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Mark-specific additive hazards regression with continuous marks

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Abstract

For survival data, mark variables are only observed at uncensored failure times, and it is of interest to investigate whether there is any relationship between the failure time and the mark variable. The additive hazards model, focusing on hazard differences rather than hazard ratios, has been widely used in practice. In this article, we propose a mark-specific additive hazards model in which both the regression coefficient functions and the baseline hazard function depend nonparametrically on a continuous mark. An estimating equation approach is developed to estimate the regression functions, and the asymptotic properties of the resulting estimators are established. In addition, some formal hypothesis tests are constructed for various hypotheses concerning the mark-specific treatment effects. The finite sample behavior of the proposed estimators is evaluated through simulation studies, and an application to a data set from the first HIV vaccine efficacy trial is provided.

Keywords

Additive hazards model; Competing risks; Confidence bands and tests; Continuous mark; HIV vaccine trial; Mark-specific vaccine effects; Survival data

1. Introduction

Competing risks data are commonly encountered in many biomedical applications, and a great deal of work has been done for the analysis of competing risks data with finitely many competing risks (Fine and Gray 1999; Sun et al. 2006; Scheike et al. 2008). However, many studies of survival data involve continuous causes-of-failure (marks). For example, in HIV vaccine efficacy trials, the mark variable is some measure of genetic distance between an HIV sequence measured from an infected subject and an HIV sequence represented in the vaccine. Because the value of the distance may be unique for almost all infected subjects, it is natural to consider the mark variable to be continuous (Gilbert et al. 2004, 2008). Other

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examples include lifetime medical cost and quality of life score associated with survival time (Olschewski and Schumacher 1990). In many biomedical applications, it is often of interest to determine whether there is a relationship between the failure time and a continuous mark.

Recently, there have been some developments of statistical methods for survival data with a continuous mark variable (Huang and Louis 1998; Gilbert et al. 2004, 2008; Sun et al. 2009; Sun et al. 2013). For example, Huang and Louis (1998) proposed a nonparametric maximum likelihood estimator of the joint distribution of the failure time and the mark. Gilbert et al. (2004, 2008) suggested procedures for testing dependence of mark-specific hazards rates and relative risks on the mark variable. Sun et al. (2009), Sun et al. (2013) and Gilbert and Sun (2014) presented estimation and testing methods for the mark-specific proportional hazards model with a univariate continuous mark and multivariate continuous marks, respectively.

A useful and important alternative to the proportional hazards model is the additive hazards model, which assumes an additive structure of a baseline hazard function and a covariate effect, and may indeed be more appropriate in many applications, particularly with respect to continuous covariates (Lin and Ying, 1994). Moreover, the additive hazards model seems to be biologically more plausible and tends to give a more intuitive interpretation for relative survival than the proportional hazards model in competing risk settings (Andersen and Vath 1989). In this article, we propose a mark-specific additive hazards model in which both the regression parameters and the baseline hazard function depend nonparametrically on a continuous mark. Specifically, let $\lambda(t, v|z(t))$ be the conditional mark-specific hazard function, which is defined as

$$\lambda(t, v|z(t)) = \lim_{h_1, h_2 \rightarrow 0} P\{T \in [t, t+h_1), V \in [v, v+h_2) | T \geq t, Z(t)=z(t)\} / h_1 h_2,$$

where T is the failure time, V is a continuous mark variable standardized on the interval $[0, 1]$, and $Z(t)$ is a time-dependent p -dimensional covariate vector. Our proposed mark-specific additive hazards model takes the form

$$\lambda(t, v|z(t)) = \lambda_0(t, v) + \beta_0(v)^T z(t), \quad (1)$$

where the baseline hazard function $\lambda_0(t, v)$ is an unknown function of t and v , and the p -dimensional regression parameter $\beta_0(v)$ are unknown continuous functions of v . The additive hazard model of Lin and Ying (1994) can be considered as a marginal model of (1) obtained by integrating out v on $[0, 1]$ for both sides of (1). The mark-specific additive hazards model adds additional modeling power than the marginal additive hazard model which does not consider mark. It facilitates evaluating the relationship between the risk of failure and the mark. The mark-specific hazards models have important applications in HIV vaccine efficacy trials and can be used to evaluate the strain-specific vaccine efficacy. The mark-specific additive hazards model describes a different aspect of the relationship between mark, covariates and the failure time than does the mark-specific proportional hazards

model. For the two-sample situation, the mark-specific additive hazards model addresses the hazard difference, while the mark-specific proportional hazards model concerns the hazard ratio. To the best of our knowledge, model (1) has never been studied in the literature, and we use the local constant method to estimate the model parameters.

For the HIV vaccine trial application, the treatment effect of the vaccine can be assessed through the mark-specific hazard differences rather than the hazard ratios. Let $\mathbf{z}(t) = (z_1, z_2(t)^T)^T$, where z_1 is the treatment group indicator, with $z_1 = 1$ for the vaccine group and $z_1 = 0$ for the placebo group, while $z_2(t)$ is other possibly time-dependent covariates. The vaccine effects on the mark-specific risk of infection can be evaluated using the mark-specific hazard difference between the vaccine group and the placebo group, defined as

$$DI(t, v) = \lambda(t, v | z_1=0, z_2(t)) - \lambda(t, v | z_1=1, z_2(t)). \quad (2)$$

Under model (1), the mark-specific hazard difference takes simple form $DI(t, v) = -\beta_{01}(v)$, which does not depend on time t , where $\beta_{01}(v)$ is the first element of $\beta_0(v)$. Since $DI(t, v)$ does not depend on t , we denote it by $DI(v)$ for simplicity and ease of notation. To test whether the vaccine provides protection for at least some of the infecting strains, we consider testing the hypothesis $H_{10} : DI(v) = 0$ for $v \in [a, b]$ against the general alternative $H_{11} : DI(v) > 0$ for some v , where $[a, b] \subset (0, 1)$. For the monotone alternative we consider $H_{12} : DI(v) > 0$, with strict inequality for at least some v . To assess whether vaccine effect varies with strain distance, we consider testing the null hypothesis H_{20} that $DI(v)$ does not depend on $v \in [a, b]$ against the general alternative H_{21} that $DI(v)$ depends on v . A monotone alternative is H_{22} that $DI(v)$ decreases as v increases.

The rest of the article is organized as follows. Section 2 presents an estimating procedure for model (1), and the asymptotic properties of the proposed estimators are established. Confidence bands, confidence intervals and formal hypothesis tests for various hypotheses of interest concerning the mark-specific vaccine effects are developed. Section 3 reports some results from simulation studies conducted for evaluating the proposed methods. An application to a data set from the first HIV vaccine efficacy trial is provided in Section 4, and some concluding remarks are made in Section 5. All proofs are given in the Appendix.

2. Estimation and inference

2.1. Estimation procedure

Suppose that the support of the mark variable V is taken to be $[0, 1]$. Let C be the censoring time that is assumed to be conditionally independent of (T, V) given $Z(\cdot)$. Also let $X = \min(T, C)$ be the event time and $\delta = I(T < C)$ be the censoring indicator. The observations $(X_i, \delta_i, \delta_i V_i, Z_i(\cdot))$ ($i = 1, \dots, n$) are assumed to be independent replicates of $(X, \delta, \delta V, Z(\cdot))$. The mark V can be observed when $\delta = 1$, whereas it is undefined and is not meaningful when $\delta = 0$.

Define $Y_i(t) = I(X_i \leq t)$, $N_i(t, v) = I(X_i \leq t, \delta_i = 1, V_i = v)$,

$S^{(0)}(t) = n^{-1} \sum_{i=1}^n Y_i(t)$, $S^{(1)}(t) = n^{-1} \sum_{i=1}^n Y_i(t) Z_i(t)$, and $\bar{Z}(t) = S^{(1)}(t)/S^{(0)}(t)$. Let

$\Lambda_0(t, v) = \int_0^t \int_0^v \lambda_0(s, u) ds du$ denote the doubly cumulative baseline hazard function.

According to Condition (C3) listed in the Appendix, we obtain that

$$M_i(t, v) = \int_0^v \int_0^t \left[N_i(ds, du) - Y_i(s) \{ \Lambda_0(ds, du) + \beta_0(u)^T Z_i(s) ds du \} \right]$$

is a zero-mean martingale with respect to $\mathcal{F}_t$ for each fixed v (Martinussen and Scheike, 2006, p.31). Thus, based on this fact and the generalized estimating equation approach (Liang and Zeger 1986), for given $\beta(\cdot)$, a reasonable estimator for $\Lambda_0(t, v)$ is the solution to

$$\sum_{i=1}^n \int_0^v \int_0^t \left[N_i(ds, du) - Y_i(s) \{ \Lambda_0(ds, du) + \beta(u)^T Z_i(s) ds du \} \right] = 0.$$

Denote this estimator by $\hat{\Lambda}_0(t, v; \beta)$, which can be expressed as

$$\hat{\Lambda}_0(t, v; \beta) = \sum_{i=1}^n \int_0^v \int_0^t \frac{N_i(ds, du) - Y_i(s) \beta(u)^T Z_i(s) ds du}{n S^{(0)}(s)}.$$

We consider the profile estimation for $\beta(\cdot)$ obtained by replacing $\Lambda_0(t, v)$ with $\hat{\Lambda}_0(t, v; \beta)$ in the estimating equation $\sum_{i=1}^n \int_0^1 \int_0^\tau M_i(t, v) = 0$. Specifically, we propose to estimate $\beta_0(\cdot)$ from the following estimating function:

$$U^*(\beta) = \sum_{i=1}^n \int_0^1 \int_0^\tau \left[N_i(ds, du) - Y_i(s) \{ \hat{\Lambda}_0(ds, du; \beta(u)) + \beta(u)^T Z_i(s) ds du \} \right],$$

which is equivalent to

$$U^*(\beta) = \sum_{i=1}^n \int_0^1 \int_0^\tau \{ Z_i(t) - \bar{Z}(t) \} \left[N_i(dt, dv) - Y_i(t) \beta(v)^T Z_i(t) dt dv \right].$$

When $\beta(v)$ does not depend on the mark v , $U^*(\beta)$ is the estimation function under the marginal additive hazard model of Lin and Ying (1994) which does not consider mark. The mark-specific additive hazards model (1) is an extension of the additive hazard model of Lin and Ying (1994) that allows studying the relationship between the risk of failure and a continuous mark.

Since the functional form of $\beta(v)$ is completely unspecified in our development, it will be estimated nonparametrically. Similar to Sun, Gilbert and McKeague (2009), we use the local constant method to construct the estimating equation for $\beta = \beta(v)$ at a fix $v \in (0, 1)$:

$$U(v, \beta) = \sum_{i=1}^n \int_0^1 \int_0^\tau K_h(u-v) \{Z_i(t) - \bar{Z}(t)\} \left[N_i(dt, du) - Y_i(t) \beta^T Z_i(t) dt du \right], \quad (3)$$

where $K_h(x) = K(x/h)/h$, $K(\cdot)$ is a kernel function with support $[-1, 1]$, $h = h_n$ is a bandwidth, and τ is the end of follow-up time. Let $\hat{\beta}(v)$ denote the solution to the above equation, and the resulting estimators have the following explicit expressions:

$$\hat{\beta}(v) = \left[\sum_{i=1}^n \int_0^1 \int_0^\tau K_h(u-v) Y_i(t) \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} dt du \right]^{-1} \times \sum_{i=1}^n \int_0^1 \int_0^\tau K_h(u-v) \{Z_i(t) - \bar{Z}(t)\} N_i(dt, du),$$

where $a^{\otimes 2} = aa^T$ for a vector a . The corresponding estimator of $\Lambda_0(t, v)$ is given by $\hat{\Lambda}_0(t, v) \equiv \hat{\Lambda}_0(t, v; \hat{\beta})$. In addition, the baseline hazard function $\lambda_0(t, v)$ can also be estimated by smoothing the increments of the estimator $\hat{\Lambda}_0(t, v)$.

We recommend to select the bandwidth using the formula $h = C \hat{\sigma}_v n_o^{-1/4}$, where n_o is the number of observed failure times and $\hat{\sigma}_v$ is the estimated standard error of the observed marks for uncensored failure times. Our simulation study shows that this works well for the mark-specific additive model. Similar bandwidth selection methods have been used in Zhou and Wang (2000) and in Sun et al. (2015). In practice, a larger C can be used if the distribution of the observed marks is skewed or marks are sparse in some areas.

2.2. Asymptotic properties

This section presents the asymptotic properties of the proposed estimators under some regularity conditions. The regularity conditions (C1)–(C4) and the proofs of the theorems are given in the Appendix. The asymptotic properties of $\hat{\beta}(v)$ are summarized in the following theorem.

Theorem 1—Under the regularity conditions (C1)–(C4), $\hat{\beta}(v)$ converges in probability to $\beta_0(v)$ uniformly in $v \in [a, b] \subset (0, 1)$, and $(nh)^{1/2} \{ \hat{\beta}(v) - \beta_0(v) \}$ converges in distribution to a zero-mean normal random vector with covariance matrix $\mu_0 A^{-1} \Sigma(v) A^{-1}$ for $v \in [a, b]$,

where $A = E \left[\int_0^\tau Y_i(t) \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} dt \right]$,

$$\Sigma(v) = E \left[\int_0^\tau \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} Y_i(t) \{ \lambda_0(t, v) + \beta_0(v)^T Z_i(t) \} dt \right],$$

$\bar{Z}(t)$ is the limit of $\bar{Z}_n(t)$ and $\mu_0 = \int K^2(u) du$.

The asymptotic variance of $(nh)^{1/2}\{\hat{\beta}(v) - \beta_0(v)\}$ can be consistently estimated by $\hat{A}^{-1}\hat{\Sigma}(v)\hat{A}^{-1}$, where $\hat{A} = n^{-1} \sum_{i=1}^n \int_0^\tau Y_i(t) \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} dt$, and

$$\hat{\Sigma}(v) = n^{-1} h \sum_{i=1}^n \int_0^1 \int_0^\tau (K_h(u-v))^2 \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} N_i(dt, du).$$

Theorem 1 enables us to construct pointwise confidence intervals for $D\ell(v)$. It is possible to construct simultaneous confidence bands over $v \in [a, b]$ in terms of the estimator $\hat{B}(v) = \int_a^v \hat{\beta}(u) du$. Let $B_0(v) = \int_a^v \beta_0(u) du$. The asymptotic distribution of $\hat{B}(v)$ is given in the next theorem.

Theorem 2—Under the regularity conditions (C1)–(C4), $n^{1/2}\{\hat{B}(v) - B_0(v)\}$ converges weakly on $v \in [a, b]$ to a mean-zero continuous Gaussian process with independent increments. The covariance matrix of the Gaussian process is $\int_a^v A^{-1} \sum(u) A^{-1} du$, which can be consistently estimated by

$$n^{-1} \sum_{i=1}^n \int_a^v \int_0^\tau \hat{A}^{-1} \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} \hat{A}^{-1} N_i(dt, du).$$

Let $s^{(j)}(t) = E[S^{(j)}(t)]$ for $j = 0, 1$, and $d(t) = \int_0^t \bar{z}(s) ds$. For ease of theoretical development, the asymptotic distributions of $\hat{\Lambda}_0(t, v)$ are stated in the next theorem.

Theorem 3—Under the regularity conditions (C1)–(C4), $n^{1/2}\{\hat{\Lambda}_0(t, v) - \Lambda_0(t, v) - [\hat{\Lambda}_0(t, a) - \Lambda_0(t, a)]\}$ converges weakly on $[0, \tau] \times [a, b]$ to a mean-zero Gaussian process with covariance function at (t_1, v_1) and (t_2, v_2) equal to $E[\Phi_A(t_1, v_1)\Phi_A(t_2, v_2)]$, where

$$\Phi_i(t, v) = \int_0^t \int_a^v \frac{M_i(ds, du)}{s^{(0)}(s)} - d(t)^T \int_a^v \int_0^\tau A^{-1} \{Z_i(s) - \bar{z}(s)\} M_i(ds, du).$$

The covariance function can be consistently estimated by $n^{-1} \sum_{i=1}^n \hat{\Phi}_i(t_1, v_1) \hat{\Phi}_i(t_2, v_2)$, where

$$\begin{aligned} \hat{\Phi}_i(t, v) &= \int_0^t \int_a^v \frac{\hat{M}_i(ds, du)}{\hat{S}^{(0)}(s)} - D(t)^T \int_a^v \int_0^\tau \hat{A}^{-1} \{Z_i(s) - \bar{Z}(s)\} \hat{M}_i(ds, du), \\ \hat{M}_i(t, v) &= \int_0^t \int_a^v \left[N_i(ds, du) - Y_i(s) \{ \hat{\Lambda}_0(ds, du) + \hat{\beta}(u)^T Z_i(s) ds du \} \right], \end{aligned}$$

and $D(t) = \int_0^t \bar{Z}(s) ds$.

2.3. Confidence bands for mark-specific vaccine effects

Let $\beta_0(v) = (\beta_{01}(v), \beta_{02}(v)^T)^T$, and $\hat{\beta}(v) = (\hat{\beta}_1(v), \hat{\beta}_2(v)^T)^T$. Then under model (1), $\widehat{\text{DI}}(v) = -\hat{\beta}_1(v)$ is the estimator of $\text{DI}(v) = -\beta_{01}(v)$. It follows from Theorem 1 that $(nh)^{1/2}\{\widehat{\text{DI}}(v) - \text{DI}(v)\}$ converges in distribution to a zero-mean normal random vector with variance $\mu_0\sigma_1^2(v)$ for $v \in [a, b]$, where $\sigma_1^2(v)$ is the first element on the diagonal of $A^{-1}\Sigma(v)A^{-1}$. Let $\hat{\sigma}^2(v)$ be the first element on the diagonal $\hat{A}^{-1}\hat{\Sigma}(v)\hat{A}^{-1}$, which is a consistent estimator for $\mu_0\sigma_1^2(v)$. Thus, a pointwise $100(1 - \alpha)\%$ confidence interval for $\text{DI}(v)$ is given by

$$\widehat{\text{DI}}(v) \pm (nh)^{-1/2} Z_{\alpha/2} \hat{\sigma}(v), \quad a \leq v \leq b, \quad (4)$$

where $Z_{\alpha/2}$ is the upper $\alpha/2$ quantile of the standard normal distribution.

Let $\text{CD}(v) = \int_a^v \text{DI}(u) du$ be the cumulative hazard difference and $\widehat{\text{CD}}(v) = \int_a^v \widehat{\text{DI}}(u) du$ its estimator. Then $n^{1/2}\{\widehat{\text{CD}}(v) - \text{CD}(v)\} = -e_1^T n^{1/2}\{\hat{B}(v) - B_0(v)\}$, where $e_1 = (1, 0, \dots, 0)^T$. By Theorem 2, $n^{1/2}\{\widehat{\text{CD}}(v) - \text{CD}(v)\}$ converges weakly on $v \in [a, b]$ to a mean-zero continuous Gaussian process with independent increments, and the covariance matrix is $R^2(v) = e_1^T \int_a^v A^{-1} \sum(u) A^{-1} du e_1$, which can be consistently estimated by

$$\hat{R}^2(v) = e_1^T n^{-1} \sum_{i=1}^n \int_a^v \int_0^\tau \hat{A}^{-1} \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} \hat{A}^{-1} N_i(dt, du) e_1.$$

Thus, a pointwise $100(1 - \alpha)\%$ confidence interval for $\text{CD}(v)$ is given by

$$\widehat{\text{CD}}(v) \pm n^{1/2} Z_{\alpha/2} \hat{R}(v), \quad a \leq v \leq b. \quad (5)$$

Let $\mathcal{V}$ be a set of values of v in $[a, b]$. Note that if $U(v)$ is a Gaussian process with independent increments, and its variance is $R^2(v)$, for $a \leq v \leq b$, then $U(v)R(b)[R^2(b) + R^2(v)]^{-1}$ has the same distribution as $B^0(R(b)/[R^2(b) + R^2(v)])$, $a \leq v \leq b$, where $B^0(\cdot)$ is a Brownian bridge. To construct simultaneous confidence band for $\text{CD}(v)$, $v \in \mathcal{V}$, we propose to use the following resampling approach. Let $(\xi_1, \dots, \xi_n)$ be independent standard normal variables that are independent of the observed data, and

$$Q^*(v) = n^{-1/2} \sum_{i=1}^n \xi_i \int_a^v \int_0^\tau \hat{A}^{-1} \{Z_i(t) - \bar{Z}(t)\} \hat{M}_i(dt, du). \quad (6)$$

According to the arguments of Lin et al. (1993), the distribution of $n^{1/2}\{\widehat{\text{CD}}(v) - \text{CD}(v)\}$ can be approximated by the conditional distribution of $e_1^T Q^*(v)$ given the observed data sequence. Thus, the distribution of

$$\sup_{v \in \mathcal{V}} |n^{1/2}\{\widehat{\text{CD}}(v) - \text{CD}(v)\} \hat{R}(b) [\hat{R}^2(b) + \hat{R}^2(v)]^{-1}|$$

can be approximated by the conditional distribution of

$$U^* = \sup_{v \in \mathcal{V}} |e_1^T Q^*(v) \hat{R}(b) [\hat{R}^2(b) + \hat{R}^2(v)]^{-1}|.$$

Let u_α^* be the $(1 - \alpha)$ -quantile of the copies of U^* obtained by repeatedly generating the normal random sample $(\xi_1, \dots, \xi_n)$ while fixing the observation data. A simultaneous $100(1 - \alpha)\%$ confidence band for $\text{CD}(v)$, $v \in \mathcal{V}$, is given by

$$\widehat{\text{CD}}(v) \pm n^{-1/2} u_\alpha^* [\hat{R}^2(b) + \hat{R}^2(v)] / \hat{R}(b). \quad (7)$$

2.4. Testing mark-specific vaccine effects

We are interested in testing the following two sets of hypotheses. The first null hypothesis is $H_{10} : \text{DI}(v) = 0$ for $v \in [a, b]$ against the following alternative hypotheses: $H_{11} : \text{DI}(v) > 0$ for some v ; and $H_{12} : \text{DI}(v) > 0$ with strict inequality for at least some $v \in [a, b]$. The second null hypothesis is $H_{20} : \text{DI}(v)$ does not depend on $v \in [a, b]$ against the following alternative hypotheses: $H_{21} : \text{DI}(v)$ depends on v ; and $H_{22} : \text{DI}(v)$ decreases as v increases.

In the following, we propose some test procedures for detecting departures from H_{10} in the direction of H_{11} or H_{12} and for detecting departures from H_{20} in the direction of H_{21} or H_{22} .

To test H_{10} , let $\hat{\Gamma}^{(1)}(v) = n^{1/2} \widehat{\text{CD}}(v) / \hat{R}(b)$, $\hat{\pi}(v) = \hat{R}^2(v) / \hat{R}^2(b)$, and $\pi(v) = R^2(v) / R^2(b)$. We consider the following three test statistics:

$$T_1 = \int_a^b (\hat{\Gamma}^{(1)}(v))^2 d\hat{\pi}(v), \quad T_2 = \int_a^b \hat{\Gamma}^{(1)}(v) d\hat{\pi}(v),$$

and

$$T_3 = (K-1)^{-1/2} \sum_{k=2}^K [\hat{\Gamma}^{(1)}(v_k) - \hat{\Gamma}^{(1)}(v_{k-1})] / [\hat{\pi}(v_k) - \hat{\pi}(v_{k-1})]^{1/2},$$

where $a = v_1 < \dots < v_K = b$ are the grid points in $[a, b]$. Clearly, the test statistic T_1 is able to capture general departures H_{11} , and the test statistics T_2 and T_3 can measure departures from H_{10} in the direction of H_{12} . It follows from Theorem 2 that under H_{10} , T_1 converges in distribution to $\int_a^b (W(\pi(v)))^2 d\pi(v)$, T_2 converges in distribution to $\int_a^b W(\pi(v)) d\pi(v)$, and T_3 converges in distribution to a standard normal random variable, where $W(\cdot)$ is a Wiener process. For given $\hat{\pi}(v)$, the distributions of T_1 and T_2 can be approximated by those of $\int_a^b (W(\hat{\pi}(v)))^2 d\hat{\pi}(v)$ and $\int_a^b W(\hat{\pi}(v)) d\hat{\pi}(v)$, respectively, which are used to determine the critical values for the tests in the numerical studies. Let c_1 and c_2 be the upper α -quantiles of these two distributions, respectively. Note that T_2 and T_3 are likely to be positive when H_{12} holds. Thus, the tests based on T_1 , T_2 and T_3 reject H_{10} if $T_1 > c_1$, $T_2 > c_2$, and $T_3 > z_\alpha$, respectively.

To test H_{20} , let $\hat{\Gamma}^{(2)}(v) = n^{1/2} \{ \frac{1}{v-a} \widehat{CD}(v) - \frac{1}{b-a} \widehat{CD}(b) \} / \hat{R}(b)$ and $\Gamma^{(2)}(v) = n^{1/2} \{ \frac{1}{v-a} W(\pi(v)) - \frac{1}{b-a} W(1) \}$. We propose the following test statistics for evaluating H_{20} :

$$T_4 = \int_{a_1}^b (\hat{\Gamma}^{(2)}(v))^2 d\hat{\pi}(v), \quad T_5 = \int_{a_1}^b \hat{\Gamma}^{(2)}(v) d\hat{\pi}(v),$$

and

$$T_6 = \hat{\Pi}_K^{-1} \sum_{k=2}^K [\hat{\Gamma}^{(2)}(v_{k-1}) - \hat{\Gamma}^{(2)}(v_k)] / \hat{\rho}_k,$$

where $a < a_1 = v_1 < \dots < v_K = b$, $\hat{\rho}_k^2$ is an estimate of the variance

$\rho_k^2 = \text{Var}(\Gamma^{(2)}(v_{k-1}) - \Gamma^{(2)}(v_k))$ and $\hat{\Pi}_K^2$ is an estimate of the variance Π_K^2 of $\sum_{k=2}^K [\Gamma^{(2)}(v_{k-1}) - \Gamma^{(2)}(v_k)] / \rho_k$. It can be shown that

$$\begin{aligned} \tau_{i,j} &= \text{Cov}(\Gamma^{(2)}(v_i), \Gamma^{(2)}(v_j)) \\ &= \frac{\pi(v_i)}{(v_i-a)(v_j-a)} - \frac{\pi(v_i)}{(v_i-a)(b-a)} - \frac{\pi(v_j)}{(v_j-a)(b-a)} + \frac{1}{(b-a)^2}, \end{aligned}$$

for $v_i < v_j$. Therefore, $\rho_k^2 = \tau_{k-1,k-1} - 2\tau_{k-1,k} + \tau_{k,k}$. Let $\Gamma = (\tau_{i,j})_{K \times K}$ and

$$\eta^T = (\rho_2^{-1}, \rho_3^{-1} - \rho_2^{-1}, \dots, \rho_K^{-1} - \rho_{K-1}^{-1}, -\rho_K^{-1}).$$

It follows that $\Pi_K^2 = \eta^T \Gamma \eta$. The estimates $\hat{\rho}_k^2$ and $\hat{\Pi}_K^2$ can be obtained by replacing $\pi(v)$ with $\hat{\pi}(v)$. It follows from Theorem 2 that under H_{20} , T_4 converges in distribution to

$\int_{a_1}^b \left\{ \frac{W(\pi(v))}{v-a} - \frac{W(1)}{b-a} \right\}^2 d\pi(v)$, T_5 converges in distribution to $\int_{a_1}^b \left\{ \frac{W(\pi(v))}{v-a} - \frac{W(1)}{b-a} \right\} d\pi(v)$, and T_6

converges in distribution to a standard normal random variable. For given $\hat{\pi}(v)$, the distributions of T_4 and T_5 can be approximated by those of $\int_{a_1}^b \left\{ \frac{W(\hat{\pi}(v))}{v-a} - \frac{W(\hat{\pi}(b))}{b-a} \right\}^2 d\hat{\pi}(v)$ and $\int_{a_1}^b \left\{ \frac{W(\hat{\pi}(v))}{v-a} - \frac{W(\hat{\pi}(b))}{b-a} \right\} d\hat{\pi}(v)$, respectively, which are used to determine the critical values for the tests in the numerical studies. Let c_3 and c_4 be the upper α -quantiles of these two distributions, respectively. Clearly, the test statistic T_4 is able to capture general departures H_{21} , and the test statistics T_5 and T_6 can measure departures from H_{20} in the direction of H_{22} . The tests based on T_4 , T_5 , and T_6 reject H_{20} if $T_4 > c_3$, $T_5 > c_4$, and $T_6 > z_\alpha$, respectively.

3. Simulation studies

In this section, we conducted simulation studies to examine the finite sample performance of the proposed estimation and hypothesis testing procedures. First, we considered the following mark-specific additive hazards model:

$$\lambda(t, v|z) = \exp(\gamma v) + (a + \beta v)z, \quad t \geq 0, \quad 0 \leq v \leq 1, \quad (8)$$

where γ , a and β are constants, and the treatment indicator z is a Bernoulli random variable with success probability 0.5. Under model (8), the baseline function is $\lambda_0(t, v) = \exp(\gamma v)$, and $DI(v) = -(a + \beta v)$. Various choices of a and β specify different alternative hypotheses for H_{10} and H_{20} .

By integrating v over $[0, 1]$ for model (8), we can obtain that

$$\lambda(t|z(t)) = \lambda_0(t) + \theta_0^T z(t), \quad (9)$$

where $\lambda_0(t) = (e^\gamma - 1)/\gamma$ and $\theta_0 = a + \beta/2$. Based on (9), it is easy to show that $F(t|z(t)) = 1 - \exp(-\int_0^t (\lambda_0(s) + \theta_0^T z(s)) ds)$, where $F(t|z(t))$ is the cumulative distribution function of T given $Z(t) = z(t)$. Then we can generate the failure time T by the inverse cumulative distribution function method. By some calculations, we have that $f(v/t, z(t)) = \lambda(t, v/z(t))/\lambda(t/z(t))$, where $f(v/t, z(t))$ is the conditional probability density function of V given $T = t$ and $Z(t) = z(t)$. Hence, given T , we can also generate V by the inverse cumulative distribution function method.

In the study, the following six models were considered:

- (M1) $(a, \beta, \gamma) = (0, 0, 0.3)$;
- (M2) $(a, \beta, \gamma) = (-0.5, 0.5, 0.3)$;
- (M3) $(a, \beta, \gamma) = (-0.5, 0.45, 0.3)$;
- (M4) $(a, \beta, \gamma) = (-0.7, 0, 0.3)$;
- (M5) $(a, \beta, \gamma) = (-0.2, 1.5, 0.3)$;

$$(M6) \quad (\alpha, \beta, \gamma) = (-0.2, 3, 0.3).$$

Model (M1) is a null model under H_{10} and model (M4) is a null model under H_{20} . The models (M2) to (M3) are considered as the alternatives for H_{11} and H_{12} . The models (M5) to (M6) are considered as the alternatives for H_{21} and H_{22} . The censoring time was generated from a uniform distribution on $(0, c)$, where c was selected to give a censoring rate of 30% under models (M1)–(M6). For the analysis, the interval for v was set as $[a, b] = [0.1, 0.9]$. The value of a_1 is 0.172. For the test T_3 , we took the grid of eight evenly spaced points in $[a, b]$ from 0.101 to 0.899. For the test T_6 , we took the grid of nine evenly spaced points in $[a, b]$ from 0.172 to 0.820. The kernel function was chosen as $K(x) = 0.75(1 - x^2)I(x/ - 1)$. The bandwidth is chosen using the formula $h = C\sigma_v n_o^{-1/4}$ with $C = 1$, where n_o is the average number of observed failure times and σ_v is the estimated standard error of the observed marks for uncensored failure times for each simulation setting. The result presented below are based on 500 replications with sample sizes $n = 500$ and 800 .

We note that without considering mark, the marginal additive hazard regression model is given by (9). The standard method for testing the marginal vaccine efficacy regardless of the mark is to test $H_0^*: \theta_0 = 0$ against $H_1^*: \theta_0 \neq 0$, or $H_2^*: \theta_0 < 0$ in case of monotone alternative. Our simulation shows that our method can be a useful complement to the currently available methods for testing treatment effects based on the marginal additive hazard regression model. Let T_1^* and T_2^* be the Wald type test statistics corresponding to the test two-sided and one-sided tests, respectively, based on the estimator of θ_0 and its estimated asymptotic standard error as derived in Lin and Ying (1994).

Table 1 presents the empirical sizes and powers of the test statistics T_1, T_2, T_3, T_1^* and T_2^* at the significance level of $\alpha = 0.05$. Table 2 presents the empirical sizes and powers of the test statistics T_4, T_5 and T_6 at the significance level of $\alpha = 0.05$. The critical value for the test T_1^* at $\alpha = 0.05$ is $z_\alpha = 1.96$, and the critical value for the tests T_2^*, T_3 and T_6 at $\alpha = 0.05$ is $z_{\alpha/2} = 1.645$. The critical values for other tests are obtained by generating 100 Wiener processes $W(\cdot)$ with time parameter equal to $\hat{\pi}(v)$ and computing the corresponding functions of $W(\hat{\pi}(v))$. The two tables also report the empirical coverage probabilities of the 95% simultaneous confidence intervals for $CD(v)$ with $v \in [a, b]$ and v in the grid. It can be seen from the tables that the empirical sizes of all tests are close to the nominal size 0.05, and the empirical coverage probabilities of the simultaneous confidence intervals for $CD(v)$ are reasonable. The results become better when the sample size increases from 500 to 800. In addition, both the tests T_1 and T_2 have greater powers than their counterparts T_1^* and T_2^* , which imply that the tests based on $DI(v)$ can be more powerful in detecting treatment effects. The test T_3 is less powerful than the tests T_1 and T_2 . Since the departure from H_{10} and H_0^* increases as the simulation model moves from (M2) to (M3), the powers of the tests increase as the model moves from (M2) to (M3). Similarly, the powers of the tests T_4, T_5 and T_6 increase as the model moves from (M5) to (M6).

To investigate further the performance of the proposed estimators for $\beta_0(v)$ and $CD(v)$, we provide the pointwise biases and the standard errors in Figures 1 and 2, respectively. The pointwise coverage probabilities for $\beta_0(v)$ and $CD(v)$ are presented in Figure 3. Since $DI(v)$

$= -\beta_0(v)$ under model (1), the similar plots for $DI(v)$ are omitted here. It appears that these plots show that the proposed estimators are practically unbiased, there is a good agreement between the estimated and the empirical standard errors, and the pointwise coverage probabilities of the 95% confidence intervals are reasonable.

We also conducted simulation studies for the case where $\lambda_0(t, v)$ and $z(t)$ depend on the t . The mark-specific additive hazards model was taken to be

$$\lambda(t, v|z) = t + \exp(\gamma v) + (\alpha_1 + \beta_1 v)z_1 + (\alpha_2 + \beta_2 v)(z_2 + t), \quad t \geq 0, \quad 0 \leq v \leq 1, \quad (10)$$

where $\gamma, \alpha_1, \beta_1, \alpha_2$ and β_2 are constants, the treatment indicator z_1 is a Bernoulli random variable with success probability 0.5, and z_2 was generated from a uniform distribution on $(0, 1)$. Under model (10), the baseline function is $\lambda_0(t, v) = t + \exp(\gamma v)$, $z(t) = (z_1, z_2 + t)^T$, $\beta(v) = (\alpha_1 + \beta_1 v, \alpha_2 + \beta_2 v)^T$ and $DI(v) = -(\alpha_1 + \beta_1 v)$. Various choices of $\alpha_1, \alpha_2, \beta_1$, and β_2 specify different alternative hypotheses for H_{10} and H_{20} .

In the study, we considered the following six models:

$$(M7) \quad (\alpha_1, \beta_1, \alpha_2, \beta_2, \gamma) = (0, 0, 0.2, 0.5, 0.3);$$

$$(M8) \quad (\alpha_1, \beta_1, \alpha_2, \beta_2, \gamma) = (-0.5, 0.5, 0.2, 0.5, 0.3);$$

$$(M9) \quad (\alpha_1, \beta_1, \alpha_2, \beta_2, \gamma) = (-0.5, 0.45, 0.2, 0.5, 0.3);$$

$$(M10) \quad (\alpha_1, \beta_1, \alpha_2, \beta_2, \gamma) = (-0.7, 0, 0.2, 0.5, 0.3);$$

$$(M11) \quad (\alpha_1, \beta_1, \alpha_2, \beta_2, \gamma) = (-0.2, 1.5, 0.2, 0.5, 0.3);$$

$$(M12) \quad (\alpha_1, \beta_1, \alpha_2, \beta_2, \gamma) = (-0.2, 3, 0.2, 0.5, 0.3).$$

Model (M7) is a null model under H_{10} and model (M10) is a null model under H_{20} . The models (M8) to (M9) are considered as the alternatives for H_{11} and H_{12} . The models (M11) to (M12) are considered as the alternatives for H_{21} and H_{22} . The other setups were the same as in Tables 1 and 2.

Model (10) implies that without considering mark, the marginal additive hazard regression model is given by

$$\lambda(t|z(t)) = \lambda_0(t) + \theta_0^T z(t), \quad (11)$$

where $\lambda_0(t) = t + (e_\gamma - 1)/\gamma$, and $\theta_0 = (\theta_{01}, \theta_{02})^T = (\alpha_1 + \beta_1/2, \alpha_2 + \beta_2/2)^T$. The standard method for testing the marginal vaccine efficacy regardless of the mark is to test $H_0^*: \theta_{01} = 0$ against $H_1^*: \theta_{01} \neq 0$, or $H_2^*: \theta_{01} < 0$ in case of monotone alternative.

Table 3 reports the empirical sizes and powers of the test statistics T_1, T_2, T_3, T_1^* and T_2^* at the significance level of $\alpha = 0.05$. Table 4 gives the empirical sizes and powers of the test statistics T_4, T_5 and T_6 at the significance level of $\alpha = 0.05$. The two tables also report the

empirical coverage probabilities of the 95% simultaneous confidence intervals for $CD(v)$ with $v \in [a, b]$ and v in the grid. We also investigated the performance of the proposed estimators for $\beta_0(v) = (\beta_{01}(v), \beta_{02}(v))^T$ and $CD(v)$. The pointwise biases and the standard errors are provided in Figures 4 and 5, respectively. The pointwise coverage probabilities for $\beta_0(v)$ and $CD(v)$ are presented in Figure 6. It can be seen that the proposed methods still perform well in these cases. Since the departure from H_{10} and H_0^* increases as the simulation model moves from (M8) to (M9), the powers of the tests increase as the model moves from (M8) to (M9). Similarly, the powers of the tests T_4 , T_5 and T_6 increase as the model moves from (M11) to (M12). Both the tests T_1 and T_2 also have greater powers than their counterparts T_1^* and T_2^* . In addition, the test T_3 is less powerful than the test T_2 , while the test T_1 is not more powerful than the test T_3 for the situation considered here.

4. Application

We now apply the proposed methods to analyze a dataset from the HIV vaccine efficacy trial that motivated the study. The trial was carried out in North America and The Netherlands and enrolled 5403 HIV-negative volunteers at risk for acquiring HIV infection (Flynn et al. 2005). Volunteers were randomly assigned to a recombinant glycoprotein 120 vaccine (AIDSVAX) and placebo groups in a 2:1 ratio, and they were monitored for HIV infection at semi-annual HIV testing visits for 36 months. The vaccine was designed to protect subjects from HIV infection by stimulating high titer antibodies that neutralize exposing HIVs. Since the HIV-gp120 region contains neutralizing epitopes that potentially can induce anti-HIV antibody responses that prevent HIV infection (Wyatt et al. 1998), we define the mark V as the percent mismatch of amino acids in the whole gp120 region (581 amino acids long), where all possible mismatches of particular pairs of amino acids (e.g., A versus C) are weighted by the estimated probability of interchange (Nickel et al. 2005). Of the 368 individuals infected during the trial, 32 had missing marks. For the remaining 336 samples which this analysis is based on, all marks were unique (217 vaccine; 119 placebo). Our application has two objectives. One is to estimate the parameters under the mark-specific additive model (1) and the other is to test the hypotheses $H_{10} : DI(v) = 0$ and H_{20} that $DI(v)$ does not depend on $v \in [a, b]$.

In the application, three covariates were considered: treatment indicator, age at enrollment and behavioral risk score (taking values 0–7) as defined in Flynn et al. (2005). Let $Z_1=1$ if the volunteer was in the vaccine group and $Z_1=0$ if the volunteer was in the placebo group. Let Z_2 be the age and Z_3 the behavioral risk score. The regression coefficient functions for Z_1 , Z_2 and Z_3 under model (1) are denoted by $\beta_1(v)$, $\beta_2(v)$ and $\beta_3(v)$, respectively. We use the Epanechnikov kernel, the test parameters a_1 and the grid points are taken same as those in the simulation study. The estimated standard error of the observed marks for uncensored failure times is $\hat{\sigma}_V = 0.1591$. The bandwidth $h = 0.1491$ is estimated using the formula $h = 4\hat{\sigma}_V n_o^{-1/4}$, where n_o is the number of observed failure times ($n_o = 336$). The plots of the estimates for $\beta_1(v)$, $\beta_2(v)$ and $\beta_3(v)$ along with their 95% pointwise confidence bands are given in Figures 7(a), (b) and (c), respectively. The plots of $CD(v)$ with its pointwise confidence bands is presented in Figure 7(d). Figure 7(b) indicates that there is a negative

correlation between age and the risk of infection. Figure 7(c) indicates that there is a positive correlation between the behavioral risk and the risk of infection.

Based on 2000 realizations of Wiener processes $W(\hat{\pi}(\nu))$, the p -value of T_1 for testing H_{10} against the general alternative H_{11} is 0.7780. The test statistics T_2 and T_3 for testing H_0 against the one-sided alternative H_{12} yield p -values of 0.3260 and 0.0520, respectively. These tests show mixed results about the vaccine protection. The p -value of 0.0520 for T_3 seems pointing to the possibility that the vaccine increases the protection from infection while T_1 and T_2 do not show significance evidence for vaccine efficacy. A likely explanation of the situation is that the test statistics T_1 and T_2 are less powerful in the situation. This testing result of T_3 supported by the negative values of $\hat{\beta}_1(\nu)$ shown in Figures 7(a), indicating, albeit weak, that the vaccine group has lower risk of HIV infection.

The standard method for testing the marginal vaccine efficacy regardless of the mark is to test $H_0^*: \theta_{01} = 0$ based on the marginal additive hazard model. The test statistic T_1^* for testing H_0^* yield a p -value of 0.2605 for the two-sided alternative and the p -value of T_2^* is 0.1130 for the one-sided alternative. The standard tests T_1^* and T_2^* do not show the significance of the vaccine protection. These results show the benefit of taking into consideration of mark in testing for vaccine efficacy. We also note that different constructions of test statistics that summarize evidence of vaccine protections across mark lead to different powers as seen in the tests T_1 , T_2 and T_3 . The tests T_4 , T_5 and T_6 do not find significant evidence that the vaccine effect varies with the mark. The test statistic T_4 for testing H_{20} against the general alternative H_{21} yields a p -value of 0.9660. The p -values for testing H_{20} against the monotone alternative H_{21} is 0.7065 for T_5 and 0.7185 for T_6 .

5. Concluding remarks

In this article, we proposed a mark-specific additive hazards model with a continuous mark variable. An estimating equation approach was developed for the model estimation. The asymptotic properties of the proposed estimators were established. Confidence bands and formal tests for various hypotheses concerning the treatment effect were developed. The simulation results showed that the proposed methods work well for the situations considered. An application to the first HIV vaccine efficacy trial was provided to illustrate our methods.

The mark-specific additive hazards model adds additional modeling power than the marginal additive hazard model which does not consider mark. It facilitates evaluating the relationship between the risk of failure and the mark which can not be treated as a covariate. The mark-specific hazards models have important applications in HIV vaccine efficacy trials and can be used to evaluate strain-specific vaccine efficacy. The proposed additive hazards model can be treated as an additive counterpart of the mark-specific proportional hazards model with continuous marks (Sun et al. 2009). Both models have sound biological and empirical bases (Lin et al. 1994; McKeague and Sasieni 1994) and the choice between the two models will be an empirical matter. Sun et al. (2015) developed some goodness-of-fit procedures for the stratified mark-specific proportional hazards model. It would be desirable to develop such tests to check the adequacy of the mark-specific additive hazards model.

Since the estimating equation (3) was given in a somewhat ad hoc fashion using the generalized estimating equation approach, it would be worthwhile to further investigate possible improvements that could result from other approaches, such as the one suggested by McKeague and Sasieni (1994) or perhaps a nonparametric maximum likelihood approach. In addition, the transformed hazards models with continuous marks (Chen et al. 2002; Zeng et al. 2005) might also be worthy of investigation.

In many applications, some continuous marks are not observed at uncensored failure times (Sun and Gilbert 2012). However, the proposed methods cannot be extended in a straightforward manner to deal with the mark-specific additive hazards model with missing marks, especially when some of the marks are missing at random (Little and Rubin 2002). This is a challenging problem and requires further research efforts.

Note that the tests T_1 and T_2 are more powerful than the test T_3 based on Table 1, and the test T_1 is not more powerful than the test T_3 based on Table 3. This implies that the test may be more powerful for one model but not for the other. Since we don't know what is the real underlying model for the data, there is no conflict in the outcomes between the simulation and data analysis. However, it is difficult to find any clue that one test may be more powerful than the other in general and merits future research.

In general, a local linear fitting is better than a local constant fitting. Note that the main purpose of this paper is to estimate the regression functions $\beta_0(v)$ at prespecified mark points, and a local constant fitting is more simple than a local linear fitting. Following Sun et al. (2009), we also used the local constant fitting to construct the estimating equation. The proposed methods for the local constant fitting can be extended to deal with local linear fitting and general local polynomial fitting, but the resulting inference procedures would be much more complicated. In addition, the proposed methods require large sample sizes to work well as demonstrated in the simulation study, and this does not cause a problem in our application to the first HIV vaccine efficacy trial, which has a sample size of 5403. However, one needs to be careful in applying the proposed approach to situations with small sample sizes.

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Appendix: Proofs of Theorems

We assume that the following regularity conditions hold for Theorems 1–3:

(C1) $\beta_0(v)$ has component wise continuous second derivatives on $[0, 1]$. The second partial derivative of $\lambda_0(t, v)$ with respect to v exists and is continuous on $[0, \tau] \times [0, 1]$. The covariate process $Z(t)$ has paths that are left continuous and of bounded variation, and satisfies the moment condition $\sup_{t \in [0, \tau]} E(\|Z(t)\|^2) < \infty$, where $\|\cdot\|$ is the maximum norm of a vector (maximum absolute value over all elements).

(C2) $P(X = \tau) > 0$, and the matrix A is nonsingular, where

$$A = E \left[\int_0^\tau Y_i(t) \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} dt \right],$$

and $\bar{Z}(t)$ is the limit of $\bar{Z}_n(t)$.

(C3) $E[N_i(dt, dv) | \mathcal{F}_{t-}] = E[N_i(dt, dv) | Y_i(t), Z_i(t)]$, where $\mathcal{F}_t = \sigma\{I(X_j = s, \delta_j = 1), I(X_j = s, \delta_j = 0), V_j I(X_j = s, \delta_j = 1), Z_j(s); 0 \leq s \leq t, i = 1, \dots, n\}$ is the right-continuous filtration generated by $\{N_i(s, v), Y_i(s), Z_i(s); 0 \leq s \leq t, 0 \leq v \leq 1, i = 1, \dots, n\}$.

(C4) The kernel function $K(\cdot)$ is symmetric with support $[-1, 1]$ and has bounded variation satisfying $\int K(u) du = 1$. The bandwidth satisfies $nh^2 \rightarrow \infty$ and $nh^5 \rightarrow 0$ as $n \rightarrow \infty$.

Conditions (C1)–(C2) are standard assumptions in the context of survival analysis (Sun et al. 2009). Condition (C4) is a standard assumption for kernel smoothing techniques. Condition (C3) implies that the mark-specific intensity of $N_i(t, v)$ with respect to $\mathcal{F}_t$ only depends on the failure status and the current covariate value. Thus, $E[N_i(dt, dv) | \mathcal{F}_{t-}] = Y_i(t) \lambda(t, v | Z_i(t)) dt dv$, and $M_i(t, v) = \int_0^t \int_0^v [N_i(ds, du) - Y_i(s) \{\Lambda_0(ds, du) + \beta_0(u)^T Z_i(s) ds du\}]$ is a martingale with respect to $\mathcal{F}_t$ for each fixed v (Martinussen and Scheike 2006, p.31). In addition, it can be shown that $M_i(\cdot, v_1)$ and $M_i(\cdot, v_2) - M_i(\cdot, v_1)$ are orthogonal square integrable martingales with respect to $\mathcal{F}_t$ for any $0 \leq v_1 \leq v_2 \leq 1$ (Aalen and Johansen 1978). A discussion of these conditions can be found in Sun et al. (2009). In order to avoid the boundary problems, we only study the asymptotic properties of $\hat{\beta}(v)$ for $v \in [a, b] \subset (0, 1)$.

The following lemma will be used to prove the uniform consistency of $\hat{\beta}(v)$.

Lemma 1

Assume that $\psi_n(v, \theta)$ are random functions and $\psi(v, \theta)$ is a fixed function of $(v, \theta) \in [a, b] \times \Theta$, $\Theta \in \mathbb{R}^p$. Let $\beta(v)$ be a fixed function of $v \in [a, b]$ taking values in Θ . Suppose that $\sup_{v, \theta} |\psi_n(v, \theta) - \psi(v, \theta)| \xrightarrow{p} 0$, and that for every $\varepsilon > 0$, there exists an $\eta > 0$ such that $\inf_{\|\theta - \beta(v)\| > \varepsilon} |\psi(v, \theta)| > \eta$, and $\psi(v, \beta(v)) = 0$ for $v \in [a, b]$. Then for any sequence of estimators $\hat{\beta}(v)$ with $\psi_n(v, \hat{\beta}(v)) = o_p(1)$ uniformly in $v \in [a, b]$, we have $\hat{\beta}(v) \xrightarrow{p} \beta(v)$ uniformly in $v \in [a, b]$.

Proof

Let $Q_n(v, \theta) = -|\psi_n(v, \theta)|$, and $Q(v, \theta) = -|\psi(v, \theta)|$. Then by using Lemma 1 of Sun et al. (2009) with the functions $Q_n(v, \theta)$ and $Q(v, \theta)$, it can be shown that $\hat{\beta}(v) \xrightarrow{p} \beta(v)$ uniformly in $v \in [a, b]$.

The next lemma will be used to prove the asymptotic distributions of $\hat{\beta}(v)$ and $\hat{B}(v)$.

Lemma 2

Under the regularity conditions (C1)–(C4), $n^{-1} \sum_{i=1}^n N_i(t, v) \xrightarrow{p} EN_1(t, v)$ uniformly in $(t, v) \in [0, \tau] \times [0, 1]$, and $n^{-1/2} \sum_{i=1}^n M_i(t, v)$ converges weakly on $[0, \tau] \times [0, 1]$ to a mean-zero continuous Gaussian process $H(t, v)$ with independent increments, and

$$Var[(H(t, v))] = \int_0^t \int_0^v [\lambda_0(s, u) s^{(0)}(s) + \beta_0(u)^T s^{(1)}(s)] du ds.$$

The proof of this lemma is similar to the proof of Lemma 2 in Sun et al. (2009).

Proof of Theorem 1

Define

$$\xi_n(v, \theta) = n^{-1} \sum_{i=1}^n \int_0^v \int_0^\tau \{Z_i(t) - \bar{z}(t)\} \left[N_i(dt, du) - Y_i(t) \theta^T Z_i(t) dt du \right],$$

and

$$\psi_n(v, \theta) = n^{-1} \sum_{i=1}^n \int_0^1 \int_0^\tau K_h(u-v) \{Z_i(t) - \bar{Z}(t)\} \left[N_i(dt, du) - Y_i(t) \theta^T Z_i(t) dt du \right].$$

The functional central limit theorem (Pollard 1990) and Condition (C1) imply that

$$\sup_{0 \leq t \leq \tau} \|\bar{Z}(t) - \bar{z}(t)\| = O_p(n^{-1/2}). \quad (\text{A.1})$$

Thus,

$$\psi_n(v, \theta) = \int_0^1 K_h(u-v) \xi_n(du, \theta) + O_p(n^{-1/2} h^{-1}), \quad (\text{A.2})$$

uniformly in $(v, \theta) \in [0, 1] \times [-M, M]^p$, where $M > 0$ is a constant such that $(v, \beta_0(v)) \in [0, 1] \times (-M, M)^p$ for all v . Let

$$\xi(v, \theta) = E \left[\int_0^v \int_0^\tau \{Z_i(t) - \bar{z}(t)\} Y_i(t) \{ \lambda_0(t, u) + \beta_0(u)^T Z_i(t) - \theta^T Z_i(t) \} dt du \right].$$

Then using the Glivenko-Cantelli and Donsker theorems (Theorems 19.4 and 19.5 of Van der vaart 1998), we have that uniformly in $(v, \theta) \in [0, 1] \times [-M, M]^p$,

$$\xi_n(v, \theta) = \xi(v, \theta) + O_p(n^{-1/2}). \quad (\text{A.3})$$

It follows from (A.2) and (A.3) that uniformly in $(v, \theta) \in [a, b] \times [-M, M]^p$,

$$\psi_n(v, \theta) = \psi(v, \theta) + O_p(n^{-1/2} h^{-1}), \quad (\text{A.4})$$

where

$$\psi(v, \theta) = E \left[\int_0^\tau \{Z_i(t) - \bar{z}(t)\} Y_i(t) \{ \lambda_0(t, v) + \beta_0^T(v) Z_i(t) - \theta^T Z_i(t) \} dt \right].$$

It can be checked that $\psi(v, \beta_0(v)) = 0$, $\psi_n(v, \hat{\beta}(v)) = 0$, and

$$\frac{\partial \psi(v, \theta)}{\partial \theta} = -E \left[\int_0^\tau Y_i(t) \{Z_i(t) - \bar{z}(t)\}^{\otimes 2} dt \right] = -A < 0.$$

Hence by the Taylor expansion and Condition (C2), we get that for every $\varepsilon > 0$, there exists an $\eta > 0$ such that $\inf_{\|\theta - \beta_0(v)\| > \varepsilon} |\psi(v, \theta)| > \eta$ for $v \in [a, b]$. Similarly to (A.4), we get that uniformly in $(v, \theta) \in [a, b] \times [-M, M]^p$,

$$\frac{\partial \psi_n(v, \theta)}{\partial \theta} \xrightarrow{p} \frac{\partial \psi(v, \theta)}{\partial \theta}. \quad (\text{A.5})$$

Note that $-M_0 \leq \beta_0(v) \leq M_0$ for $a \leq v \leq b$ with some $M_0 < M$. It then follows from (A.4) and (A.5) that for every $\alpha > 0$ and all large n ,

$$P(-M \leq \hat{\beta}(v) \leq M, a \leq v \leq b) > 1 - \alpha.$$

Thus, using Lemma 1, we obtain that for every $\varepsilon > 0$,

$$\begin{aligned}
& P\left(\sup_{a \leq v \leq b} \|\hat{\beta}(v) - \beta_0(v)\| > \varepsilon\right) \\
& \leq \alpha + P\left(\sup_{a \leq v \leq b} \|\hat{\beta}(v) - \beta_0(v)\| > \varepsilon, -M \leq \hat{\beta}(v) \leq M, a \leq v \leq b\right) \\
& \rightarrow \alpha \quad \text{as } n \rightarrow \infty.
\end{aligned}$$

Since α can be arbitrarily small, we have

$$P\left(\sup_{a \leq v \leq b} \|\hat{\beta}(v) - \beta_0(v)\| \geq \varepsilon\right) \rightarrow 0.$$

To prove the asymptotic normality of $\hat{\beta}(v)$, using the second-order Taylor expansion of $\beta_0(v)$ around v and Condition (C1), we have that uniformly in $v \in [a, b]$,

$$\begin{aligned}
U(v, \beta_0(v)) &= \sum_{i=1}^n \int_0^1 \int_0^\tau K_h(u-v) \{Z_i(t) - \bar{Z}(t)\} \left[M_i(dt, du) - Y_i(t) \{\beta_0(v) - \beta_0(u)\}^T Z_i(t) \right] dt du \\
&= \sum_{i=1}^n \int_0^1 \int_0^\tau K_h(u-v) \{Z_i(t) - \bar{Z}(t)\} M_i(dt, du) + O_p(nh^2).
\end{aligned}$$

(A.6)

It follows from (A.1) that $h^{1/2} K_h(u-v) \|\bar{Z}(t) - Z(t)\| = O_p(n^{-1/2} h^{-1/2})$ uniformly in $t \in [0, \tau]$, $u \in [0, 1]$ and $v \in [a, b]$. In addition, it follows from Lemma 2 that $n^{-1/2} \sum_{i=1}^n M_i(t, v)$ converges weakly to a mean-zero Gaussian process. Thus, applying (A.6) and Lemma 2 of Gilbert et al. (2008), we obtain that uniformly in $v \in [a, b]$,

$$\begin{aligned}
n^{-1/2} h^{1/2} U(v, \beta_0(v)) &= n^{-1/2} h^{1/2} \sum_{i=1}^n \int_0^1 \int_0^\tau K_h(u-v) \{Z_i(t) - \bar{Z}(t)\} M_i(dt, du) + O_p(n^{1/2} h^{5/2}) + O_p(n^{-1/2} h^{-1/2}) \\
&= h^{1/2} \int_0^1 K_h(u-v) dG_n(u) + O_p(n^{1/2} h^{5/2}) + O_p(n^{-1/2} h^{-1/2}),
\end{aligned}$$

(A.7)

where

$$G_n(v) = n^{-1/2} \sum_{i=1}^n \int_0^v \int_0^\tau \{Z_i(t) - \bar{Z}(t)\} M_i(dt, du).$$

Following the same lines as the proof of Theorem 1 in Sun et al. (2009), we can show that $G_n(v)$ converges weakly on $[0, 1]$ to a p -dimensional mean-zero continuous Gaussian

process $G(v)$ with independent increments. The covariance matrix of $G(v)$ is $\int_0^v \sum(u) du$. By the strong embedding theorem (Shorack and Wellner 1986, p.47–48), there exist $G_n^*(v)$ and $G_*(v)$ on some probability space with the same distributions and sample paths as $G_n(v)$ and $G(v)$, respectively, such that $G_n^*(v)$ converges almost surely to $G(v)$ uniformly in $v \in [0, 1]$. Since $K(\cdot)$ has bounded variation, by integration by parts, we get

$$\int_0^1 K_h(u-v) dG_n^*(u) = \int_0^1 K_h(u-v) dG^*(u) + O_p(n^{-1/2}h^{-1}).$$

Note that $h^{1/2} \int_0^1 K_h(u-v) dG^*(u)$ is a mean-zero Gaussian random vector with covariance matrix $h \int_0^1 K_h^2(u-v) \sum(u) du \rightarrow \mu_0 \sum(v)$. Then $h^{1/2} \int_0^1 K_h(u-v) dG_n(u)$ converges in distribution to a zero-mean normal random vector with covariance matrix $\mu_0 \sum(v)$. It follows from (A.7) and the Slutsky's theorem that $n^{-1/2} h^{1/2} U(v, \beta_0(v))$ converges in distribution to a zero-mean normal random vector with covariance matrix $\mu_0 \sum(v)$. Note that $h \rightarrow 0$ as $n \rightarrow \infty$. Then it is easy to show that for all sufficiently large n , $\int_0^1 K_h(u-v) du = 1$ for $v \in [a, b] \subseteq (0, 1)$, and

$$\hat{\beta}(v) - \beta_0(v) = n^{-1} \hat{A}^{-1} U(v, \beta_0(v)).$$

Not that

$$\hat{A} = n^{-1} \sum_{i=1}^n \int_0^T Y_i(t) \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} dt \rightarrow A$$

almost surely by the uniform strong law of large numbers. Thus,

$$n^{1/2} h^{1/2} \{\hat{\beta}(v) - \beta_0(v)\} = A^{-1} n^{-1/2} h^{1/2} U(v, \beta_0(v)) + o_p(1), \quad (\text{A.8})$$

uniformly in $v \in [a, b]$. It follows that $n^{1/2} h^{1/2} \{\hat{\beta}(v) - \beta_0(v)\}$ converges in distribution to a zero-mean normal random vector with covariance matrix $\mu_0 A^{-1} \sum(v) A^{-1}$ for $v \in [a, b]$.

Proof of Theorem 2

It follows from (A.7) and (A.8) that uniformly in $v \in [a, b]$ and Condition (C4),

$$\begin{aligned}
n^{1/2}\{\hat{B}(v)-B_0(v)\} &= \int_a^v n^{1/2}\{\hat{\beta}(u)-\beta_0(u)\}du \\
&= \int_a^v A^{-1} \int_0^1 K_h(x-u) dG_n(x) du + o_p(1) \\
&= \int_0^1 \int_a^v A^{-1} K_h(x-u) dG_n(x) du + o_p(1) \\
&= \int_{a+h}^{v-h} \left[\int_a^v A^{-1} K_h(x-u) du \right] dG_n(x) + \int_{v-h}^{v+h} \left[\int_a^v A^{-1} K_h(x-u) du \right] dG_n(x) + o_p(1).
\end{aligned}$$

(A.9)

Note that $G_n(x)$ converges weakly to a mean-zero continuous Gaussian process with independent increments, and $\int_a^v K_h(x-u) du = 1$ for $x \in (a+h, v-h)$ (since $\int_{-1}^1 K(u) du = 1$). Then the first term on the right-hand side of (A.9) is $\int_a^v A^{-1} dG_n(x) + o_p(1)$ uniformly in $v \in [a, b]$. In a similar manner, the second and the third terms are $o_p(1)$ uniformly in $v \in [a, b]$. Thus,

$$n^{1/2}\{\hat{B}(v)-B_0(v)\} = \int_a^v A^{-1} dG_n(x) + o_p(1), \quad (\text{A.10})$$

which implies that $n^{1/2}\{\hat{B}(v)-B_0(v)\}$ converges weakly to a p -dimensional mean-zero continuous Gaussian process with independent increments. The covariance matrix of the Gaussian process equals to $\int_a^v A^{-1} \sum(u) A^{-1} du$.

Using the Glivenko-Cantelli theorem (Theorem 19.4 of Van der vaart 1998), we have that uniformly in $v \in [a, b]$,

$$n^{-1} \sum_{i=1}^n \int_a^v \int_0^\tau \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} N_i(dt, du) = \int_a^v \sum(u) du + o_p(1).$$

Also note that $\hat{A} \rightarrow A$ almost surely. Thus, we obtain

$$n^{-1} \sum_{i=1}^n \int_a^v \int_0^\tau \hat{A}^{-1} \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} \hat{A}^{-1} N_i(dt, du) = \int_a^v A^{-1} \sum(u) A^{-1} du + o_p(1).$$

Therefore, the covariance matrix $\int_a^v A^{-1} \sum(u) A^{-1} du$ can be consistently estimated by

$$n^{-1} \sum_{i=1}^n \int_a^v \int_0^\tau \hat{A}^{-1} \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} \hat{A}^{-1} N_i(dt, du).$$

Proof of Theorem 3

It can be checked that

$$n^{1/2}\{\hat{\Lambda}_0(t, v) - \Lambda_0(t, v) - [\hat{\Lambda}_0(t, a) - \Lambda_0(t, a)]\} = \int_0^t \int_a^v \frac{n^{-1/2} \sum_{i=1}^n M_i(ds, du)}{S^{(0)}(s)} - D(t)^T n^{1/2}\{\hat{B}(v) - B_0(v)\},$$

where $D(t) = \int_0^t \bar{Z}(s) ds$. Note that by the uniform strong law of large numbers, $S^{(0)}(s)$ converges almost surely to $s^{(0)}(s)$ uniformly in $s \in [0, \tau]$. Then using Lemma 2 of Gilbert et al. (2008), Lemma 2 and (A.10), we have that uniformly in $(t, v) \in [0, \tau] \times [0, 1]$,

$$n^{1/2}\{\hat{\Lambda}_0(t, v) - \Lambda_0(t, v) - [\hat{\Lambda}_0(t, a) - \Lambda_0(t, a)]\} = \int_0^t \int_a^v \frac{n^{-1/2} \sum_{i=1}^n M_i(ds, du)}{s^{(0)}(s)} - d(t)^T \int_a^v A^{-1} dG_n(u) + o_p(1),$$

where $d(t) = \int_0^t \bar{z}(s) ds$. Since $n^{-1/2} \sum_{i=1}^n M_i(t, v)$ and $G_n(x)$ converge weakly to mean-zero continuous Gaussian processes, and $s^{(0)}(s)$ and $d(t)$ are deterministic functions, thus $n^{1/2}\{\hat{\Lambda}_0(t, v) - \Lambda_0(t, v) - [\hat{\Lambda}_0(t, a) - \Lambda_0(t, a)]\}$ converges weakly on $[0, \tau] \times [a, b]$ to a mean-zero Gaussian process. Further, we can write

$$n^{1/2}\{\hat{\Lambda}_0(t, v) - \Lambda_0(t, v) - [\hat{\Lambda}_0(t, a) - \Lambda_0(t, a)]\} = n^{-1/2} \sum_{i=1}^n \Phi_i(t, v) + o_p(1),$$

where

$$\Phi_i(t, v) = \int_0^t \int_a^v \frac{M_i(ds, du)}{s^{(0)}(s)} - d(t)^T \int_a^v \int_0^\tau A^{-1} \{Z_i(s) - \bar{z}(s)\} M_i(ds, du).$$

Thus, the covariance function of the Gaussian process at (t_1, v_1) and (t_2, v_2) equal to $E[\Phi_i(t_1, v_1)\Phi_i(t_2, v_2)]$.

Figure 1.

Plots of estimates for $\beta_0(v)$ and $CD(v)$ under the models M1, M2 and M3 for $n = 500$, $h = \hat{\sigma}_v n_0^{-1/4}$. and The first row is for model M1, the second row for model M2 and the third row for model M3. The solid dark lines are the true functions and the dashed lines are the averages of the estimates based on 500 repetitions.

Figure 2.

Plots of the standard errors under the models M1, M2 and M3 for $n = 500$, $h = \hat{\sigma}_v n_0^{-1/4}$. The first row is for model M1, the second row for model M2 and the third row for model M3.

The dashed lines are the averages of the estimated standard errors of $\hat{\beta}(v)$ and $\hat{CD}(v)$, while the solid lines are the sample standard deviations of $\hat{\beta}(v)$ and $\hat{CD}(v)$, based on 500 repetitions.

Figure 3.

Plots of the point wise coverage probabilities for $\beta_0(v)$ and for $CD(v)$, based on $n = 500$, $h = \hat{\sigma}_v n_0^{-1/4}$ and 500 repetitions. The first row is for model M1, the second row for model M2 and the third row for model M3.

Figure 4.

Plots of estimates for $\beta_{01}(v)$, $\beta_{02}(v)$ and $CD(v)$ under the models M7, M8 and M9 for $n = 500$, $h = \hat{\sigma}_v n_0^{-1/4}$. The first row is for model M7, the second row for model M8 and the third row for model M9. The solid dark lines are the true functions and the dashed lines are the averages of the estimates based on 500 repetitions.

Figure 5.

Plots of the standard errors under the models M7, M8 and M9 for $n = 500$, $h = \hat{\sigma}_v n_0^{-1/4}$. The first row is for model M7, the second row for model M8 and the third row for model M9.

The dashed lines are the averages of the estimated standard errors of $\hat{\beta}_1(v)$, $\hat{\beta}_2(v)$ and $\widehat{CD}(v)$, while the solid lines are the sample standard deviations of $\hat{\beta}_1(v)$, $\hat{\beta}_2(v)$ and $\widehat{CD}(v)$, based on 500 repetitions.

Figure 6.

Plots of the point wise coverage probabilities for $\beta_{01}(v)$, $\beta_{02}(v)$ and for $CD(v)$, based on $n = 500$, $h = \hat{\sigma}_v n_0^{-1/4}$ and 500 repetitions. The first row is for model M7, the second row for model M8 and the third row for model M9.

Figure 7.

Plots of the estimates for $\beta_{01}(v)$, $\beta_{02}(v)$, $\beta_{03}(v)$ and $CD(v)$ along with their 95% point wise confidence bands for the vaccine trial data with $h=4\hat{\sigma}_v n_o^{-1/4}$: (a) for $\beta_{01}(v)$, (b) for $\beta_{02}(v)$, (c) for $\beta_{03}(v)$, and (d) for $CD(v)$. Figure 7(d) also includes 95% simultaneous confidence bands for $CD(v)$. The dashed lines are 95% point wise confidence bands and the dotted lines are 95% simultaneous confidence bands.

Empirical sizes and powers of the tests T_1 , T_2 and T_3 at the significant level 0.05 and the coverage probabilities of the 95% simultaneous confidence bands for $CD(v)$ with $v \in [a, b] = [0.1, 0.9]$ and on the grid of eight evenly spaced points from 0.101 to 0.899. The marginal tests T_1^* and T_2^* are the standard Wald tests without considering marks.

Table 1

Model	(α, β, γ)	n	Size/Power				Coverage	
			T_1	T_2	T_3	T_1^*	T_2^*	[a,b]
M1	(0,0,0.3)	500	4.0	4.2	3.8	5.6	5.2	98.8
		800	5.4	4.8	3.6	5.8	4.6	98.2
M2	(-0.5,0.5,0.3)	500	64.0	77.4	58.6	61.6	74.4	97.4
		800	86.8	92.6	77.0	81.6	88.4	97.6
M3	(-0.5,0.45,0.3)	500	67.6	79.4	65.4	67.4	78.0	98.6
		800	91.4	95.2	85.0	88.8	93.2	97.8

Table 2

Empirical sizes and powers of the tests T_4 , T_5 and T_6 at the significant level 0.05 and the coverage probabilities of the 95% simultaneous confidence bands for $CD(v)$ with $v \in [a, b] = [0.1, 0.9]$ and on the grid of eight evenly spaced points from 0.172 to 0.820.

Model	(α, β, γ)	n	Size/Power			Coverage	
			T_4	T_5	T_6	grid	[a,b]
M4	(0.7,0.0.3)	500	4.0	5.6	3.8	98.2	98.2
		800	3.8	4.0	4.0	97.2	98.0
M5	(-0.2,1.5,0.3)	500	46.2	68.0	48.0	98.2	98.8
		800	74.8	87.0	70.2	97.2	97.6
M6	(-0.2,3.0.3)	500	86.6	95.0	82.8	96.8	97.0
		800	97.2	99.4	95.2	96.6	97.0

Table 3

Empirical sizes and powers of the tests T_1 , T_2 and T_3 at the significant level 0.05 and the coverage probabilities of the 95% simultaneous confidence bands for $CD(v)$ with $v \in [a, b] = [0.1, 0.9]$ and on the grid of eight evenly spaced points from 0.101 to 0.899. The marginal tests T_1^* and T_2^* are the standard Wald tests without considering marks.

Model	$(\alpha_1, \beta_1, \alpha_2, \beta_2, \gamma)$	n	Size/Power					Coverage	
			T_1	T_2	T_3	T_1^*	T_2^*	grid	[a,b]
M7	(0,0,0.2,0.5,0.3)	500	5.2	5.0	4.4	4.8	5.0	97.0	97.6
		800	6.0	6.8	5.4	4.6	4.6	97.4	97.8
M8	(-0.5,0.5,0.2,0.5,0.3)	500	27.0	38.0	25.2	26.4	35.6	97.0	98.0
		800	41.8	56.2	39.4	38.0	49.4	96.0	97.0
M9	(-0.5,0.45,0.2,0.5,0.3)	500	32.6	44.6	32.8	30.2	43.0	98.2	98.6
		800	46.4	59.8	49.0	45.8	59.6	97.8	98.4

Table 4

Empirical sizes and powers of the tests T_4 , T_5 and T_6 at the significant level 0.05 and the coverage probabilities of the 95% simultaneous confidence bands for $CD(v)$ with $v \in [a, b] = [0.1, 0.9]$ and on the grid of eight evenly spaced points from 0.172 to 0.820.

Model	$(\alpha_1, \beta_1, \alpha_2, \beta_2, \gamma)$	n	Size/Power			Coverage	
			T_4	T_5	T_6	grid	[a,b]
M10	(0.7,0.0,2.0,5.0,3)	500	2.8	5.8	3.6	97.0	97.6
		800	2.6	5.0	3.6	96.0	96.8
M11	(-0.2,1.5,0.2,0.5,0.3)	500	26.6	42.0	27.6	98.4	98.4
		800	39.0	57.8	41.0	96.8	97.6
M12	(-0.2,3.0,2.0,5.0,3)	500	64.4	80.2	63.8	95.8	97.2
		800	82.6	92.0	77.6	96.8	97.4