Statistica Sinica Preprint No: SS-2017-0357	
Title	Nonparametric Inference for Right Censored Data Using Smoothing Splines
Manuscript ID	SS-2017-0357
URL	http://www.stat.sinica.edu.tw/statistica/
DOI	10.5705/ss.202017.0357
Complete List of Authors	Meiling Hao Yuanyuan Lin and Xingqiu Zhao
Corresponding Author	Yuanyuan Lin
E-mail	ylin@sta.cuhk.edu.hk

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Statistica Sinica

Nonparametric Inference for Right-Censored Data Using Smoothing Splines

Meiling Hao

School of Statistics, University of International Business and Economics, Beijing, China

Yuanyuan Lin

Department of Statistics, The Chinese University of Hong Kong, Hong Kong

Xingqiu Zhao

Department of Applied Mathematics, The Hong Kong Polytechnic University, Hong Kong

Abstract: This study introduces a penalized nonparametric maximum likelihood estimation of the log-hazard function for analyzing right-censored data. Smoothing splines are employed for a smooth estimation. Our main discovery is a functional Bahadur representation, which serves as a key tool for nonparametric inferences of an unknown function. The asymptotic properties of the resulting smoothing-spline estimator of the unknown log-hazard function are established under regularity conditions. Moreover, we provide a local confidence interval for this function, as well as local and global likelihood ratio tests. We also discuss the asymptotic efficiency of the estimator. The theoretical results are validated using extensive simulation studies. Lastly, we demonstrate the estimator by applying it to a real data set.

Key words and phrases: Functional Bahadur representation; Likelihood ratio test;

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Nonparametric inference; Penalized likelihood; Right-censored data; Smoothing splines.

1. Introduction

In a survival analysis, the outcome variable of interest is the time till the occurrence of an event, such as the occurrence of a disease, death, divorce, and so on. The time to the event, or survival time, is usually measured in days, weeks or years, and is typically positive. Censored observations, for which the survival time is incomplete, are common in medical studies, reliability, and many other fields related to survival analyses. The most common case is right censoring. To accommodate censoring, several statistical models and methodologies have been developed, including parametric, semiparametric, and nonparametric methods, see Kalbfleisch and Prentice (2011) for an overview.

Parametric approaches assume that the underlying distributions of the times to an event are known. For example, the exponential, lognormal, and Weibull distributions are among those commonly used. Parametric methods are appealing to practitioners owing to their convenience and ease of interpretation (Johnson and Kotz, 1970; Mann *et al.*, 1974; Lawless, 1982; Kalbfleisch and Prentice, 2011). The most extensively used semiparametric model for the analysis of survival data is Cox's proportional-hazards

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

model. This model assumes that the hazard function of the survival time is multiplicatively related to an unknown baseline function and the covariates; see Cox (1972, 1975), Cox and Oake (1984), Lin and Wei (1989), Lin and Ying (1994), Chen (2004), and Chen *et al.* (2010). In contrast to parametric models, Cox's model makes no assumption on the shape of the baseline hazard function, and provides easy-to-interpret information on the relationship between the hazard function of the survival time and the covariates. The parameter for the covariate effect in Cox's model is usually estimated by maximizing the partial likelihood, and its large-sample properties are justified well by the martingale theory; see Anderson and Gill (1982), Kosorok (2008), and Fleming and Harrington (2011). In analyses of survival data, important alternative semiparametric models to Cox's model are the accelerated failure time (AFT) model and the transformation models. These models assume the logarithm of the survival time or an unknown, but monotonic transformation of the survival time is linearly related to the covariates; see Kalbfleisch and Prentice (2011), Cox and Oakes (1984), Wei (1992), Chen, Jin, and Ying (2002), and Zeng and Lin (2007a, 2007b). Inference methods for the AFT model and transformation models have been studied thoroughly in the literature; see Buckley and James (1979), Prentice (1978), Ritov (1990), Tsiatis (1990), Wei *et al.* (1990),

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Lai and Ying (1991a, b), Ying (1993), Lin and Chen (2013), and Zeng *et al.*(2009). The additive hazards model has also been found to be useful in modeling survival data; see Breslow and Day (1987), Lin and Ying (1994), and Jiang and Zhou (2007).

Parametric and semiparametric methods rely on distributional or model assumptions. However, the underlying distribution or model is often unknown. As a result, inferences based on parametric and semiparametric models may suffer from mis-specification. In contrast, the nonparametric inferences proposed in the literature do not make assumptions about the unknown distribution or an actual model form, see Cox (2018) for an overview. Such inferences focus on the hazard rate, survival function, or density function. Furthermore, the hazard function has a direct relationship with a survival function or a density function. The well-known Kaplan−Meier estimator (Kaplan and Meier, 1958) is a nonparametric maximum likelihood estimator (MLE) of an unknown survival function, and is characterized by self-consistency and asymptotic normality; see also Efron (1967), Breslow and Crowley (1967), Lo and Singh (1986), and Chen and Lo (1997), among many others. Note that some Bahadur-type independent and identically (i.i.d) representations of the product-limit estimator with right-censored data can be found in Lo and Singh (1986). However, the discontinuous na-

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

ture of the Kaplan−Meier estimator makes inferences complicated. Therefore, we develop smoothed estimators of the hazard or density function. For censored data, kernel smoothing and nearest-neighbor smoothing on the time axis are popular approaches to estimating the density function or hazard function; see Beran (1981), Tanner and Wong (1983), Dabrowska (1987), Lo, Mack, and Wang (1989), Gray (1992), and Müller and Wang (1994). Penalized likelihood methods based on smoothing splines have also been proposed in the literature; see Anderson and Senthilselvan (1980), O'Sullivan (1988), and Rosenberg (1995). It is known that kernel estimates reflect mostly the local structure of the data, whereas an estimator of a density or hazard function based on smoothing splines with a global smoothing parameter enjoys certain global properties (O'Sullivan *et al.* 1986).

However, to the best of our knowledge, with the exception of some consistency results for the smoothing splines hazard estimate (Cox and O'Sullivan, 1990), few studies examine the asymptotic properties of the smoothing-spline estimator of the hazard function. In addition, the existing asymptotic representations of the product-limit estimator (Lo and Singh, 1986) or the kernel-smoothing estimator of the hazard function (Tanner and Wong, 1986) are not directly applicable to the smoothing-spline estimator. Moreover, nonparametric inferences for the hazard function are subject to

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

a positive constraint, which makes the computation complicated. Recently, Shang and Cheng (2013) introduced a novel unified asymptotic framework for inferences of smoothing-spline estimations, which has broad applications for statistical inferences. In this study, similarly to Kooperberg *et al.* (1995), we focus on the log-hazard rate in a nonparametric framework and provide a penalized likelihood estimate based on smoothing splines. Our major contribution is to establish the asymptotic properties of the proposed log-hazard estimator with right-censored data.

The rest of the paper is organized as follows. Some background and preliminaries are given in Section 2. In Section 3, we establish a new functional Bahadur representation (FBR) in the Sobolev space and study the asymptotic properties of the resulting smoothing-spline estimator of the log-hazard function. We discuss the hypothesis test in Section 4 and present our simulation results in Section 5. The proposed method is applied to a non-Hodgkin's lymphoma data set in Section 6. All technical proofs are deferred to the Supplementary Material.

2. Preliminaries

2.1 Notation and Methodology

Here, we introduce the notation that will be used throughout this paper. Let T be the survival time, C be the censoring time, and τ be the end of the study. We define the observed time $Y = \min(T, C)$ and the censoring indicator $\Delta = I(T \le C)$, where $I(\cdot)$ is the indicator function. Moreover, denote $\lambda(t)$ as the hazard-rate function of the survival time and $g_0(t) = \log\{\lambda(t)\}$. The hazard function $\lambda(t) : [0, \tau] \mapsto \mathbb{R}$ is bounded away from 0 and infinity. Without loss of generality, we consider $\mathbb{I} \doteq [0, \tau] = [0, 1]$. Suppose that the observed data $(Y_i, \Delta_i), i = 1, \ldots, n$, are i.i.d copies of (Y, Δ). Then, the log-likelihood of g is

$$l_n(g) = -\int_{\mathbb{I}} \exp\{g(t)\} S_n(t)\, dt + \frac{1}{n} \sum_{i=1}^{n} \Delta_i g(Y_i),$$

where $S_n(t) = n^{-1} \sum_{i=1}^{n} I(Y_i \ge t)$ is the empirical survival function of Y; see O'Sullivan (1988). Let $l(g) \equiv E\{l_n(g)\}$. A direct calculation yields

$$l(g) = -\int_{\mathbb{I}} \exp\{g(t)\} S(t)\, dt + \int_{\mathbb{I}} \exp\{g_0(t)\} g(t) S(t)\, dt,$$

where $S(t) = Pr(Y \ge t)$. Throughout this paper, we suppose the true target function $g_0(t)$ belongs to the mth-order Sobolev space $\mathcal{H}^m(\mathbb{I})$, which we abbreviate to $\mathcal{H}^m$:

$$\mathcal{H}^m(\mathbb{I}) = \{g : \mathbb{I} \mapsto \mathbb{R} | g^{(j)} \text{ is absolutely continuous for } j = 0, 1, \ldots, m-1, \\ g^{(m)} \in L_2(\mathbb{I})\},$$

where the constant $m > 1/2$ and is assumed to be known, $g^{(j)}$ is the j derivative of g, and $L_2(\mathbb{I})$ is the L_2 space defined in $\mathbb{I}$. Define $J(g, \tilde{g}) =$

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

$\int_{\mathbb{I}} g^{(m)}(t)\tilde{g}^{(m)}(t)\,dt$. The penalized likelihood of $g(\cdot)$ is defined as

$$l_{n,\lambda}(g) = l_n(g) - \frac{\lambda}{2}J(g,g),$$

where $J(g,g)$ is the roughness penalty and λ is the smoothing parameter, which converges to zero as $n \to \infty$.

For the inference of $g_0(t)$, we propose using B-splines to approximate g in $l_{n,\lambda}(g)$. For the finite closed interval $\mathbb{I}$, we define a partition of $\mathbb{I}$:

$$0 = t_1 = \ldots = t_m < t_{m+1} < \ldots < t_{m_n+m} < t_{m_n+m+1} = \ldots = t_{m_n+2m} = 1,$$

which is used to partition the interval $[0,1]$ into $m_n + 1$ subintervals with knots set at $\mathcal{I} \equiv \{t_i\}^{m_n+2m}$, and $m_n = o(n^v)$ for $0 < v < 1/2$. Let $\{B_{i,m}, 1 \le i \le q_n\}$ denote the B-spline basis functions, with $q_n = m_n + m$. Let $\Psi_{m,\mathcal{I}}$ (with order m and knots $\mathcal{I}$) be the linear space spanned by the B-spline functions; that is,

$$\Psi_{m,\mathcal{I}} = \left\{ \sum_{i=1}^{q_n} \theta_i B_{i,m} : \theta_i \in \mathbb{R}, i = 1, \ldots, q_n \right\}.$$

It follows from Schumaker (1981) that there exists a smoothing spline $g_n(t) \in \Psi_{m,\mathcal{I}}$ such that $\|g_n(t) - g_0(t)\|_\infty = O(n^{-vm})$ and $\|g(t)\|_\infty \equiv \sup_{t\in\mathbb{I}} |g(t)|$. Hence, we define

$$\begin{aligned} \hat{g}_{n,\lambda} &\equiv \arg\max_{g\in\Psi_{m,\mathcal{I}}} l_{n,\lambda}(g) \\ &= \arg\max_{g\in\Psi_{m,\mathcal{I}}} \left\{ l_n(g) - \frac{\lambda}{2}J(g,g) \right\} \end{aligned}$$

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

as the estimator of $g_0(t)$. A numerical solution to the above objective function is available in O'Sullivan (1988) with a fast computation algorithm. Moreover, a data-driven method based on the AIC is suggested to select the smoothing parameter λ.

2.2 Reproducing Kernel Hilbert Space

We now present several useful properties of the reproducing kernel Hilbert space (RKHS); see Shang and Cheng (2013). Under conditions (C1) and (C3) in the Appendix, $\mathcal{H}^m$ is an RKHS with an inner product

$$< g, \tilde{g} >_\lambda = \int_{\mathbb{I}} g(t)\tilde{g}(t)\exp\{g_0(t)\}S(t)\,dt + \lambda J(g, \tilde{g}),$$

and norm $\|g\|_\lambda^2 =< g, g >_\lambda$. Furthermore, there exists a positive-definite self-adjoint operator $W_\lambda : \mathcal{H}^m \mapsto \mathcal{H}^m$ that satisfies $< W_\lambda g, \tilde{g} >_\lambda = \lambda J(g, \tilde{g})$ for any $g, \tilde{g} \in \mathcal{H}^m$. Denote $V(g, \tilde{g}) = \int_{\mathbb{I}} g(t)\tilde{g}(t)\exp\{g_0(t)\}S(t)\,dt$. Then, it follows directly that

$$< g, \tilde{g} >_\lambda = V(g, \tilde{g}) + < W_\lambda g, \tilde{g} >_\lambda .$$

Let $K(\cdot, \cdot)$ be the reproducing kernel of $\mathcal{H}^m$ defined on $\mathbb{I}\times\mathbb{I}$, which is known to possess the following properties:

(P_1) $K_t(\cdot) = K(t, \cdot)$ and $< K_t, g >_\lambda = g(t)$ for any g in $\mathcal{H}^m$ and any t in $\mathbb{I}$.

(P_2) There exists a constant c_m depending only on m, such that $\|K_t\|_\lambda \leq c_m h^{-1/2}$ for any $t \in \mathbb{I}$ and $h = \lambda^{1/(2m)}$. Hence, we have $\|g(t)\|_\infty \leq$

$c_m h^{-1/2}\|g\|_\lambda$ for any $g \in \mathcal{H}^m$.

We denote two positive sequences a_n and b_n as $a_n \asymp b_n$ if $\lim_{n\to\infty}(a_n/b_n) = c > 0$. There exists a sequence of eigenfunctions $h_j \in \mathcal{H}^m$ and eigenvalues γ_j satisfying the following properties:

(P_3) $\sup_{j\in\mathcal{N}} \|h_j\|_\infty < \infty$, $\gamma_j \asymp j^{2m}$, where $\mathcal{N} = \{0, 1, \ldots\}$.

(P_4) $V(h_i, h_j) = \delta_{ij}$, $J(h_i, h_j) = r_j\delta_{ij}$, where δ_{ij} is a Kronecker delta; that is, $\delta_{ij} = 1$ when $i = j$, and $\delta_{ij} = 0$ otherwise.

(P_5) For any $g \in \mathcal{H}^m$, we have $g = \sum_{j=0}^{\infty} V(g, h_j)h_j$, with convergence in the $\|\cdot\|_\lambda$-norm.

(P_6) For any $g \in \mathcal{H}^m$ and $t \in \mathbb{I}$, we have $\|g\|_\lambda^2 = \sum_{j=0}^{\infty} V(g, h_j)^2(1 + \lambda\gamma_j)$, $K_t(\cdot) = \sum_{j=0}^{\infty} h_j(t)h_j(\cdot)/(1 + \lambda\gamma_j)$, and $(W_\lambda h_j)(\cdot) = (\lambda\gamma_j)/(1 + \lambda\gamma_j)h_j(\cdot)$.

Following the arguments in Shang and Cheng (2013, page 2613), the eigenvalues and eigenfunctions can be solved using the following ordinary differential equations (ODEs):

$$\begin{aligned} &(-1)^m h_j^{(2m)}(\cdot) = \gamma_j \exp\{g_0(\cdot)\}S(\cdot)h_j(\cdot), \\ &\qquad h_j^{(k)}(0) = h_j^{(k)}(1) = 0, \qquad\qquad k = m, m+1, \cdots, 2m-1. \end{aligned} \tag{2.1}$$

For ease of presentation, we introduce additional notation related to Fréchet derivatives. Let $\mathcal{S}_n(g)$ and $\mathcal{S}_{n,\lambda}(g)$ be the Fréchet derivatives of

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

$l_n(g)$ and $l_{n,\lambda}(g)$, respectively. Similarly, let $\mathcal{S}(g)$ and $\mathcal{S}_\lambda(g)$ be the Fréchet derivatives of $l(g)$ and $l_\lambda(g)$, respectively. Let D be the Fréchet derivative operator and $g_1, g_2, g_3 \in \mathcal{H}^m$ be any direction. Then, we have

$$\begin{aligned} Dl_{n,\lambda}(g)g_1 &= -\int_{\mathbb{I}} \exp\{g(t)\}g_1(t)S_n(t)\,dt + \frac{1}{n}\sum_{i=1}^n \Delta_i g_1(Y_i) - < W_\lambda g, g_1 >_\lambda \\ &= < \mathcal{S}_n(g), g_1 >_\lambda - < W_\lambda g, g_1 >_\lambda \\ &= < \mathcal{S}_{n,\lambda}(g), g_1 >_\lambda, \end{aligned}$$

where $\mathcal{S}_n(g) = -\int_{\mathbb{I}} \exp\{g(t)\}K_t S_n(t)\,dt + n^{-1}\sum_{i=1}^n \Delta_i K_{Y_i}$ and $\mathcal{S}_{n,\lambda}(g) = \mathcal{S}_n(g) - W_\lambda g$. Moreover,

$$D^2 l_{n,\lambda}(g)g_1g_2 = -\int_{\mathbb{I}} \exp\{g(t)\}g_1(t)g_2(t)S_n(t)\,dt - < W_\lambda g_1, g_2 >_\lambda,$$

$$D^3 l_{n,\lambda}(g)g_1g_2g_3 = -\int_{\mathbb{I}} \exp\{g(t)\}g_1(t)g_2(t)g_3(t)S_n(t)\,dt.$$

Furthermore, a direct calculation yields

$$\mathcal{S}(g) = Dl(g) = -\int_{\mathbb{I}} \exp\{g(t)\}K_t S(t)\,dt + \int_{\mathbb{I}} \exp\{g_0(t)\}K_t S(t)\,dt = E\{\mathcal{S}_n(g)\},$$

as well as $\mathcal{S}_\lambda(g) = \mathcal{S}(g) - W_\lambda g$. In addition,

$$D\{\mathcal{S}(g)g_1\}g_2 = D^2 l(g)g_1g_2 = -\int_{\mathbb{I}} \exp\{g(t)\}g_1(t)g_2(t)S(t)\,dt.$$

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Hence, we obtain the following result:

$$
\begin{aligned}
< D\mathcal{S}_\lambda(g_0)f, g >_\lambda &= < D\{\mathcal{S}(g_0) - W_\lambda g_0\}f, g >_\lambda \\
&= < D\mathcal{S}(g_0)f, g >_\lambda - < W_\lambda f, g >_\lambda \\
&= < -\int_{\mathbb{I}} \exp\{g_0(t)\} f(t) K_t S(t)\, dt, g >_\lambda - < W_\lambda f, g >_\lambda \\
&= -\int_{\mathbb{I}} g(t) f(t) \exp\{g_0(t)\} S(t)\, dt - \lambda J(g, f) \\
&= - < f, g >_\lambda .
\end{aligned}
$$

Proposition 1. $D\mathcal{S}_\lambda(g_0) = -id$, *where id is the identity operator in* $\mathcal{H}^m$.

This proposition plays an important role in deriving an FBR of the proposed estimator.

3. The FBR

In this section, we derive and present our key technical tool, namely the FBR, which provides a theoretical foundation for the statistical inference procedures in later sections. With the help of the FBR, we establish the asymptotic normality of the proposed smoothing-spline estimate. The likelihood ratio test (LRT) procedure is also justified rigorously. To begin with, we present a lemma on the consistency of the proposed estimate for obtaining the FBR. All theoretical conditions and proofs are deferred to the Appendix.

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Lemma 1. *(Consistency). Suppose conditions* $(C1)-(C3)$ *given in the Appendix hold. If* $\lambda(n^{(1-v)/2}+n^{vm})\to 0$ *as* $n\to\infty$ *for* $0<v<1/2$*, then for sufficiently large* n*,*

$$\|\hat{g}_{n,\lambda}-g_0\|_\infty = o_p(1),$$
$$J(\hat{g}_{n,\lambda}-g_0,\hat{g}_{n,\lambda}-g_0) < \tilde{C},$$

where $\tilde{C}$ *is a constant greater than one.*

In fact, the consistency of the estimator with the infinity norm can be derived along the lines of Cox and O'Sullivan (1990). However, the second result in Lemma 1 is our own.

To obtain the rate of convergence of the proposed estimator, we next derive a concentration inequality for a certain empirical process. Define $\mathcal{G}=\{g\in\mathcal{H}^m:\|g\|_\infty\le 1, J(g,g)\le\tilde{C}\}$, with $\tilde{C}$ specified as in Lemma 1. We next define

$$\mathcal{Z}_n(g)\equiv\frac{1}{\sqrt{n}}\sum_{i=1}^{n}[\varphi_n(Y_i,g)-E\{\varphi_n(Y_i,g)\}],$$

where $\varphi_n(Y_i,g)$ is a real-valued function in $\mathcal{H}^m$.

Lemma 2. *Suppose that* $\varphi_n(Y,g)$ *satisfies the following condition:*

$$\|\varphi_n(Y,f)-\varphi_n(Y,g)\|_\lambda\le\|f-g\|_\infty,\qquad \textit{for any}\qquad f,g\in\mathcal{G}. \tag{3.1}$$

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Then,

$$\lim_{n\to\infty} P\left[\sup_{g\in\mathcal{G}} \frac{\|\mathcal{Z}_n(g)\|_\lambda}{\|g\|_\infty^{1-1/(2m)} + n^{-1/2}} \le \{5\log\log(n)\}^{1/2}\right] = 1.$$

By Lemmas 1 and 2, we obtain the convergence rate of our estimate, which is presented in the following theorem:

Theorem 1. *(Convergence Rate). Assume conditions* $(C1)-(C3)$ *hold. Then, when* $\log\{\log(n)\}/(nh^2) \to 0$ *and* $\lambda\{n^{(1-v)/2} + n^{vm}\} \to 0$ *as* $n \to \infty$*,*

$$\|\hat{g}_{n,\lambda} - g_0\|_\lambda = O_p\big((nh)^{-1/2} + h^m\big).$$

Remark 1. When $h \asymp n^{-1/(2m+1)}$, Theorem 1 suggests that $\hat{g}_{n,\lambda}$ achieves an optimal rate of convergence when we estimate $g_0 \in \mathcal{H}^m$, that is, $O_p(n^{-\frac{m}{2m+1}})$. This result is in accordance with that of Gu (1991).

Using Theorem 1, we are ready to present the key technical tool of this study, namely, a new version of the FBR of Shang and Cheng (2013). Define $M_i(t) \equiv N_i(t) - \int_0^t I(Y_i \ge s)\exp\{g_0(s)\}\,ds$, which is a martingale.

Theorem 2. *(FBR). Assume conditions* $(C1)-(C3)$ *hold. If* $\log\{\log(n)\}/(nh^2) \to 0$, $\lambda(n^{(1-v)/2} + n^{vm}) \to 0$ *as* $n \to \infty$*, we have*

$$\|\hat{g}_{n,\lambda} - g_0 - \mathcal{S}_{n,\lambda}(g_0)\|_\lambda = O_p(\alpha_n),$$

where

$$\mathcal{S}_{n,\lambda}(g_0) = \frac{1}{n}\sum_{i=1}^n \int_{\mathbb{I}} K_t\, dM_i(t) - W_\lambda g_0,$$

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

and

$$\alpha_n = n^{-1/2-vm} + n^{-vm}\{(nh)^{-1/2} + h^m\} + h^{-1/2}\{(nh)^{-1} + h^{2m}\}$$
$$+ h^{-(6m-1)/(4m)} n^{-1/2}\{\log\log(n)\}^{1/2}\{(nh)^{-1/2} + h^m\}.$$

In fact, Proposition 1 is crucial to deriving the FBR in Theorem 2; see the Appendix for the proof of the theorem. Moreover, Theorem 2 reveals that the "bias" of our estimate $\hat{g}_{n,\lambda}$ can be approximated by $\mathcal{S}_{n,\lambda}(g_0)$, the sum of a martingale integral. Applying this result, we immediately obtain the asymptotic normality.

Theorem 3. *Assume conditions* $(C1)-(C3)$ *hold. For* $m > 3/4 + \sqrt{5}/4$ *and* $1/(4m) \leq v \leq 1/(2m)$*, suppose* $nh^{4m-1} \to 0$ *and* $nh^3 \to \infty$ *as* $n \to \infty$*. Then, for any* $t_0 \in \mathbb{I}$*,*

$$\sqrt{nh}\{\hat{g}_{n,\lambda}(t_0) - g(t_0) + (W_\lambda g_0)(t_0)\} \xrightarrow{d} N(0, \sigma_{t_0}^2),$$

where $\sigma_{t_0}^2 \equiv \lim_{h\to 0} h \sum_{j=0}^{\infty} h_j^2(t_0)/(1+\lambda\gamma_j)^2$ *and* $\xrightarrow{d}$ *means convergence in distribution.*

Corollary 1. *Assume conditions* $(C1)-(C3)$ *hold. For* $m > 3/2$ *and* $1/(4m) \leq v \leq 1/(2m)$*, suppose* $nh^{2m} \to 0$ *and* $nh^3 \to \infty$ *as* $n \to \infty$*. Then, for any* $t_0 \in \mathbb{I}$*,*

$$\sqrt{nh}\{\hat{g}_{n,\lambda}(t_0) - g_0(t_0)\} \xrightarrow{d} N(0, \sigma_{t_0}^2),$$

where $\sigma_{t_0}^2$ *is defined as in Theorem 3.*

Remark 2. Corollary 1 implies that, under certain under-smoothing conditions, the asymptotic bias for the estimation of $g_0(t_0)$ vanishes. Hence, Corollary 1, together with the so-called Delta method, immediately gives the pointwise confidence interval (CI) for some real-valued smooth function of $g_0(t)$ at any fixed point $t_0 \in \mathbb{I}$, denoted by $\rho\big\{g_0(t_0)\big\}$. Let $\dot{\rho}(\cdot)$ be the first derivative of $\rho(\cdot)$. By Corollary 1, for any fixed point $t_0 \in \mathbb{I}$ and $\dot{\rho}\big\{g_0(t_0)\big\} \neq 0$, we have

$$P\left(\rho\big\{g_0(t_0)\big\} \in \left[\rho\big\{\hat{g}_{n,\lambda}(t_0)\big\} \pm \Phi_{\frac{\alpha}{2}} \frac{\dot{\rho}\big\{g_0(t_0)\big\}\sigma_{t_0}}{\sqrt{nh}}\right]\right) \to 1 - \alpha$$

as $n \to \infty$, where $\Phi(\cdot)$ is the standard normal cumulative distribution function and Φ_α is the lower α-th quantitile of $\Phi(\cdot)$; that is $\Phi(\Phi_\alpha) = 1 - \alpha$.

4. The LRT

With the help of the FBR, we consider further inferences of $g_0(\cdot)$ by testing local and global hypotheses. In this section, we use LRTs to test $g_0(\cdot)$.

4.1 Local LRT

We consider the following hypothesis for some pre-specified (t_0, ω_0):

$$H_0 : g(t_0) = \omega_0 \qquad \text{versus} \qquad H_1 : g(t_0) \neq \omega_0.$$

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

The penalized log-likelihood under H_0, or the "constrained" penalized log-likelihood of Shang and Cheng (2013), is defined as:

$$L_{n,\lambda}(g) = -\int_{\mathbb{I}} \exp\{g(t)+\omega_0\} S_n(t)\,dt + \frac{1}{n}\sum_{i=1}^{n}\Delta_i\{g(Y_i)+\omega_0\} - \frac{\lambda}{2}J(g,g),$$

where $g \in \mathcal{H}_0 = \{g \in \mathcal{H}^m : g(t_0) = 0\}$. We consider the following LRT statistic:

$$\mathrm{LRT}_{n,\lambda} = L_{n,\lambda}(\omega_0 + \hat{g}^0_{n,\lambda}) - L_{n,\lambda}(\hat{g}_{n,\lambda}),$$

where $\hat{g}^0_{n,\lambda} \equiv \arg\max_{g\in\Psi^0_{m,\mathcal{I}}} L_{n,\lambda}(g)$ is the MLE of g in

$$\Psi^0_{m,\mathcal{I}} = \{\sum_{i=1}^{q_n}\theta_i B_{i,m}, \sum_{i=1}^{q_n}\theta_i B_{i,m}(t_0) = 0\}.$$

Clearly, $\mathcal{H}_0$ is a closed subset in $\mathcal{H}^m$, and hence it is a Hilbert space endowed with the norm $\|\cdot\|_\lambda$.

The following proposition states the reproducing kernel and penalty operator of $\mathcal{H}_0$ inherited from $\mathcal{H}^m$ (without proofs).

Proposition 2. *The reproducing kernel and penalty operator of $\mathcal{H}_0$ inherited from $\mathcal{H}^m$ satisfy the following properties:*

(a) Recall that $K(t_1,t_2)$ is the reproducing kernel for $\mathcal{H}^m$ under $<\cdot,\cdot>_\lambda$. Then, the bivariate function

$$K^*(t_1,t_2) = K(t_1,t_2) - K(t_0,t_1)K(t_0,t_2)/K(t_0,t_0)$$

is a reproducing kernel for $(\mathcal{H}_0, <\cdot,\cdot>_\lambda)$*. That is, for any* $t \in \mathbb{I}$ *and* $g \in \mathcal{H}_0$*, we have* $K_t^* \equiv K^*(t,\cdot) \in \mathcal{H}_0$ *and* $<K_t^*, g>_\lambda = g(t)$*. Moreover, we have* $\|K^*\|_\lambda \leq \sqrt{2}c_m h^{-1/2}$*, where* c_m *is defined as in* P_2*.*

(b) The operator W_λ^**, defined as* $W_\lambda^* g \equiv W_\lambda g - W_\lambda g(t_0) K_{t_0}/K(t_0,t_0)$*, is bounded linear from* $\mathcal{H}_0$ *to* $\mathcal{H}_0$ *and satisfies* $<W_\lambda^* g, \tilde{g}> = \lambda J(g,\tilde{g})$*, for any* $g, \tilde{g} \in \mathcal{H}_0$*.*

Based on Proposition 2, we can now derive the FBR for $\hat{g}_{n,\lambda}^0$ under the null hypothesis, the so-called "restricted" FBR for $\hat{g}_{n,\lambda}^0$, which will be used to obtain the limiting distribution under the null. A direct calculation yields the Fréchet derivatives of $L_{n,\lambda}$ (along directions in $\mathcal{H}_0$). Consider $g_1, g_2, g_3 \in \mathcal{H}_0$. The first-order Fréchet derivative of $L_{n,\lambda}$, denoted by $\mathcal{S}_{n,\lambda}^0$,

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

can be calculated as follows:

$$
\begin{aligned}
&DL_{n,\lambda}(g)g_1 \\
&= -\int_0^1 \exp\{g(t)+\omega_0\}S_n(t)g_1(t)\,dt + \frac{1}{n}\sum_{i=1}^n \Delta_i g_1(Y_i) - < W_\lambda^* g, g_1 >_\lambda \\
&= -\int_0^1 \exp\{g(t)+\omega_0\}S_n(t) < K_t^*, g_1 >_\lambda \; dt + \frac{1}{n}\sum_{i=1}^n \Delta_i < K_{Y_i}^*, g_1 >_\lambda \\
&\qquad\qquad - < W_\lambda^* g, g_1 >_\lambda \\
&=< -\int_0^1 \exp\{g(t)+\omega_0\}S_n(t)K_t^*\,dt, g_1 >_\lambda + \frac{1}{n}\sum_{i=1}^n \Delta_i < K_{Y_i}^*, g_1 >_\lambda \\
&\qquad\qquad - < W_\lambda^* g, g_1 >_\lambda \\
&=< \mathcal{S}_n^0(g), g_1 >_\lambda - < W_\lambda^* g, g_1 >_\lambda \\
&=< \mathcal{S}_{n,\lambda}^0(g), g_1 >_\lambda,
\end{aligned}
$$

where $\mathcal{S}_n^0(g) = -\int_0^1 \exp\{g(t)+\omega_0\}S_n(t)K_t^*\,dt + n^{-1}\sum_{i=1}^n \Delta_i K_{Y_i}^*$ and $\mathcal{S}_{n,\lambda}^0(g) = \mathcal{S}_n^0(g) - W_\lambda^* g$. Define $\mathcal{S}^0(g) \equiv E\{\mathcal{S}_n^0(g)\}$ and $\mathcal{S}_\lambda^0(g) \equiv \mathcal{S}^0(g) - W_\lambda^* g$. Next, we denote the second- and third-order Fréchet derivatives of $L_{n,\lambda}(g)$ as $D^2 L_{n,\lambda}(g)g_1g_2$, and $D^3 L_{n,\lambda}(g)g_1g_2g_3$, respectively. Further calculations yield

$$
D^2 L_{n,\lambda}(g)g_1g_2 = -\int_0^1 \exp\{g(t)+\omega_0\}S_n(t)g_1(t)g_2(t)\,dt - < W_\lambda^* g_2, g_1 >_\lambda
$$

and

$$
D^3 L_{n,\lambda}(g)g_1g_2g_3 = -\int_0^1 \exp\{g(t)+\omega_0\}S_n(t)g_1(t)g_2(t)g_3(t)\,dt.
$$

We consider the derivative of $\mathcal{S}_\lambda^0(g)$, obtaining

$$D\mathcal{S}_\lambda^0(g)g_1g_2 = -\int_0^1 \exp\{g(t)+\omega_0\}S(t)g_1(t)g_2(t)\,dt - < W_\lambda^* g_2, g_1 >_\lambda .$$

Then, by defining $g_0^0(t) = g_0(t) - \omega_0$, we have the following important equation:

$$\begin{aligned} < D\mathcal{S}_\lambda^0(g_0^0)f, g >_\lambda &= < D\{\mathcal{S}^0(g_0^0)\}f, g >_\lambda - < W_\lambda^* f, g > \\ &= -\int_0^1 \exp\{g_0^0(t)+\omega_0\}S(t)f(t)g(t)\,dt - < W_\lambda^* f, g >_\lambda \\ &= - < f, g > . \end{aligned}$$

We state this result as the next proposition.

Proposition 3. $D\mathcal{S}_\lambda^0(g_0^0) = -id$, *where id is the identity operator.*

Similarly to Theorem 1 in Section 3, we need to prove the rate of convergence of the resulting estimator in order to obtain the FBR.

Proposition 4. *(Convergence Rate). Assume conditions* $(C1)-(C3)$ *hold. Under* H_0, *if* $\log\{\log(n)\}/(nh^2) \to 0$ *and* $\lambda(n^{(1-v)/2} + n^{vm}) \to 0$ *as* $n \to \infty$, *we have*

$$\|\hat{g}_{n,\lambda}^0 - g_0^0\|_\lambda = O_p\big((nh)^{-1/2} + h^m\big).$$

The proof of Proposition 4 is similar to that of Theorem 1 and, thus is omitted. The next theorem follows directly from Propositions $2-4$.

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Theorem 4. *(Restricted FBR). Assume conditions* $(C1)-(C3)$ *hold. In addition, we assume that under* H_0, $\log\{\log(n)\}/(nh^2) \to 0$ *and* $\lambda(n^{(1-v)/2}+n^{vm}) \to 0$ *as* $n \to \infty$*. Then,*

$$\|\hat{g}^0_{n,\lambda} - g^0_0 - \mathcal{S}^0_{n,\lambda}(g^0_0)\|_\lambda = O_p(\alpha_n),$$

where α_n *is defined as in Theorem 2.*

Our main result on the local LRT follows immediately from Theorem 4, and is presented below.

Theorem 5. *(Local LRT). Assume conditions* $(C1)-(C3)$ *hold. For* $m > (5+\sqrt{21})/4$ *and* $1/(4m) \leq v \leq 1/(2m)$*, suppose that* $nh^{2m} \to 0$ *and* $nh^4 \to \infty$ *as* $n \to \infty$*. Furthermore, for any* $t_0 \in \mathbb{I}$*, if* $\sigma_{t_0} \neq 0$*, let* $c_{t_0} = \lim_{h\to 0} V(K_{t_0}, K_{t_0})/\|K_{t_0}\|^2_\lambda \in (0,1]$*. Then, under* H_0*,*

(i) $\|\hat{g}_{n,\lambda} - \hat{g}^0_{n,\lambda} - \omega_0\|_\lambda = O_p(n^{-1/2})$;

(ii) $-2nLRT_{n,\lambda} = n\|\hat{g}_{n,\lambda} - \hat{g}^0_{n,\lambda} - \omega_0\|^2_\lambda + o_p(1)$;

(iii) $-2nLRT_{n,\lambda} \xrightarrow{d} c_{t_0}\chi^2_1$.

Remark 3. The central Chi-square limiting distribution in part (iii) of the theorem is established under the under-smoothing assumptions in Theorem 5. Relaxing those conditions for h yields a noncentral Chi-square limiting distribution. Note that the convergence rate stated in theorem 5 is reasonable under a local restriction.

4.2 Global LRT

It is important that we study the global behavior of a smooth function. In this section, we consider the following "global" hypothesis:

$$H_0^{global} : g = g_0 \qquad \text{versus} \qquad H_1 : g \neq g_0,$$

where $g_0 \in \mathcal{H}^m$ can be either known or unknown. The penalized likelihood ratio rest (PLRT) statistic is defined as

$$\mathrm{PLRT}_{n,\lambda} \equiv l_{n,\lambda}(g_0) - l_{n,\lambda}(\hat{g}_{n,\lambda}).$$

We next derive the null limiting distribution of $\mathrm{PLRT}_{n,\lambda}$.

Theorem 6. *Assume conditions $(C1) - (C3)$ hold. For $m > (3+\sqrt{5})/4$ and $1/(4m) \leq v \leq 1/(2m)$, suppose that $nh^{2m+1} = O(1)$ and $nh^3 \to \infty$ as $n \to \infty$. Define $\sigma_\lambda^2 \equiv \sum_{j=0}^{\infty} h/(1+\lambda\gamma_j)$, $\rho_\lambda^2 \equiv \sum_{j=0}^{\infty} h/(1+\lambda\gamma_j)^2$, $\gamma_\lambda \equiv \sigma_\lambda^2/\rho_\lambda^2$, and $\nu_\lambda \equiv h^{-1}\sigma_\lambda^4/\rho_\lambda^2$. Then, under H_0^{global},*

$$(2\nu_\lambda)^{-1/2}(-2n\gamma_\lambda PLRT_{n,\lambda} - n\gamma_\lambda \|(W_\lambda g_0)(t)\|_\lambda^2 - \nu_\lambda) \xrightarrow{d} N(0,1).$$

Note that this null limiting distribution remains unchanged even when g_0 in the null hypothesis is unknown. Moreover, it can be easily verified that $h \asymp n^{-d}$, with $1/(2m+1) \leq d < 1/3$, satisfies the conditions in Theorem 6. We can also show that $n\|W_\lambda g_0\|^2 = o(h^{-1}) = o(\nu_\lambda)$. Thus, $-2n\gamma_\lambda \mathrm{PLRT}_{n,\lambda}$ is asymptotical $N(\nu_\lambda, 2\nu_\lambda)$, which approaches $\chi^2_{\nu_\lambda}$ as n goes to infinity. In

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

other words, we have

$$-2n\gamma_\lambda \mathrm{PLRT}_{n,\lambda} \xrightarrow{d} \chi^2_{\nu_\lambda},$$

suggesting that the Wilks phenomenon holds for the PLRT.

Lastly, to conclude this section, we show that the PLRT achieves the optimal minimax rate of testing given by Ingster (1993), based on the uniform version of the FBR. To this end, we consider the alternative hypothesis $H_{1n} : g = g_{n_0}$, where $g_{n_0} = g_0 + g_n$, $g_0 \in \mathcal{H}^m$ and g_n belongs to the alternative value set $\mathcal{A} = \{g \in \mathcal{H}^m, \exp\{g_n(t)\} \leq \zeta, J(g,g) \leq \zeta\}$, for some constant $\zeta > 0$.

Theorem 7. *Assume that conditions $(C1)$–$(C3)$ hold. For $m > (3+\sqrt{5})/4$ and $1/(4m) \leq v \leq 1/(2m)$, suppose that $h \asymp n^{-d}$ for $1/(2m+1) \leq d < 1/3$ and uniformly over $g_n \in \mathcal{A}$, and that $\|\hat{g}_{n,\lambda} - g_{n_0}\|_\lambda = O_p\big((nh)^{-1/2} + h^m\big)$ holds under $H_{1n} : g = g_{n_0}$. Then, for any $\delta \in (0,1)$, there always exist positive constants b_0 and N, such that*

$$\inf_{n \geq N} \inf_{g_n \in \mathcal{A}, \|g_n\|_\lambda \geq b_0 \eta_n} P(\textit{reject} \quad H_0^{global} | H_{1n} \ \textit{is} \ \ \textit{true}) \geq 1 - \delta,$$

where $\eta_n \geq \sqrt{h^{2m} + (nh^{1/2})^{-1}}$. Moreover, the minimal lower bound of η_n is $n^{-2m/(4m+1)}$, which is achieved when $h = h^{**} = n^{-2/(4m+1)}$.

Importantly, when $h = h^{**} = n^{-2/(4m+1)}$, Theorem 7 suggests that the PLRT can detect any local alternatives with a separation rate no faster

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

than $n^{-2m/(4m+1)}$, which is exactly the minimax rate of hypothesis testing stated in Ingster (1993).

5. Simulation Studies

To evaluate the theoretical results, we present several simulation results. In the simulation studies, we set $v = 1/5$ and the number of knots to $[3 \times n^{1/5}]$ for the spline approximation, where $[x]$ is the largest positive integer part of x. Fore ease of presentation, additional notation is needed. We define

$$H \equiv \int_0^1 \exp\{g(t)\}B(s)B(s)^\top S_n(s)\,ds,$$
$$\Omega_{lk} \equiv \int_0^1 \ddot{B}_{k,m}(s)\ddot{B}_{l,m}(s)\,ds, \qquad k,l = 1,2,\ldots,q_n,$$

where $\Omega \equiv (\Omega_{lk})$ is a matrix with the (l,k)-element being Ω_{lk}, and $\ddot{B}_{l,m}(s)$ is the second derivative of $B_{l,m}(s)$. The following AIC proposed by O'Sullivan (1988) is used to select the smoothing parameter λ:

$$AIC(\lambda) = -l_n(\hat{g}_{n,\lambda}) + \frac{trace[(\hat{H} + \lambda\Omega)^{-1}\hat{H}]}{n}.$$

In linear algebra, the trace of an n-by-n square matrix A is defined to be the sum of the elements on the main diagonal (the diagonal from the upper left to the lower right) of A.

To examine the performance of the pointwise CI given in Section 3, we compare our results with the average length of the Bayesian CI proposed by Wahba (1983), denoted by LBCI. The Bayesian coverage probability is denoted by BCP. We refer to the average length of our proposed pointwise (local) CI and its coverage probability as LLCI and LCP, respectively.

To generate data, we suppose that the failure time follows a truncated Weibull distribution on $[1, \infty]$, with density function

$$f(t) \propto (t/\tau)^{k-1} \exp\{-(t/\tau)^k\}, \qquad t \in [1, \infty],$$

with $k = 1.5$ and $\tau = 1.2$. We generate the censoring time from a truncated Weibull distribution on $[1, 2]$ with $\tau = 3$; k is chosen to yield a 30% and a 40% censoring rate, respectively. For the estimate of g_0, we compared our estimator to the kernel-smoothed Nelson estimator (Müller and Wang, 1994), denoted as Smoothed NE. The results show that the spline estimate is more stable than the kernel method is, especially at the boundary region. Here, we set $m = 2$. Similarly to Shang and Cheng (2013), we obtain the eigenvalues and eigenfunctions using the ODE function in (2.1), and then substitute in the formula for the definition of σ_{t_0}. The simulation results are presented in Figures $1 - 2$. We observe that the average length of our proposed LLCI is shorter than that of Wahba (1983). The LCP is close to 95% for $t \in [1.2, 1.7]$ and $t \in [1.2, 1.6]$, with censoring rates of 30% and 40%, respectively. The BCP is almost one, owing to over-estimation in the variance.

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

To assess the performance of the global LRT given in Section 4, we compute the size and power of the test based on simulated data for different situations. For this purpose, we consider the null hypothesis $H_0^{global} : g = g_0$ against $H_1 : g \neq g_0$, where $g_0(t) = \log(k) + (k-1)\log(t) - k\log(\tau)$, with $k = 1.5$ and $\tau = 1.2$. Take $g_1(t) = \log(k) + (k-1)\log(t) - k\log(\tau) + c\{\log(t) - \log(\tau)\} + \log(1 + c/k)$, with $c = 0, 0.5, 1, 1.5$. To perform the test, we generate the failure time from a truncated Weibull distribution on $[1, \infty]$ with log-hazard g_1, and the censoring time from a Weibull distribution on $[1, 2]$ with $\lambda = 5$; k is chosen to yield a 30% and a 40% censoring rate, respectively. Again, by solving the ODE in (2.1), we obtain the eigenvalues of g_0 as $\gamma_j \approx (\alpha j)^{2m}$, with $\alpha = 1.8852$ or 1.8920 for the 30% censoring rate, with $n = 250$ or 500, respectively. For the 40% censoring rate, we obtain $\alpha = 1.9944$ or 2.0126, with $n = 250$ or 500, respectively. Substituting in the value of α and using Lemma 6.1 in Shang and Cheng (2013), we obtain $\gamma_\lambda = 1.333$, and $h\nu_\lambda = 0.7856$ or 0.7828 for the 30% censoring rate, with $n = 250$ or 500, respectively, and $h\nu_\lambda = 0.7426$ or 0.7359 for the 40% censoring rate, with $n = 250$ or 500, respectively. The results of the global LRTs are reported in Table 1. The estimated size is around 5% for $c = 0$, and the estimated power approaches one as the sample size or c increases, showing that the test has good power.

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

6. Application

To illustrate our method, we apply it to analyze the study of non-Hodgkin's lymphoma (Dave *et al.*, 2004). The goal of the experiment is to detect the effect of a follicular lymphoma on a patient's survival time. The data were obtained from seven institutions, covering the period 1974 to 2001. The samples are from 191 patients with untreated follicular lymphoma who were diagnosed between the ages of 23 and 81 years (median 51). The follow-up times range from 1.0 to 28.2 years (median 6.6). After removing four samples with missing censoring indicators and observation times, we have $n = 187$ samples and around a 50% censoring rate. As suggested by Iglewicz and Hoaglin (1973), we also calculate an outlier statistic: $Z_i = 0.6745|Y_i - \text{median}(Y)|/\text{mad}(Y)$, where i refers to the ith subject, and median(Y) and mad(Y) are the median and median absolute deviation, respectively, of the 187 observation times. According to Iglewicz and Hoaglin (1973), an observation is an outlier if $Z > 3.5$. In this analysis, we observe that the 170th subject is an outlier, and so we omit it from the sample. We standardize the survival times to range from 0 to 1. The results are summarized in Figure 3.

For comparison, we also compute the Kaplan$-$Meier estimate (KME), the smoothed Kaplan$-$Meier estimate (Smoothed KME), and our proposed estimate of the cumulative hazard function $\Lambda(t)$. The results are presented in the left panel of Figure 3. Our approach provides similar estimates to those of the other methods. The right panel in Figure 3 presents the estimation results for the log-hazard of our proposed method, the LCI, and the BCI. It can be seen that the pointwise interval of our proposal is shorter than that of Wahba (1983), which is accordance with the simulation results.

7. Conclusion

This study focuses on nonparametric inferences of the log-hazard function for right-censored data. The major advantage of doing so is that there is no constraint on the target function, which simplifies the computation. It is well known that the penalized nonparametric MLE is useful for balancing the smoothness and goodness-of-fit of the resulting estimator. Therefore, we adopt this approach to estimate the log-hazard function in the presence of right censoring. On the other hand, smoothing B-splines have been used in the literature for a smooth estimation; see, for example, Schumaker (1981). Our main contribution is an FBR established in the Sobolev space $\mathcal{H}^m$ with a proper inner product, which serves as a key tool for nonparametric inferences of an unknown parameter/function. The asymptotic properties of the resulting estimate of the unknown log-hazard function are justified rigorously. The local CI of the unknown log-hazard function is provided, as

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

well as the local and global LRTs. Note that the penalized global LRT is able to detect any local alternatives with a minimax separation rate, in the sense of Ingster (1993), which is closely related to the asymptotic efficiency. As suggested by one anonymous reviewer, we can extend our method to inferences of a survival function of the form $S_T(t) = \exp\{-\int_0^t \lambda(s)ds\}$. The inference procedures described in sections $3-4$ can be modified accordingly.

We do not consider the penalization on the coefficient of the B-spline function. Hence, we cannot provide a constant estimate, even when the true function takes a constant value. The proposed inference approach can also be extended to handle other complicated data, for example, interval-censored data. Although this extension seems to be conceptually straightforward, much more effort is needed to establish the theoretical properties of the estimators. In particular, it is a nontrivial task to develop an appropriate inner product for the Sobolev space. This problem is under investigation and is beyond the scope of this study.

Supplementary Material

The Supplementary Material includes all technical proofs.

Acknowledgments

The authors are indebted to the Editor, the Associate Editor, and two anonymous reviewers for their professional review and insightful comments that lead to substantial improvements in the paper. Yuanyuan Lin's research is supported in part by the Hong Kong Research Grants Council (Grants No. 509413 and 14311916) and Direct Grants for Research, The Chinese University of Hong Kong. Xingqiu Zhao's research is supported in part by the National Natural Science Foundation of China (No. 11771366) and the Hong Kong Polytechnic University. Meiling Hao's research is supported by the Fundamental Research Funds for the Central Universities in UIBE (No. CXTD10-10).

References

ANDERSEN, P. K. AND GILL, R. D. (1982). Cox's regression model for counting processes: a large sample study. *Ann. Statist.* **10**, 1100-1120.

ANDERSON, J. AND SENTHILSELVAN, A. (1980). Smooth estimates for the hazard function. *J. R. Statist. Soc. B* **42**, 322-327.

BERAN, R. (1981). Nonparametric regression with randomly censored survival data. *Technical Report.* Univ. California, Berkeley.

BRESLOW, N. AND CROWLEY, J. (1974). A large sample study of the life table and product limit estimates under random censorship. *Ann. Statist.* **2**, 437-453.

BRESLOW, N. E. AND DAY, N. E. (1987).*Statistical Models in Cancer Research 2: The Design* *and Analysis of Cohort Studies*. International Agency for Research on Cancer, Lyon.

Buckley, J. and James, I. (1979). Linear regression with censored data. *Biometrika* **66**, 429-436.

Chen, K. (2004). Statistical estimation in the proportional hazards model with risk set sampling. *Ann. Statist.* **32**, 1513-1532.

Chen, K., Guo, S., Sun, L. and Wang, J. L. (2010). Global partial likelihood for nonparametric proportional hazards models. *J. Amer. Statist. Assoc.* **105**, 750-760.

Chen, K., Jin, Z. and Ying, Z. (2002). Semiparametric analysis of transformation models with censored data. *Biometrika* **89**, 659-668.

Chen, K. and Lo, S. H. (1997). On the rate of uniform convergence of the product-limit estimator: strong and weak laws. *Ann. Statist.* **25**, 1050-1087.

Cox, D. D. and OSullivan, F. (1990). Asymptotic analysis of penalized likelihood and related estimators. *Ann. Statist.* **18**, 1676-1695.

Cox, D. R. (1972). Regression models and life-tables (with discussion). *J. R. Statist. Soc. B* **34**, 187-220.

Cox, D. R. (1975). Partial likelihood. *Biometrika* **62**, 269-276.

Cox, D. R. (2018). *Analysis of survival data*. Routledge.

Cox, D. R. and Oakes, D. (1984). *Analysis of Survival Data.* London: Chapman and Hall.

Dave, S. S., Wright, G., Tan, B., Rosenwald, A., Gascoyne, R. D., Chan, W. C., Fish-

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

er, R. I., Braziel, R. M., Rimsza, L. M., Grogan, T. M., Miller, T. P., Leblanc, M., Greiner, T. C., Weisenburger, D. D., Lynch, J. C., Vose, J., Armitage, J. O., Smeland, E. B., Kvaloy, S., Holte, H., Delabie, J., Connors, J. M., Lansdorp, P. M., Ouyang, Q., Lister, T. A., Davies, A. J., Norton, A. J., MÜller-Hermelink, H. K., Ott, G., Campo, E., Montserrat, E., Wilson, W. H., Jaffe, E. S., Simon, R., Yang, L., Powell, J., Zhao, H., Goldschmidt, N., Chiorazzi, M. and Staudt, L. M. (2004). Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N. Engl. J. Med.* **351**, 2159-2169.

Dabrowska, D. M. (1987). Non-parametric Regression with Censored Survival Time Data. *Scand. J. Statist.* **14**, 181-197.

Efron, B. (1967). The two sample problem with censored data. *Proc. Fifth Berkeley Symp. on Math. Statist. and Prob.* **4**, 831-853.

Fleming, T. R. and Harrington, D. P. (2011). *Counting processes and survival analysis.* John Wiley and Sons.

Gray, R. J. (1992). Flexible methods for analyzing survival data using splines, with applications to breast cancer prognosis. *J. Amer. Statist. Assoc.* **87**, 942-951.

Gu,C. (1991). Penalized Likelihood Hazard Estimation. *Technical Report.* Purdue Univeristy.

Hao, M., Song, X. and Sun, L. (2014). Reweighting estimators for the additive hazards model with missing covariates. *Can. J. Statist.* **42**(2), 285-307.

Hoeffding, W. (1963). Probability inequalities for sums of bounded random variables. *J.*

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Amer. Statist. Assoc. **58**, 13-30.

INGSTER, Y. I. (1993). Asymptotically minimax hypothesis testing for nonparametric alternatives $I-III$. *Math. Methods Statist.* **2**, 85-114; **3**, 171-189; **4**, 249-268.

IGLEWICZ, B. AND HOAGLIN, D. C. (1993). *How to Detect and Handle Outliers.* Asq Press.

JIANG, J. AND ZHOU, H. (2007). Additive hazard regression with auxiliary covariates. *Biometrika* **94** (2), 359-369.

JONG, D. P. (1987). A central limit theorem for generalized quadratic forms. *Probab. Theory Related Fields* **75**(2), 261-277.

JOHNSON, N. L. AND KOTZ, S. (1970). *Distributions in Statistics: Continuous Univariate Distributions.* Boston: Houghton Mifflin.

KALBFLEISCH, J. D. AND PRENTICE, R. L. (2011). *The statistical analysis of failure time data.* John Wiley and Sons.

KAPLAN, E. L. AND MEIER, P. (1958). Nonparametric estimation from incomplete observations. *J. Amer. Statist. Assoc.* **53**, 457-481.

KOOPERBERG, C., STONE, C. J. AND TRUONG, Y. K. (1995). Hazard regression. *J. Amer. Statist. Assoc.* **90**, 78-94.

KOSOROK, M. R. (2008). *Introduction to empirical processes and semiparametric inference.* Springer Science and Business Media.

LAI, T. L. AND YING, Z. (1991a). Large sample theory of a modified Buckley-James estimator for regression analysis with censored data. *Ann. Statist.* **19**, 1370-1402.

Lai, T. L. and Ying, Z. (1991b). Rank regression methods for left-truncated and right-censored data. *Ann. Statist.* **19**, 531-556.

Lawless, J. F. (1982). *Statistical Models and Methods for Lifetime Data.* New York: Wiley.

Lin, D. Y. and Ying, Z. (1994). Semiparametric analysis of the additive risk model. *Biometrika* **81**, 61-71.

Lin, D. Y. and Wei, L. J.(1989). The robust inference for the Cox proportional hazards model. *J. Amer. Statist. Assoc.* **84** , 1074-1078.

Lin, D. Y., Wei, L. J. and Ying, Z. (1993). Checking the Cox model with cumulative sums of martingale-biased residuals. *Biometrika* **85**, 605-619.

Lin, Y. and Chen, K. (2013). Efficient estimation of the censored linear regression model. *Biometrika* **100**, 525-530.

Lo, S. H., Mack, Y. P., and Wang, J. L. (1989). Density and hazard rate estimation for censored data via strong representation of the Kaplan−Meier estimator. *Prob. Theory and Related Fields* **30**(3), 461-473.

Lo, S. H. and Singh, K. (1986). The product-limit estimator and the bootstrap: some asymptotic representations. *Prob. Theory and Related Fields* **71**, 455-465.

Mann, N. R., Schafer, R. E. and Singpurwalla, N. D. (1974). *Methods for statistical Analysis of Reliability and Lifetime Data.* New York: Wiley.

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Müller, H. G., and Wang, J. L.(1994). Hazard rate estimation under random censoring with varying kernels and bandwidths. *Biometrics* **50**, 61-76.

Prentice, R. L. (1978). Linear rank tests with right censored data. *Biometrika* **65**, 167-179.

Ritov, Y. (1990). Estimation in a linear regression model with censored data. *Ann. Statist.* **18**, 303-328.

Rosenberg, P. S. (1995). Hazard function estimation using B-splines. *Biometrics* **51**, 874-887.

O'Sullivan, F. (1988). Fast computation of fully automated log-density and log- hazard estimators. *SIAM J. Sci. Statist. Comp.* **9**, 363- 379.

O'Sullivan, F., Yandell, B. S. and Raynor, W. J. (1986). Automatic Smoothing of Regression Functions in Generalized Linear Models. *J. Amer. Statist. Assoc.* **81**, 96-103.

Shang, Z. and Cheng, G. (2013). Local and global asymptotic inference in smoothing spline models. *Ann. Statist.* **41**(5), 2608-2638.

Tanner, M. A. and Wong, W. H. (1983). The estimation of the hazard function from randomly censored data by the kernel method. *Ann. Statist.* **11**, 989-993.

Tsiatis, A. A. (1990). Estimating regression parameters using linear rank tests for censored data. *Ann. Statist.* **18**, 354-372.

Van Der Vaart, A. W. and Wellner, J. A. (1996). *Weak Convergence.* Springer New York.

Wahba, G. (1983). Bayesian confidence intervals for the cross-validated smoothing spline, *J. R. Statist. Soc. B* **45**,133-150.

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Wang, H., Li, R. and Tsai, C. L. (2007). Tuning parameter selectors for the smoothly clipped absolute deviation method. *Biometrika* **94**, 553-568.

Wei, L. J. (1992). The accelerated failure time model: a useful alternative to the Cox regression model in survival analysis. *Statist. Med.* **11**, 1871-1879.

Wei, L., Ying, Z. and Lin, D. (1990). Linear regression analysis of censored survival data based on rank tests. *Biometrika* **77**, 845-851.

Zeng, D., Chen, Q. and Ibrahim, J. G. (2009). Gamma frailty transformation models for multivariate survival times. *Biometrika* **96**, 277-291.

Zeng, D. and Lin, D. Y. (2007a). Efficient estimation for the accelerated failure time model. *J. Am. Statist. Assoc.* **102**, 1387-96.

Zeng, D. and Lin, D. Y. (2007b). Maximum likelihood estimation in semiparametric regression models with censored data. *J. R. Statist. Soc. B.* **69**, 507-564.

Meiling Hao, School of Statistics, University of International Business and Economics, Beijing, China

E-mail: meilinghao@uibe.edu.cn

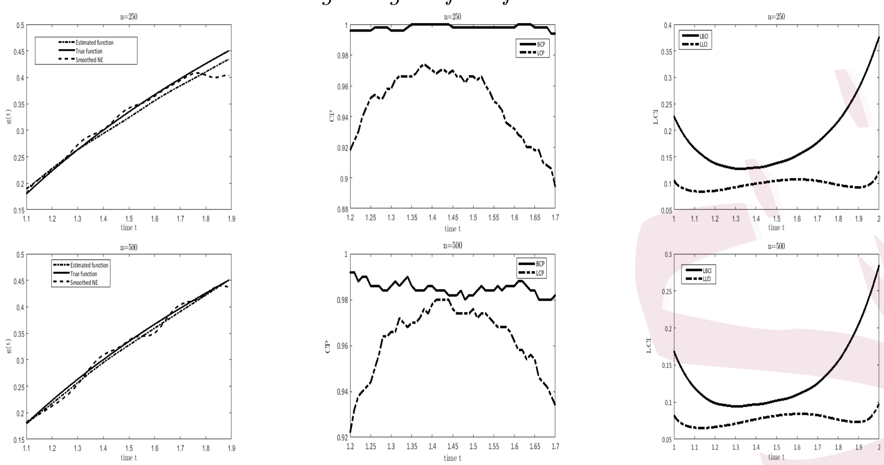
Yuanyuan Lin, Department of Statistics, The Chinese University of Hong Kong, Hong Kong

E-mail: ylin@sta.cuhk.edu.hk

Xingqiu Zhao, Department of Applied Mathematics, The Hong Kong Polytechnic University, Hong Kong

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Figure 1. *Simulation results with a 30% censoring rate. CP: coverage probablity; LCI: average length of confidence interval.*



E-mail: xingqiu.zhao@polyu.edu.hk

Table 1. *The estimated size and power of the PLRT.*

Censoring rate	n	$c = 0$	$c = 0.5$	$c = 1$	$c = 1.5$
30%	250	0.056	0.984	1.000	1.000
	500	0.048	1.000	1.000	1.000
40%	250	0.068	0.962	1.000	1.000
	500	0.052	0.998	1.000	1.000

Statistica Sinica: Preprint
doi:10.5705/ss.202017.0357

Figure 2. *Simulation results with a 40% censoring rate. CP: coverage probablity; LCI: average length of confidence interval.*

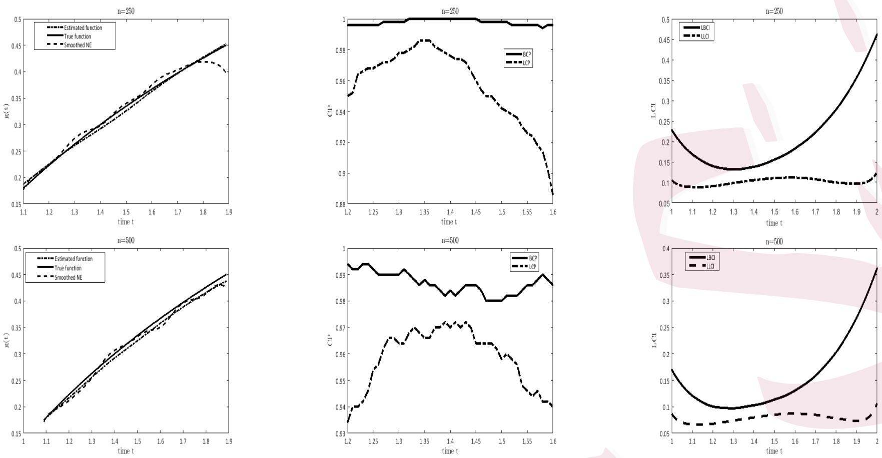


Figure 3. *Analysis results of the real data. The left panel displays the cumulative hazard estimation and the right panel presents the log-hazard estimation and its CI using different methods.*