beta, \hat{p}, t) - \Lambda_0(t)\}$ converges weakly to a Gaussian process with zero mean and covariance function at (s, t) given by $\mathcal{E}\{\phi_1(\beta_0, p_0, s)\phi_1(\beta_0, p_0, t)\}$.

4. Numerical Studies

Simulation studies are conducted to examine the finite sample properties of the proposed estimators. In the study, we generate the clustered failure time data from $n = 100$ clusters. m_i are simulated from a binomial $(50, 0.8)$ distribution for $i = 1, \dots, n$, with $u = \mathcal{E}(m_i) = 40$. The total number in the whole queue is about 4000. The covariate Z_{ij} takes values 1 and 0, with probabilities 0.5 and 0.5, respectively. The failure time $T_{i1}, T_{i2}, \dots, T_{im_i}$ in the i -th cluster is simulated by the joint survival function (for details, see [16]):

$$S(t_{i1}, \dots, t_{im_i} | z_{i1}, \dots, z_{im_i}) = \left(\sum_{j=1}^{m_i} \exp \left[\frac{\int_0^{t_{ij}} (2t + \beta^T z_{ij}) dt}{\kappa} \right] - (m_i - 1) \right)^{-\kappa} \quad (9)$$

where $\kappa > 0$ is a parameter representing the degree of dependence among variables. Smaller value of κ represents stronger correlation.

In our experiments, we choose $\kappa = 0.5$ or 2 and $\beta_0 = \log(0.5)$ or 0 . The censoring times C_{ij} are constant and equal to 1. The observed-event probabilities of p are equal to 0.45 or 0.63.

For each data generation, for Design A, individuals within each cluster are selected into the subcohort by Bernoulli sampling with equal probability 0.2 or 0.15. For Design B, we select clusters by Bernoulli sampling with probability 0.2 or 0.15. For Design C, we first sample clusters by Bernoulli sampling with probability 0.4 or 0.3 and then sample individuals from those selected clusters by Bernoulli sampling with probability 0.5. Therefore, for each design, we would expect approximately 800 or 600 individuals in the subcohort.

To assess the performance of the proposed estimator, we calculate the estimated standard error based on the bootstrap method. Because the failure clusters inside and outside the subcohort have different structures, we use the following method to conduct bootstrap sampling. Suppose the failure clusters in the subcohort contain M failures and Q nonfailures, whereas the failure clusters outside the subcohort contain D failures only. For each bootstrap sampling, we propose to obtain a bootstrap sample by sampling D failures from the original D failures outside the subcohort with replacement and then sampling M failures and Q nonfailures from the original M failures and Q nonfailures in the subcohort, respectively. The simulation results are based on 1000 replications.

Tables 1 and 2 report the simulation results of our proposed estimators. For simplicity, the notation Bias denotes the difference of the average of the estimates and the

TABLE 2: Simulation results for the estimation of $\beta_0 = 0$.

Design	κ	Method	$n = 100, n_s = 800$					$n = 100, n_s = 600$				
			Bias	SE	SEE	BSE	CP	Bias	SE	SEE	BSE	CP
A	0.5	SC	-0.0023	0.0730	0.0723	0.0748	0.945	-0.0018	0.0839	0.0823	0.0841	0.950
		WC	-0.0012	0.0739	0.0722	0.0717	0.940	0.0001	0.0841	0.0823	0.0791	0.943
		T	0.0002	0.0716	0.0723	0.0745	0.746	0.0013	0.0825	0.0820	0.0868	0.949
	2	SC	-0.0010	0.0725	0.0736	0.0664	0.947	-0.0022	0.0825	0.0831	0.0808	0.947
		WC	-0.0017	0.0732	0.0729	0.0683	0.932	0.0012	0.0837	0.0830	0.0709	0.937
		T	0.0021	0.0721	0.0730	0.0710	0.944	0.0031	0.0819	0.0827	0.0806	0.948
B	0.5	SC	-0.0013	0.0741	0.0714	0.0708	0.938	-0.0057	0.0857	0.0800	0.0684	0.924
		WC	-0.0002	0.0736	0.0716	0.0765	0.931	0.0053	0.0855	0.0799	0.0783	0.925
		T	0.0021	0.0734	0.0709	0.0619	0.927	-0.0030	0.0842	0.0806	0.0756	0.933
	2	SC	-0.0023	0.0738	0.0725	0.0625	0.938	-0.0042	0.0849	0.0813	0.0878	0.928
		WC	-0.0015	0.0724	0.0721	0.0697	0.934	0.0019	0.0858	0.0824	0.0774	0.930
		T	0.0032	0.0741	0.0714	0.0725	0.931	-0.0028	0.0836	0.0813	0.0833	0.940
C	0.5	SC	0.0005	0.0732	0.0715	0.0708	0.949	0.0007	0.0843	0.0811	0.0746	0.937
		WC	0.0002	0.0737	0.0718	0.0766	0.948	-0.0022	0.0814	0.0858	0.0878	0.937
		T	-0.0007	0.0707	0.0721	0.0744	0.948	-0.0035	0.0809	0.0813	0.0836	0.941
	2	SC	0.0014	0.0739	0.0723	0.0726	0.941	0.0014	0.0838	0.0820	0.0806	0.941
		WC	0.0010	0.0741	0.0730	0.0685	0.938	-0.0022	0.0823	0.0800	0.0763	0.935
		T	-0.0022	0.0712	0.0731	0.0709	0.948	-0.0015	0.0821	0.0817	0.0746	0.944

Estimate of β_0 from four methods: SC=estimating p_0 using the subcohort $\hat{p}_s$; WC=estimating p_0 using the whole cohort, $\hat{p}_w$; T=using true value, p_0 .

true values, SE denotes the average of standard errors, SEE denotes the average asymptotic standard error, BSE denotes the estimated standard error based on the bootstrap method, and CP denotes the coverage probability of the nominal 95% confidence interval.

It can be seen from Tables 1 and 2 that the estimates of both regression parameters $\beta_0 = \log(0.5)$ and $\beta_0 = 0$ are unbiased, and both the estimated standard deviation and the empirical standard deviation are also close. The coverage probability of the nominal 95% confidence intervals seems to be very reasonable. Furthermore, when $n_s = 600$ for Design B in Tables 1 and 2, we can obtain that the values of SEE and CP are slightly underestimated. It is due to the small number of clusters in the subcohort. In addition, with the increase of the capacity of the subcolumns, i.e., when n_s is increased to 800, the effect of the estimation is obviously improved. Among the above three designs, Design A and Design C are more effective than Design B. The conclusion is consistent with that in [13]. By comparing SE, SEE, and BSE, SE and SEE agree with the BSE. Furthermore, the bootstrap standard errors and the simulated standard errors are similar. The proposed semiparametric estimator works well. Therefore, one may use the bootstrap variance estimate for statistical inference in practice.

5. Conclusion

This paper proposed methods of fitting additive hazard regression models for clustered survival data from case-cohort studies. Risk difference can provide information

value to medical research. Specifically, risk differences can provide information regarding the reduction in the number of cases developing a certain disease due to a decrease in a particular exposure. An advantage of the additive hazard models is that risk difference between different exposure groups can be readily derived from the coefficients in the additive hazard models. With respect to differing observed-event probability, we propose three procedures for parameter estimator. Consistency and asymptotic normality of the proposed estimators are established. The simulation results show that Design A results are more efficient estimators than Design C, and Design C has greater efficiency than Design B when subcohort size is approximately equal. It can be attributed to differences in the number of sampled clusters in the subcohort.

Appendix

Proof of Theorems

Proof of Theorem 1. Evaluated at the true values, one can write

$$U(\beta_0, p_0) = \sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} \int_0^{\tau} \{Z_{ij}(t) - \bar{Z}(t)\} \cdot \{dN_{ij}(t) - Y_{ij}(t)\beta_0^T Z_{ij}(t)dt\}, \quad (\text{A.1})$$

where $\rho_{ij} = (p_0/(N_1/N))\delta_{ij} + ((1-p_0)/(n_0/N))(1-\delta_{ij})$
 $H_i H_{ij}$.

Then, we have

$$\begin{aligned}
 n^{-(1/2)}U(\beta, p_0) &= n^{-(1/2)} \sum_{i=1}^n \sum_{j=1}^{m_i} \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) \\
 &\quad + n^{-(1/2)} \sum_{i=1}^n \sum_{j=1}^{m_i} \int_0^\tau \{e(t) - \bar{Z}(t)\} dM_{ij}(t) \\
 &\quad + n^{-(1/2)} \sum_{i=1}^n \sum_{j=1}^{m_i} (\rho_{ij} - 1) \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) \\
 &\quad + n^{-(1/2)} \sum_{i=1}^n \sum_{j=1}^{m_i} (\rho_{ij} - 1) \int_0^\tau \{e(t) - \bar{Z}(t)\} dM_{ij}(t).
 \end{aligned} \tag{A.2}$$

The second term on the right-hand side of (A.2) can be shown to converge to zero. Specially, for fixed t , $E\{dM_{ij}(t)\} = 0$. The third term on the right-hand side of (A.2) can be written as

$$\begin{aligned}
 &n^{-(1/2)} \sum_{i=1}^n \sum_{j=1}^{m_i} \delta_{ij} \left\{ \frac{p_0}{(N_1/N)} - 1 \right\} \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) \\
 &\quad + n^{-(1/2)} \sum_{i=1}^n \sum_{j=1}^{m_i} (1 - \delta_{ij}) \left\{ \frac{(1 - p_0)H_i H_{ij}}{(n_0/N)} - 1 \right\} \int_0^t \{Z_{ij}(t) - e(t)\} dM_{ij}(t).
 \end{aligned} \tag{A.3}$$

By functional Taylor expansion, we can obtain that the first term of (A.3) is written as

$$\begin{aligned}
 &n^{-(1/2)} \sum_{i=1}^n G_{1i}(p_0) \times \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{\delta_{ij}}{\mu} \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) \\
 &\quad - n^{-(1/2)} \sum_{i=1}^n G_{2i}(p_0) \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{\delta_{ij}}{\mu p_0} \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) + o_p(1).
 \end{aligned} \tag{A.4}$$

Similarly, the second term of (A.3) is written as

$$\begin{aligned}
 &n^{-(1/2)} \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{1 - \delta_{ij}}{\gamma\theta} (H_i H_{ij} - \gamma\theta) \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) \\
 &\quad + n^{-(1/2)} G_{1i}(p_0) \times \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{1}{\mu\gamma\theta} (1 - \delta_{ij}) H_i H_{ij} \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) \\
 &\quad - n^{-(1/2)} \sum_{i=1}^n G_{3i}(p_0) \times \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{1}{\mu(\gamma\theta)^2(1 - p_0)} (1 - \delta_{ij}) H_i H_{ij} \\
 &\quad \times \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) + o_p(1).
 \end{aligned} \tag{A.5}$$

Combining (A.4) and (A.5), it follows that

$$n^{-(1/2)}U(\beta, p_0) = n^{-(1/2)} \sum_{i=1}^n \mathbf{W}_i(\beta, p_0) + o_p(1), \quad (\text{A.6})$$

where

$$\begin{aligned} \mathbf{W}_i(\beta, p) = & \sum_{j=1}^{m_i} \left\{ \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) + \frac{1 - \delta_{ij}}{\gamma\theta} (H_i H_{ij} - \gamma\theta) \int_0^\tau \{Z_{ij}(t) - e(t)\} dM_{ij}(t) \right\} \\ & + D_1(\beta) \left\{ \frac{G_{1i}(p) - G_{1i}(p_0)}{p} \right\} + D_2(\beta) \left\{ \frac{G_{1i}(p) - G_{3i}(p)}{\gamma\theta} \right\}. \end{aligned} \quad (\text{A.7})$$

Since $M_{ij}(t) = N_{ij}(t) - \int_0^t Y_{ij}(u) [\lambda_0(u) + \beta_0 Z_{ij}] du$ is a zero mean process, $\mathcal{E}\{1 - (\gamma\theta)^{-1} H_i H_{ij}\} = 0$, $\mathcal{E}\{dM_{ij}(t)\} = 0$, $\mathcal{E}\{G_{1i}\} = 0$, $\mathcal{E}\{G_{2i}\} = 0$, and $\mathcal{E}\{G_{3i}\} = 0$, we have

$$\mathcal{E}\{\mathbf{W}_i(\beta_0, p_0)\} = 0, \quad (\text{A.8})$$

for $i = 1, \dots, n$.

Under the general regular condition, $\{\mathbf{W}_i(\beta, p_0)\}_{i=1}^n$ is an independent and identically distributed random variable with a mean value of zero and $\mathcal{E}\{\mathbf{W}_1(\beta_0, p_0)^{\otimes 2}\}$. It follows from the multidimensional central limit theorem that $n^{-(1/2)}U(\beta_0, p_0) \xrightarrow{D} N(0, \sum(\beta_0, p_0))$. $\square$

Proof of Theorem 2. To prove the consistency of $\hat{\beta}$, we only use the inverse function theorem [17] by verifying the following conditions:

- (i) $(\partial U(\beta, p_0)/\partial \beta^T)$ exists and is continuous in an open neighborhood $\mathcal{B}$ of β_0 .

(ii) $(-n^{-1} \partial U(\beta, p_0)/\partial \beta^T)|_{\beta=\beta_0}$ is positive definite with probability going to one as $n \rightarrow \infty$.

(iii) $(-n^{-1} \partial U(\beta, p_0)/\partial \beta^T)$ converges in probability to $\mathbf{A}(\beta)$, uniformly in an open neighborhood $\mathcal{B}$ of β_0 .

(iv) Asymptotic unbiasedness of the estimating functions: $-n^{-1}U(\beta_0, p_0) \rightarrow^p 0$.

One can write

$$-\frac{\partial n^{-1}U(\beta, p_0)}{\partial \beta^T} = n^{-1} \sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} \int_0^\tau Y_{ij}(t) \{Z_{ij}(t) - \bar{Z}(t)\}^{\otimes 2} dt. \quad (\text{A.9})$$

By the continuity of each component and (A.9), (i) is clearly satisfied. Now, (A.9) can be decomposed as follows:

$$\begin{aligned} & n^{-1} \sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} \int_0^\tau Y_{ij}(t) \{Z_{ij}(t) - \bar{Z}(t)\}^{\otimes 2} dt \\ &= n^{-1} \sum_{i=1}^n \sum_{j=1}^{m_i} \int_0^\tau Y_{ij}(t) \{Z_{ij}(t) - \bar{Z}(t)\}^{\otimes 2} dt \\ &+ n^{-(1/2)} \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{1 - \delta_{ij}}{\gamma\theta} (H_i H_{ij} - \gamma\theta) \int_0^\tau Y_{ij}(t) \{Z_{ij}(t) - e(t)\}^{\otimes 2} dt \\ &+ n^{-1} \sum_{i=1}^n \left\{ \frac{G_{1i}(p_0) - G_{2i}(p_0)}{p_0} \right\} \times \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{\delta_{ij}}{\mu} \int_0^\tau \{Z_{ij}(t) - e(t)\}^{\otimes 2} dt \\ &+ n^{-1} \sum_{i=1}^n \left\{ \frac{G_{1i}(p_0) - G_{3i}(p_0)}{\gamma\theta} \right\} \times \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{1}{\mu\gamma\theta} (1 - \delta_{ij}) H_i H_{ij} \int_0^\tau \{Z_{ij}(t) - e(t)\}^{\otimes 2} dt. \end{aligned} \quad (\text{A.10})$$

Note that $\bar{Z}(t)$ uniformly converges to $e(t) = (\mathcal{E}\{Y_{11}(t)Z_{11}(t)\}/\mathcal{E}\{Z_{11}(t)\})$ in t . Then, it follows that the first term on the right-hand side of (A.10) converges to $A(\beta_0, p_0)$ in probability as $n \rightarrow \infty$. Each of the

remaining terms on the right-hand side of (A.10) can be shown to converge to zero as $n \rightarrow \infty$. Hence, we have

$$-\frac{\partial n^{-1}U(\beta, p_0)}{\partial \beta^T} \xrightarrow{p} A(\beta_0, p_0). \quad (\text{A.11})$$

$\square$

Proof of Theorem 3. Here we prove results of $\widehat{\beta}_s$ since results of $\widehat{\beta}_w$ can be proved similarly. By two Taylor expansions, the score function can be decomposition as follows:

$$\begin{aligned} n^{-(1/2)}U(\widehat{\beta}_s, \widehat{p}_s) &= n^{-(1/2)}U(\beta_0, \widehat{p}_s) - \widehat{A}(\beta_*, \widehat{p}_s)(\widehat{\beta}_s - \beta_0) \\ &\quad + o_p(1), \end{aligned} \quad (\text{A.12})$$

$$\begin{aligned} n^{-(1/2)}U(\beta_0, \widehat{p}_s) &= n^{-(1/2)}U(\beta_0, p_0) + \widehat{B}(\beta_0, p_*)(\widehat{p}_s - p_0) \\ &\quad + o_p(1), \end{aligned} \quad (\text{A.13})$$

where β_* is on the line segment between $\widehat{\beta}_s$ and β_0 , p_* is on the line segment between $\widehat{p}$ and p_0 , and

$$\begin{aligned} \widehat{A}(\beta, p) &= -n^{-1} \frac{\partial U(\beta, p)}{\partial \beta^T} \\ &= n^{-1} \sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} \int_0^\tau Y_{ij}(t) \{Z_{ij}(t) - \bar{Z}(t)\}^{\otimes 2} dt, \end{aligned} \quad (\text{A.14})$$

$$\begin{aligned} \widehat{B}(\beta, p) &= n^{-1} \frac{\partial U(\beta, p)}{\partial p} \\ &= \sum_{i=1}^n \sum_{j=1}^{m_i} \eta_{ij} \int_0^\tau Y_{ij}(t) \{Z_{ij}(t) - \bar{Z}(t)\} \\ &\quad \cdot \{dN_{ij}(t) - Y_{ij}(t)\beta_0^T Z_{ij}(t)dt\} \\ &\quad - \sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} \int_0^\tau \{\bar{\eta}(t) - \bar{Z}(t)\bar{W}(t)\} \\ &\quad \cdot \{dN_{ij}(t) - Y_{ij}(t)\beta_0^T Z_{ij}(t)dt\}, \end{aligned} \quad (\text{A.15})$$

where $\bar{\eta}(t) = (\sum_{i=1}^n \sum_{j=1}^{m_i} \eta_{ij} Y_{ij}(t) Z_{ij}(t) / \sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} Y_{ij}(t))$, $\eta_{ij} = (\partial \rho_{ij} / \partial p) = (1/(N_1/N))\delta_{ij} - (1/(n_0/N))(1 - \delta_{ij})H_i H_{ij}$, and $\bar{W}(t) = (\sum_{i=1}^n \sum_{j=1}^{m_i} \eta_{ij} Y_{ij}(t) / \sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} Y_{ij}(t))$.

Since $\widehat{\beta}_s \xrightarrow{p} \beta_0$ and $\|\beta_* - \beta_0\| \leq \|\beta_s - \beta_0\|$, we can obtain that $\beta_* \xrightarrow{p} \beta_0$. Using the fact that $\widehat{p}_s \xrightarrow{p} p_0$, we have

$$\widehat{A}(\beta_*, p_s) = \int_0^\tau Y_{ij}(t) \{Z_{ij}(t) - \bar{Z}(t)\}^{\otimes 2} dt. \quad (\text{A.16})$$

Since $p_s \xrightarrow{p} p_0$ and $\|p_* - p_0\| \leq \|\widehat{p}_s - p_0\|$, we obtain that $p_* \xrightarrow{p} p_0$. Then, by continuous mapping, it follows that

$$\begin{aligned} \widehat{B}(\beta_0, p_*) &\xrightarrow{p} \sum_{j=1}^{m_i} \eta_{ij} \int_0^\tau Y_{ij}(t) \{Z_{ij}(t) - \bar{Z}(t)\} \\ &\quad \cdot \{dN_{ij}(t) - Y_{ij}(t)\beta_0^T Z_{ij}(t)dt\} \\ &\quad - \sum_{j=1}^{m_i} \rho_{ij} \int_0^\tau \{\bar{\eta}(t) - \bar{Z}(t)\bar{W}(t)\} \\ &\quad \cdot \{dN_{ij}(t) - Y_{ij}(t)\beta_0^T Z_{ij}(t)dt\}. \end{aligned} \quad (\text{A.17})$$

Using the fact that

$$\begin{aligned} \widehat{p}_s - p_0 &= \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} H_i H_{ij} \delta_{ij}}{\sum_{i=1}^n \sum_{j=1}^{m_i} H_i H_{ij}} - p_0 \\ &= \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} H_i H_{ij} (\delta_{ij} - p_0)}{\sum_{i=1}^n \sum_{j=1}^{m_i} H_i H_{ij}} \\ &= n^{-1} \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} H_i H_{ij} (\delta_{ij} - p_0)}{\sum_{i=1}^n \sum_{j=1}^{m_i} (H_i H_{ij} / n)}, \end{aligned} \quad (\text{A.18})$$

we have

$$n^{1/2}(\widehat{p}_s - p_0) = n^{-(1/2)} \sum_{i=1}^n Q_i(p_0) + o_p(1). \quad (\text{A.19})$$

Note that $\mathcal{E}\{H_i H_{ij} (\delta_{ij} - p_0)\} = 0$; then, $\mathcal{E}\{Q_i(p_0)\} = 0$. Therefore, using (A.13) and (A.15)–(A.19), we have

$$n^{-(1/2)}U(\beta_0, \widehat{p}_s) = n^{-(1/2)} \sum_{i=1}^n \psi_i(\beta_0, p_0) + o_p(1). \quad (\text{A.20})$$

It follows from $\mathcal{E}\{\psi_i(\beta_0, p_0)\} = 0$ and the multidimensional central limit theorem that

$$n^{-(1/2)}U(\beta_0, \widehat{p}_s) \xrightarrow{D} N(0, \Omega(\beta_0)), \quad (\text{A.21})$$

where $\Omega(\beta_0) = \mathcal{E}\{\psi_i(\beta_0, p_0)^{\otimes 2}\}$.

Since $U(\widehat{\beta}_s, \widehat{p}_s) = 0$, using (A.12) and (A.21), we have

$$n^{1/2}(\widehat{\beta}_s - \beta_0) = \widehat{A}(\beta_*, \widehat{p}_s)^{-1} \times U(\beta_0, \widehat{p}_s). \quad (\text{A.22})$$

Note that $\widehat{A}(\beta_*, \widehat{p}_s) \xrightarrow{p} A(\beta_0)$. By Slutsky's theorem, we have

$$n^{1/2}(\widehat{\beta}_s - \beta_0) \xrightarrow{D} N(0, A(\beta_0)^{-1} \Omega(\beta_0) A(\beta_0)^{-1}). \quad (\text{A.23})$$

□

Proof of Theorem 4. One can make decomposition

$$\begin{aligned} n^{1/2}\{\widehat{\Lambda}_0(\widehat{\beta}, \widehat{p}, t) - \Lambda_0(t)\} &= n^{1/2}\{\widehat{\Lambda}_0(\widehat{\beta}, \widehat{p}, t) - \widehat{\Lambda}_0(\widehat{\beta}, p_0, t)\} \\ &\quad + n^{1/2}\{\widehat{\Lambda}_0(\widehat{\beta}, p_0, t) - \widehat{\Lambda}_0(\beta_0, p_0, t)\} \\ &\quad + n^{1/2}\{\widehat{\Lambda}_0(\beta_0, p_0, t) - \Lambda_0(t)\}. \end{aligned} \quad (\text{A.24})$$

By the Taylor expansion, the first term of (A.24) can be written as

$$n^{1/2}\{\widehat{\Lambda}_0(\widehat{\beta}, \widehat{p}, t) - \widehat{\Lambda}_0(\widehat{\beta}, p_0, t)\} = n^{1/2}\Gamma(t)(\widehat{p} - p_0), \quad (\text{A.25})$$

where

$$\Gamma(t) = \int_0^t \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} \{\eta_{ij} - \rho_{ij} \bar{\eta}_{ij}\} [dN_{ij}(t) - Y_{ij}(u) \bar{\beta}^T Z_{ij}(u) du]}{\sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} Y_{ij}(u)}. \quad (\text{A.26})$$

Since p converges to in probability to p_0 , we have

$$\widehat{\Lambda}_0(\widehat{\beta}, \widehat{p}, t) - \widehat{\Lambda}_0(\widehat{\beta}, p_0, t) \xrightarrow{p} 0. \quad (\text{A.27})$$

By computing, the remaining terms of (A.24) can be written as

$$\begin{aligned}
 & n^{1/2} \{ \widehat{\Lambda}_0(\widehat{\beta}, p_0, t) - \widehat{\Lambda}_0(\beta_0, p_0, t) \} + n^{1/2} \{ \widehat{\Lambda}_0(\beta_0, p_0, t) - \Lambda_0(t) \} \\
 &= \int_0^t \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} (\widehat{\beta} - \beta_0)^T Y_{ij}(u) Z_{ij}(u) du}{\sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} Y_{ij}(u)} + \int_0^t \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} dM_{ij}(u)}{\sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} Y_{ij}(u)} \\
 &+ \int_0^t \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} (\rho_{ij} - 1) dM_{ij}(u)}{\sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} Y_{ij}(u)}.
 \end{aligned} \tag{A.28}$$

$\overline{Z}(t)$ uniformly converges to $e(t)$ in t . The second term of (A.28) follows immediately that

$$\int_0^t \frac{1}{E[\sum_{j=1}^{m_i} Y_{1j}(u)]} d \left\{ n^{-(1/2)} \sum_{i=1}^n \sum_{j=1}^{m_i} M_{ij}(\beta_0, u) \right\} + o_p(1). \tag{A.29}$$

For the last term of (A.28), using Theorem 1, we can obtain that

$$\begin{aligned}
 & \int_0^t \frac{\sum_{i=1}^n \sum_{j=1}^{m_i} (\rho_{ij} - 1) dM_{ij}(u)}{\sum_{i=1}^n \sum_{j=1}^{m_i} \rho_{ij} Y_{ij}(u)} \\
 &= n^{-(1/2)} \sum_{i=1}^n \sum_{j=1}^{m_i} \frac{1 - \delta_{ij}}{\gamma\theta} (H_i H_{ij} - \gamma\theta) \int_0^t \{Z_{ij}(t) - e(t)\} \frac{dM_{ij}(t)}{E[\sum_{j=1}^{m_i} Y_{1j}(u)]} \\
 &+ \frac{D_1(\beta)}{E[\sum_{j=1}^{m_i} Y_{1j}(u)]} \times n^{-(1/2)} \sum_{i=1}^n \left\{ \frac{G_{1i}(p_0) - G_{2i}(p_0)}{p_0} \right\} \\
 &+ \frac{D_2(\beta)}{E[\sum_{j=1}^{m_i} Y_{1j}(u)]} \times n^{-(1/2)} \sum_{i=1}^n \left\{ \frac{G_{1i}(p_0) - G_{3i}(p_0)}{\gamma\theta} \right\} + o_p(1).
 \end{aligned} \tag{A.30}$$

Combining (A.28)–(A.30) and $n^{1/2}(\widehat{\beta}_s - \beta_0) = \widehat{A}(\beta_*, \widehat{p}_s)^{-1} \times U(\beta_0, \widehat{p}_s)$, we have that

$$\begin{aligned}
 & n^{1/2} \{ \widehat{\Lambda}_0(\widehat{\beta}, \widehat{p}, t) - \Lambda_0(t) \} \\
 &= n^{-(1/2)} \Gamma(t) \sum_{i=1}^n Q_i(p_0) + n^{-(1/2)} r_k(\beta_0, t)^T A(\beta_0)^{-1} U(\beta_0, \widehat{p}_s) + n^{-(1/2)} \sum_{i=1}^n \vartheta_i(\beta_0, p_0, t) + o_p(1) \\
 &= n^{-(1/2)} \Gamma(t) \sum_{i=1}^n Q_i(p_0) + n^{-(1/2)} r_k(\beta_0, t)^T A(\beta_0)^{-1} \sum_{i=1}^n \psi_i(\beta_0, p_0) \\
 &+ n^{-(1/2)} \sum_{i=1}^n \vartheta_i(\beta_0, p_0, t) + o_p(1) \\
 &= n^{-(1/2)} \sum_{i=1}^n \phi_i(\beta_0, p_0, t) + o_p(1),
 \end{aligned} \tag{A.31}$$

where

$$\begin{aligned}
 \vartheta_i(\beta_0, p_0, t) = & \int_0^t \frac{1}{E\left[\sum_{j=1}^{m_i} Y_{1j}(u)\right]} d\left\{n^{-(1/2)} \sum_{j=1}^{m_i} M_{ij}(\beta_0, u)\right\} \\
 & + n^{-(1/2)} \sum_{j=1}^{m_i} \frac{1 - \delta_{ij}}{\gamma\theta} (H_i H_{ij} - \gamma\theta) \int_0^\tau \{Z_{ij}(t) - e(t)\} \frac{dM_{ij}(t)}{E\left[\sum_{j=1}^{m_i} Y_{1j}(u)\right]} \\
 & + \frac{D_1(\beta)}{E\left[\sum_{j=1}^{m_i} Y_{1j}(u)\right]} \times n^{-(1/2)} \left\{ \frac{G_{1i}(p_0) - G_{2i}(p_0)}{p_0} \right\} \\
 & + \frac{D_2(\beta)}{E\left[\sum_{j=1}^{m_i} Y_{1j}(u)\right]} \times n^{-(1/2)} \left\{ \frac{G_{1i}(p_0) - G_{3i}(p_0)}{\gamma\theta} \right\}.
 \end{aligned} \tag{A.32}$$

It follows immediately from the multidimensional central limit theorem that $n^{1/2}\{\widehat{\Lambda}_0(\widehat{\beta}, \widehat{p}, t) - \Lambda_0(t)\}$ converges to a multivariate normal with zero mean and covariance function at (s, t) given by $\mathcal{E}\{\phi_1(\beta_0, p_0, s)\phi_1(\beta_0, p_0, t)\}$. It also proves that $n^{1/2}\{\widehat{\Lambda}_0(\widehat{\beta}, \widehat{p}, t) - \Lambda_0(t)\}$ is tight.

Using the functional central limit theorem, we can obtain that $n^{1/2}\{\widehat{\Lambda}_0(\widehat{\beta}, \widehat{p}, t) - \Lambda_0(t)\}$ converges weakly to a zero mean Gaussian process with covariance function at (s, t) given by $\mathcal{E}\{\phi_1(\beta_0, p_0, s)\phi_1(\beta_0, p_0, t)\}$. $\square$

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

Liu's work presented in this paper was supported by the Natural Science Research Project of Universities of Anhui Province (no. KJ2018A0390), and Zhang's work was supported by the Xulun Scholar Program of Shanghai Lixin University of Accounting and Finance.

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