A presmoothing approach for estimation in semiparametric mixture cure models

Eni Musta¹, Valentin Patilea² and Ingrid Van Keilegom¹

¹ORSTAT, KU Leuven, Belgium, e-mail: *e.musta@uva.nl; **ingrid.vankeilegom@kuleuven.be
²CREST, Ensai, France, e-mail: valentin.patilea@ensai.fr

Abstract: A challenge when dealing with survival analysis data is accounting for a cure fraction, meaning that some subjects will never experience the event of interest. Mixture cure models have been frequently used to estimate both the probability of being cured and the time to event for the susceptible subjects, by usually assuming a parametric (logistic) form of the incidence. We propose a new estimation procedure for a parametric cure rate that relies on a preliminary smooth estimator and is independent of the model assumed for the latency. We investigate the theoretical properties of the estimators and show through simulations that, in the logistic/Cox model, presmoothing leads to more accurate results compared to the maximum likelihood estimator. To illustrate the practical use, we apply the new estimation procedure to two studies of melanoma survival data.

Keywords and phrases: cure models, kernel smoothing, logistic model, survival analysis.

1. Introduction

There are many situations in survival analysis problems where some of the subjects will never experience the event of interest. For instance, as significant progress is being made for treatment of different types of cancers, many of the patients get cured of the disease and do not experience recurrence or cancer-related death. Other examples include study of time to natural conception, time to default in finance and risk management, time to early failure of integrated circuits in engineering, time to find a job after a layoff. However, because of the finite duration of the studies and censoring, the cured subjects (for which the event never takes place) cannot be distinguished from the ‘susceptible’ ones. We can just get an indication of the presence of a cure fraction from the context of the study and a long plateau (containing many censored observations) with height greater than zero in the Kaplan-Meier estimator of the survival function. Predicting the probability of being cured given a set of characteristics is often of particular interest in order to make better decisions in terms of treatment, management strategies or public policies. This lead to the development of mixture cure models.

Mixture cure models were first proposed by [5] and [4]. They assume that the population is a mixture of two groups: the cured and the susceptible subjects.
Within this very wide class of models, various approaches have been considered in the literature for modelling and estimating the incidence (probability of being uncured) and the latency (survival function of the uncured subjects). Initially, fully parametric models with a logistic regression form of the incidence and various parametric distributions for the latency were used in [11, 31, 15]. Later on, more flexible semi-parametric approaches were proposed for the latency based on the Cox proportional hazards model [24, 21] or accelerated failure time models [17, 32]. However, they still maintain the logistic regression model for the incidence. More recently, nonparametric methods have been developed for both or one of the model components in [30, 20, 2]. In this wide range of models, probably the most commonly used one in practice is the logistic/Cox mixture cure model [23, 29, 16].

There have been different proposals for estimation in the logistic/Cox mixture cure model. The presence of a latent variable (the unknown cure status), does not allow for a ‘direct’ approach as in the classical Cox proportional hazards model. [15] adapted a marginal likelihood approach computed through Monte Carlo approximations, whereas [21] and [24] computed the maximum likelihood estimator via the Expectation-Maximization algorithm. Asymptotic properties of the latter estimators are investigated in [18], while the procedure is implemented in the package smcure [7]. One concern about the previous estimators is that they are obtained by iterative procedures which could be unstable in practice. In particular, when the sample size is small there are situations in which the EM algorithm fails to converge (even though the smcure package can still provide without error the estimates obtained when the maximum number of iterations is reached). Such problems are for example reported in [14]. In addition, the maximum likelihood estimator for the incidence component depends on which variables are included in the latency model (see for example the illustration in Section 7) and this instability might in practice lead to unobserved effects (when the effect is not very strong). In particular, if the latency model is misspecified, even the estimators of the incidence parameters suffer from induced bias (see for example [6]).

In this paper, we introduce an alternative estimation method which applies very broadly and, in particular, for the logistic/Cox mixture cure model. Our approach focuses on direct estimation of the cure probability without using distributional assumptions on the latency and iterative algorithms. It relies on a preliminary nonparametric estimator for the incidence which is then ‘projected’ on a parametric class of functions (like logistic functions). The idea of constructing a parametric estimator by nonparametric estimation has been previously proposed for the classical linear regression by [9]. Later on it was shown to be effective also in the context of variable selection and functional linear regression [1, 12]. However, its extension to nonlinear setups has been very little investigated. Here we show that in the context of mixture cure models, even when a parametric form is assumed for the incidence, the use of a presmoothed estimator as an intermediate step for obtaining the parameter estimates often leads to more accurate results. Once the cure fraction is estimated, we estimate the survival distribution of the uncured subjects. In the case of the logistic/Cox
cure model, this is done by maximizing the Cox component of the likelihood. In this step, an iterative algorithm is used to compute the estimators of the baseline cumulative hazard and the regression parameters. This new approach is of practical relevance given the popularity of the semiparametric logistic/Cox mixture cure model. However, the method can be applied more in general to a mixture cure model with a parametric form of the incidence and other type of models for the uncured subjects, such as the semiparametric proportional odds model or the semiparametric AFT model. Our findings suggest that presmoothing has potential to improve parameter estimation for small and moderate sample size.

The paper is organized as follows. In Sections 2 and 3 we describe the model and the estimation procedure. Section 4 focuses on the estimation method in the case of the logistic/Cox mixture cure model. Consistency and asymptotic normality of the estimators are shown in Section 5. Thanks to the presmoothing, we are able to present theoretical results under more reasonable assumptions and thus we contribute to fill a gap between unrealistic technical conditions and applications. The finite sample performance of the method is investigated through a simulation study and results are reported in Section 6. For practical purposes, we propose to make simple and commonly used choices for the bandwidth and the kernel function in the presmoothing step, and we show that these choices provide satisfactory results. The proposed estimation procedure is applied to two medical datasets about studies of patients with melanoma cancer (see Section 7). We conclude in Section 8 with some discussion and ideas for further research. Finally, some of the proofs can be found in Section 9, while the remaining proofs and additional simulation results are collected in the online Supplementary Material.

2. Model description

In the mixture cure model the survival time $T$ can be decomposed as

$$T = BT_0 + (1 - B)\infty,$$

where $T_0$ represents the finite survival time for an uncured individual and $B$ is an unobserved 0-1 random variable giving the uncured status: $B = 1$ for uncured individuals and $B = 0$ otherwise. By convention $0 \cdot \infty = 0$. Let $C$ be the censoring time and $(X', Z')'$ a $(p+q)$-dimensional vector of covariates, where $x'$ denotes the transpose of the vector $x$. Let $X$ and $Z$ be the supports of $X$ and $Z$ respectively. Observations consist of $n$ i.i.d. realizations of $(Y, \Delta, X, Z)$, where $Y = \min(T, C)$ is the finite follow-up time and $\Delta = 1_{\{T \leq C\}}$ is the censoring indicator. Since $Y$ is finite, then necessarily $\Pr(C < \infty) = 1$, that means the censoring times are finite (which makes sense given the limited duration of the studies). As a result, censored survival times of the uncured subjects cannot be distinguished from the cured ones.

The covariates included in $X$ are those used to model the cure rate, while the ones in $Z$ affect the survival conditional on the uncured status. This allows in general to use different variables for modelling the incidence and the latency.
but does not exclude situations in which the two vectors $X$ and $Z$ share some components or are exactly the same. Apart from the standard assumption in survival analysis that $T_0 \perp (C, X)|Z$, here we also need

$$B \perp (C, T_0, Z)|X.$$  

This implies in particular that

$$T \perp C|(X, Z)$$

(see Lemma 1 in the Suplementary Material). Moreover, (1) implies

$$P(T = \infty | X, Z) = P(T = \infty | X).$$

In addition, in the cure model context we need that the event time $T_0$ has support $[0, \tau_0]$, i.e. $\{T > \tau_0\} = \{T = \infty\}$, such that

$$\inf_x P(C > \tau_0 | X = x) > 0.$$  

(If the support of $T_0$ given $Z = z$ depends on $z$, then we let $\tau_0 = \sup \tau_0(z)$, where $\tau_0(z)$ is the right endpoint of this support.) This condition tells us that all the observations with $Y > \tau_0$ are cured. Even if it might seem restrictive, it is reasonable when a cure model is justified by a ‘good’ follow-up beyond the time when most of the events occur and it is commonly accepted in the cure model literature in order for the mixture cure model to be identifiable and not to overestimate the cure rate. Since $T_0 \perp X|Z$, we have

$$P(T_0 \leq t | X, Z) = P(T_0 \leq t | Z), \quad \forall t \in [0, \tau_0].$$

We assume a parametric model for the cure rate and we denote by $\pi_0(x)$ the cure probability of a subject with covariate $x$, i.e

$$\pi_0(x) = P(T = \infty | X = x) = 1 - \phi(\gamma_0, x),$$

for some parametric model $\{\phi(\gamma, x) : \gamma \in G\}$ and $\gamma_0 \in G$. The first component of $X$ is equal to one and the first component of $\gamma$ corresponds to the intercept. In order for $\gamma$ to be identifiable we need the following condition

$$P(\phi(\gamma, X) = \phi(\tilde{\gamma}, X)) = 1 \quad \text{implies that} \quad \gamma = \tilde{\gamma}. \quad (5)$$

Choosing a parametric model for the incidence seems quite standard in the literature of mixture cure models ([20, 6, 22]) because of its simplicity and ease of interpretability (particularly for multiple covariates). To check the fit of this model in practice, one can compare the prediction error with that of a more flexible single-index model as done in [2] and for our real data application in Section 7. It is also possible to test whether this assumption is reasonable using the test proposed in [19], but this is currently developed only for one covariate.
Among the parametric models for the incidence component, the most common example is the logistic model, where
\[ \phi(\gamma, x) = 1/(1 + \exp(-\gamma x)). \] (6)

We state the results in Section 5 for a general parametric model for the incidence, but then we focus on the logistic function in the simulation study in Section 6 since it is more of interest in practice. For the uncured subjects, we can consider a general semiparametric model defined through the survival function
\[ S_u(t|z) = S_u(t|z; \beta, \Lambda) = P(T_0 > t|Z = z, B = 1) \quad \text{and} \quad S_u(\tau_0|z) = 0, \] (7)

where the conditional survival function \( S_u \) is allowed to depend on a finite-dimensional parameter, denoted by \( \beta \in B \), and/or an infinite-dimensional parameter, denoted by \( \Lambda \in H \), with \( B \) and \( H \) the respective parameter sets. Let \( \beta_0 \in B \) and \( \Lambda_0 \in H \) be the true values of these parameters. As a result, the conditional survival function corresponding to \( T \) is then
\[ S(t|x, z) = P(T > t|X = x, Z = z) = 1 - \phi(\gamma_0, x) + \phi(\gamma_0, x)S_u(t|z). \]

The main example we keep in mind is the Cox proportional hazards (PH) model where \( \Lambda_0 \) is the baseline cumulative hazard. In this case
\[ S_u(t|z) = S_0(t)^{\exp(\beta_0 z)} = \exp(-\Lambda_0(t)\exp(\beta_0'z)), \] (8)

where \( S_0 \) is the baseline survival and \( \beta_0 \) does not contain an intercept.

3. Presmoothing estimation approach

The estimation method we propose is based on a two step procedure. We first estimate nonparametrically the cure probability for each observation and then compute an estimator of \( \gamma \) as the maximizer of the logistic likelihood, ignoring the model for the uncured subjects. In the second step, we plug-in this estimator of \( \gamma \) in the full likelihood of the mixture cure model and fit the latency model using maximum likelihood estimation. In what follows, we describe in more details these two steps.

**Step 1.** Even though a parametric model is assumed for the incidence, we start by computing a nonparametric estimator of the cure probability for each observation. One possibility is to use the method followed by [20] (see also [30]), but other estimators are possible as well, as long as the conditions given in Section 5 are satisfied. The estimator of [20] is defined as follows:
\[ \hat{\pi}(x) = \prod_{t \in \mathbb{R}} \left( 1 - \frac{\hat{H}_1(dt|x)}{\hat{H}(t, \infty)|x} \right), \] (9)

where \( \hat{H}(t, \infty)|x = \hat{H}_1([t, \infty)|x) + \hat{H}_0([t, \infty)|x), \hat{H}_1(dt|x) = \hat{H}_1((t - dt, t]|x) \) for small \( dt \) and

\[ \hat{H}_k([t, \infty)|x) = \sum_{i=1}^{n} \frac{K_b(X_i - x)}{\sum_{j=1}^{n} K_b(X_j - x)} 1_{\{Y_i \geq t, \Delta_i = k\}}, \quad k = 0, 1, \]
are estimators of
\[ H_k([t,\infty)|x] = \mathbb{P}(Y \geq t, \Delta = k|X = x), \]
\[ H([t,\infty)|x] = H_1([t,\infty)|x) + H_0([t,\infty)|x). \]
Here \( \tilde{K}_b \) is a multidimensional kernel function defined in the following way. If \( X \) is composed of continuous and discrete components, \( X = (X_c, X_d) \in \mathcal{X}_c \times \mathcal{X}_d \subset \mathbb{R}^{p_c} \times \mathbb{R}^{p_d} \) with \( p_c + p_d = p \), then
\[ \tilde{K}_b(X_c - x_c) = k_b(x_c) \mathbb{I}_{\{x_c = x_c\}}, \]
where \( b = b_n \) is a bandwidth sequence, \( K_b(\cdot) = K(\cdot/b)/b^{p_c} \) and \( K(u) = \prod_{j=1}^{p_c} k(u_j) \), with \( k \) a kernel. Note that, one can compute this estimator with any covariate but here we only use \( X \) because of our assumption (3). The estimator \( \hat{\pi}(x) \) coincides with the Beran estimator of the conditional survival function \( S \) at the largest observed event time \( Y_{(n)} \) and does not require any specification of \( \tau_0 \). Since \( \hat{H}_1(dt|x) \) is different from zero only at the observed event times, computation of \( \hat{\pi}(x) \) requires only a product over \( t \) in the set of the observed event times. Afterwards, we consider the logistic likelihood
\[ \hat{L}_{n,1}(\gamma) = \prod_{i=1}^{n} \phi(\gamma, X_i)^{1-\hat{\pi}(X_i)}(1 - \phi(\gamma, X_i))^{\hat{\pi}(X_i)}, \]
and define \( \hat{\gamma}_n \) as the maximizer of
\[ \log \hat{L}_{n,1}(\gamma) = \sum_{i=1}^{n} \left\{ [1 - \hat{\pi}(X_i)] \log \phi(\gamma, X_i) + \hat{\pi}(X_i) \log [1 - \phi(\gamma, X_i)] \right\}. \]
Existence and uniqueness of \( \hat{\gamma}_n \) holds under the same conditions as for the maximum likelihood estimator in the binary outcome regression model where \( 1 - \hat{\pi}(X_i) \) is replaced by the outcome \( B_i \). For example, in the logistic model, it is required that \( p < n \) and the matrix of the variables \( X \) has full rank.

Step 2. Now we consider the likelihood of the mixture cure model. Let
\[ f_u(t|z; \beta, \Lambda) = -\left(\frac{\partial}{\partial t}\right)S_u(t|z; \beta, \Lambda) \]
with \( S_u(t|z; \beta, \Lambda) \) as defined in (7), denote an element in the model for the conditional density of \( T_0 \) given \( Z = z \), which is supposed to exist and belong to the model. Assuming non informative censoring and that the distribution of the covariates does not carry information on the parameters \( \beta, \Lambda \), the likelihood criterion is then
\[ L_{n,2}(\beta, \Lambda, \gamma) = \prod_{i=1}^{n} \{ \phi(\gamma, X_i)f_u(Y_i|Z_i; \beta, \Lambda) \}^{\Delta_i} \{ 1 - \phi(\gamma, X_i) + \phi(\gamma, X_i)S_u(Y_i|Z_i; \beta, \Lambda) \}^{1-\Delta_i}, \]
and we maximize it w.r.t. \( \beta \) and \( \Lambda \) for \( \gamma = \hat{\gamma}_n \), i.e. \( (\hat{\beta}_n, \hat{\Lambda}_n) \) are the maximizers of
\[ \hat{l}_n(\beta, \Lambda, \hat{\gamma}_n) = \frac{1}{n} \sum_{i=1}^{n} l(Y_i, \Delta_i, X_i, Z_i; \beta, \Lambda, \hat{\gamma}_n), \]
over a set of possible values for $\beta$ and $\Lambda$, where
\[
\ell(Y_i, \Delta_i, X_i, Z_i; \beta, \Lambda, \gamma) = \Delta_i \log f_u(Y_i | Z_i; \beta, \Lambda) \\
+ (1 - \Delta_i) \log \left\{ 1 - \phi(\gamma, X_i) + \phi(\gamma, X_i) S_u(Y_i | Z_i; \beta, \Lambda) \right\}.
\] (13)

4. Presmoothing estimation for the parametric/Cox mixture cure model

In the sequel we focus on the case of a Cox PH model defined in (8) for the conditional law of $T_0$. The criterion defined in (12) becomes
\[
\hat{l}_n(\beta, \Lambda, \hat{\gamma}_n) = \frac{1}{n} \sum_{i=1}^n \left\{ 1 \cdot \log \Delta \Lambda(Y_i) + \beta' Z_i \right\} \\
+ \frac{1}{n} \sum_{i=1}^n (1 - \Delta_i) \log \left\{ 1 - \phi(\hat{\gamma}_n, X_i) + \phi(\hat{\gamma}_n, X_i) \exp \left( -\Lambda(Y_i) e^{\beta' Z_i} \right) \right\},
\] (14)
and has to be maximized with respect to $\beta$ and $\Lambda$ in the class of step functions $\Lambda$ defined on $[0, \tau_0]$ (thus by definition $\Lambda(t) = \infty$ if $t > \tau_0$), with jumps of size $\Delta \Lambda$ at the event times. The indicator of the event $\{Y_i < \tau_0\}$ in the first term is needed in case the distribution of the event times has a jump at $\tau_0$ meaning that $\mathbb{P}(T_0 = \tau_0 | Z) > 0$. In such a case $f_u(\tau_0 | Z; \beta, \Lambda) = \exp(-\Lambda(\tau_0) e^{\beta' Z})$ where $\Lambda(\tau_0) = \lim_{t \uparrow \tau_0} \Lambda(t)$. Otherwise, if $\mathbb{P}(T_0 = \tau_0 | Z) = 0$, then for all uncensored observations we have $1 \cdot \mathbb{I}_{Y < \tau_0} = 1$ with probability one. Thus, the presence of the indicator function can be neglected. As in [18], it can be shown that
\[
(\hat{\beta}_n, \hat{\Lambda}_n) = \arg \max_{\beta, \Lambda} \hat{l}_n(\beta, \Lambda, \hat{\gamma}_n)
\] (15)
exists and it is finite. Moreover, for any given $\beta$ and $\gamma$, the $\Lambda_{\beta, \gamma}$ which maximizes $\hat{l}_n(\beta, \Lambda, \gamma)$ in (14), with respect to $\Lambda$ with jumps at the event times, can be characterized as
\[
\Lambda_{\beta, \gamma}(t) = \frac{1}{n} \sum_{i=1}^n \frac{\Delta_i \mathbb{I}_{Y_i \leq t < \tau_0}}{\sum_{j=1}^n \mathbb{I}_{Y_j \leq Y_i \leq \tau_0} \exp(\beta' Z_j) \left\{ \Delta_j + (1 - \Delta_j) g_j(Y_j, \Lambda_{\beta, \gamma}) \right\}},
\] (16)
where
\[
g_j(t, \Lambda, \beta, \gamma) = \frac{\phi(\gamma, X_j) \exp(\Lambda(t) \exp(\beta' Z_j))}{1 - \phi(\gamma, X_j) + \phi(\gamma, X_j) \exp(-\Lambda(t) \exp(\beta' Z_j))}.
\] (17)
Next, we could define
\[
\hat{\beta}_n = \arg \max_{\beta} \hat{l}_n(\beta, \Lambda_{\beta, \gamma}, \hat{\gamma}_n) \quad \text{and} \quad \hat{\Lambda}_n = \Lambda_{\hat{\beta}_n, \hat{\gamma}_n}.
\]
To compute \((\hat{\beta}_n, \hat{\Lambda}_n)\) we use an iterative algorithm based on profiling. To be precise, we start with initial values which are the maximum partial likelihood estimator and the Breslow estimator (as if there was no cure fraction) and we iterate between the next two steps until convergence:

a) Compute the weights

\[
w^{(m)}_j = \Delta_j + (1 - \Delta_j) \frac{\phi(\hat{\gamma}_n, X_j) \hat{S}^{(m)}_u(Y_j | Z_j)}{1 - \phi(\hat{\gamma}_n, X_j) + \phi(\hat{\gamma}_n, X_j) \hat{S}^{(m)}_u(Y_j | Z_j)},
\]

where

\[
\hat{S}^{(m)}_u(Y_j | Z_j) = \exp \left( -\hat{\Lambda}^{(m)}_n(Y_j) \exp \left( \hat{\beta}^{(m)}_n Z_j \right) \right),
\]

using the estimators \(\hat{\Lambda}^{(m)}_n\), \(\hat{\beta}^{(m)}_n\) of the previous step.

b) Using the previous weights, update the estimators for \(\Lambda\) and \(\beta\), i.e. \(\hat{\beta}^{(m+1)}_n\) is the maximizer of

\[
\prod_{i=1}^{n} \left\{ \frac{e^{\beta' Z_i}}{\sum_k Y_k \geq Y_i w^{(m)}_k e^{\beta' Z_k}} \right\} \Delta_i,
\]

and

\[
\hat{\Lambda}^{(m+1)}_n(t) = \sum_{i=1}^{n} \frac{\Delta_i \mathbb{1}\{Y_i \leq t, Y_i < \tau_0\}}{\sum_{j=1}^{n} \mathbb{1}\{Y_j \leq Y_i \leq \tau_0\} w^{(m)}_j \exp \left( \hat{\beta}^{(m+1)}_n Z_j \right)}. \tag{18}
\]

The update of \(\Lambda\) an \(\beta\) in Step (b) coincides with the maximization step of the EM algorithm and the weights \(w^{(m)}\) correspond to the expectation of the latent variable \(B\) given the observed data and the current parameter values. However, unlike the maximum likelihood estimation [24], we are keeping \(\hat{\gamma}_n\) fixed while performing this iterative algorithm. The estimator \(\hat{\Lambda}_n\) seems to depend on the unknown \(\tau_0\). However, with data at hand, one could easily proceed without knowing \(\tau_0\). Indeed, if there are ties at the last uncensored observation, then \(\tau_0\) is revealed by the data. On the other hand, if there are no ties, all uncensored observations will be smaller than \(\tau_0\), hence no need to know \(\tau_0\).

As suggested in [25, 24], we impose the zero-tail constraint, meaning that \(\hat{S}^{(m)}_u\) is forced to be equal to zero beyond the last event. In this way, all censored observations in the plateau are assigned to the cured group.

5. Asymptotic results

We first explain why presmoothing allows for more realistic asymptotic results in semiparametric mixture cure models. Next, we show consistency and asymptotic normality of the proposed estimators \(\hat{\gamma}_n\), \(\hat{\beta}_n\) and \(\hat{\Lambda}_n\) for the parametric/Cox mixture cure model when, in Step 1, we use a general nonparametric estimator \(\hat{\pi}\) of \(\pi_0\) that satisfies certain assumptions. Afterwards, we verify these conditions.
for the particular estimator \( \hat{\pi} \) in (9). Some of the proofs can be found in Section 9 and the rest in the online Supplementary Material. The assumptions mentioned in Section 2 are assumed to be satisfied throughout this section. In addition \( \text{Var}(Z) \) is supposed to have full rank.

### 5.1. A challenge with mixture cure models

To derive asymptotic results, in most of the existing literature it has been assumed that

\[
\inf_z \mathbb{P}(T_0 \geq \tau_0 | Z = z) > 0, \tag{19}
\]

[18, 20]. In nonparametric approaches such a condition keeps the denominators away from zero. In the parametric/Cox mixture cure model, it guarantees that the baseline distribution stays bounded on the compact support \([0, \tau_0]\). However, condition (19) implies that \( \inf_z \mathbb{P}(Y = \tau_0, \Delta = 1 | Z = z) > 0 \), a condition which is not frequently satisfied in real-data applications.

One could imagine that, instead of imposing condition (19), it could be possible to proceed as follows: first restrict to events on \([0, \tau^*]\) for some \( \tau^* < \tau_0 \) such that

\[
\inf_z \mathbb{P}(Y \geq \tau^*, \Delta = 1 | Z = z) > 0, \tag{20}
\]

next derive the asymptotics, and finally let \( \tau^* \) tend to \( \tau_0 \). This idea is used, for instance, in Cox PH model, see [13] chapter 8, or [3]. However, this idea does not seem to work for mixture cure models without suitable adaptation. This is because it implicitly requires that \( \beta_0 \) and \( \Lambda_0 \) are identifiable from the restricted data. Here, identifiability means that the true values \( \beta_0 \) and \( \Lambda_0 \) of the parameters maximize the expectation of the criterion maximized to obtain the estimators. Two aspects have to be taken into account when analyzing this identifiability. The first aspect is related to the parameter identifiability in the semiparametric model for \( T_0 \) when the events are restricted to \([0, \tau^*]\). This property is satisfied in the common models, in particular it holds true in the Cox PH model as soon as \( \text{Var}(Z) \) has full rank. The second aspect is the additional complexity induced by the mixture with a cure fraction. If the cure fraction is unknown and one decides to restrict to events on \([0, \tau^*]\), the parameter identifiability is likely lost because the events \( \{T_0 \in (\tau^*, \tau_0]\} \) and \( \{T = \infty\} \) are not distinguishable. The usual remedy for this is to impose (19), so that \( \tau^* \) could be taken equal to \( \tau_0 \).

Presmoothing allows to avoid condition (19) and thus to fill the gap between the technical conditions and the reality of the data. This is possible because, when using the presmoothing, the conditional probability of the event \( \{T = \infty\} \) is identified by other means. We are thus able to prove the consistency of \( \hat{\beta} \) and \( \hat{\Lambda} \) without imposing (19). Deriving the asymptotic normality without (19) remains an open problem which will be addressed elsewhere.
5.2. Consistency

We first prove consistency of $\hat{\gamma}_n$ and then use that result to obtain consistency of $\hat{\Lambda}_n$ and $\hat{\beta}_n$. In order to proceed with our results, the following conditions will be used.

(AC1) $\sup_{x \in X} |\hat{\pi}(x) - \pi_0(x)| \to 0$ almost surely.

(AC2) The parameters $\beta_0$ and $\gamma_0$ lie in the interior of compact sets $B \subset \mathbb{R}^q$, $G \subset \mathbb{R}^p$.

(AC3) There exist some constants $a > 0$, $c > 0$ such that $|\phi(\gamma_1, x) - \phi(\gamma_2, x)| \leq c \|\gamma_1 - \gamma_2\|^a$, $\forall \gamma_1, \gamma_2 \in G$, $\forall x \in X$, where $\|\cdot\|$ denotes the Euclidean distance.

(AC4) $\inf_{x \in X} \inf_{\gamma \in G} \phi(\gamma, x) > 0$ and $\inf_{x \in X} \inf_{\gamma \in G} \phi(\gamma, x) < 1$.

(AC5) The covariates are bounded: $P(\|Z\| < m$ and $\|X\| < m) = 1$ for some $m > 0$.

(AC6) The baseline hazard function $\lambda_0(t) = \Lambda'_0(t)$ is strictly positive and continuous on $[0, \tau_0)$.

(AC7) With probability one, the conditional distribution function of the censoring times $F_C(t|x, z)$ is continuous in $t$ on $[0, \tau_0]$ and there exists a constant $C > 0$ such that

$$\inf_{0 \leq t_1 < t_2 \leq \tau_0} \inf_{x, z} \frac{F_C(t_2|x, z) - F_C(t_1|x, z)}{t_2 - t_1} > C.$$  

(AC1) is a minimal assumption given that we want to match $\phi(\gamma, \cdot)$ to $\hat{\pi}(\cdot)$.

(AC2) to (AC4) are mild conditions satisfied by usual binary regression models, like for instance the logistic one, and (AC5) is always satisfied in practice for large $m$.

Theorem 1. Let the estimator $\hat{\gamma}_n$ be defined as in (10). Assume that (AC1)-(AC4) hold. Then, $\hat{\gamma}_n \to \gamma_0$ almost surely.

Theorem 2. Let the estimators $\hat{\beta}_n$ and $\hat{\Lambda}_n$ be defined as in Section 4. Assume that (AC1)-(AC7) hold. Then, with probability one, $\|\hat{\beta}_n - \beta_0\| \to 0$, where $\|\cdot\|$ denotes the Euclidean distance. Moreover, for any $\tau^* \leq \tau_0$ satisfying (20), with probability one,

$$\sup_{t \in [0, \tau^*]} \left| \hat{\Lambda}_n(t) - \Lambda_0(t) \right| \to 0.$$  

When condition (19) is satisfied and $\tau^* = \tau_0$ in the previous Theorem, we are referring to the continuous version of $\Lambda_0$, i.e. $\Lambda_0(\tau_0) = \lim_{t \uparrow \tau_0} \Lambda_0(t)$. Note that, by definition, we also have $\hat{\Lambda}_n(\tau_0) = \lim_{t \uparrow \tau_0} \hat{\Lambda}_n(t)$.

5.3. Asymptotic normality

We first derive asymptotic normality of $\hat{\gamma}_n$ following the approach in [8]. Theorem 2 in that paper provides sufficient conditions for the $\sqrt{n}$ normality of
parametric estimators obtained by minimizing an objective function that depends on a preliminary infinite dimensional estimator \( \hat{\pi} \). In our case, since \( \hat{\gamma}_n \) solves
\[
\frac{1}{n} \nabla_{\gamma} \log \hat{L}_{n,1}(\gamma) = 0,
\]
where \( \nabla_{\gamma} \) denotes the vector-valued partial differentiation operator with respect to the components of \( \gamma \), it follows that \( \hat{\gamma}_n \) minimizes the function
\[
\left\| \frac{1}{n} \nabla_{\gamma} \log \hat{L}_{n,1}(\gamma) \right\| = \left\| \frac{1}{n} \sum_{i=1}^{n} m(X_i; \gamma, \hat{\pi}) \right\|,
\]
where
\[
m(x; \gamma, \pi) = \left[ \frac{1 - \pi(x)}{\phi(\gamma, x)} - \frac{\pi(x)}{1 - \phi(\gamma, x)} \right] \nabla_{\gamma} \phi(\gamma, x).
\] (21)

Hence, we only need to check that the conditions of Theorem 2 in [8] are satisfied. To do that, we need the following assumptions which are stronger than the previous (AC1)-(AC4).

(AN1) The parameter \( \gamma_0 \) lies in the interior of a compact set \( G \subset \mathbb{R}^p \) and, for each \( x \in X \), the function \( \gamma \mapsto \phi(\gamma, x) \) is twice continuously differentiable with uniformly bounded derivatives in \( G \times X \) and satisfies (AC4).

(AN2) \( \pi_0(\cdot) \) belongs to a class of functions \( \Pi \) such that
\[
\int_0^\infty \sqrt{\log N(\epsilon, \Pi, \| \cdot \|_{\infty})} \, d\epsilon < \infty,
\]
where \( N(\epsilon, \Pi, \| \cdot \|_{\infty}) \) denotes the \( \epsilon \)-covering number of the space \( \Pi \) with respect to \( \| \pi \|_{\infty} = \sup_{x \in X} |\pi(x)| \).

(AN3) The matrix \( E[\nabla_{\gamma} \phi(\gamma_0, X) \nabla_{\gamma} \phi(\gamma_0, X)^t] \) is positive definite.

(AN4) The estimator \( \hat{\pi}(\cdot) \) satisfies the following properties:

(i) \( P(\hat{\pi}(\cdot) \in \Pi) \to 1 \).

(ii) \( \| \hat{\pi}(x) - \pi_0(x) \|_{\infty} = o_P(n^{-1/4}) \).

(iii) There exists a function \( \Psi \) such that
\[
E^* \left[ \left( \hat{\pi}(X) - \pi_0(X) \right) \left( \frac{1}{\phi(\gamma_0, X)} + \frac{1}{1 - \phi(\gamma_0, X)} \right) \nabla_{\gamma} \phi(\gamma_0, X) \right]
= \frac{1}{n} \sum_{i=1}^{n} \Psi(Y_i, \Delta_i, X_i) + R_n,
\]
where \( E^* \) denotes the conditional expectation given the sample, taken with respect to the generic variable \( X \). Moreover, \( E[\Psi(Y, \Delta, X)] = 0 \) and \( \| R_n \| = o_P(n^{-1/2}) \).

**Theorem 3.** Let the estimator \( \hat{\gamma}_n \) be defined as in (10). Assume that (AN1)-(AN4) hold. Then,
\[
n^{1/2} (\hat{\gamma}_n - \gamma_0) \overset{d}{\to} N(0, \Sigma_{\gamma})
\]
with covariance matrix \( \Sigma_{\gamma} \) defined in (A28).
For deriving the asymptotic distribution of $\hat{\beta}_n$ and $\hat{\Lambda}_n$ we assume, for simplicity, that condition (19) is satisfied. In such case, in Theorem 2 we can take $\tau^* = \tau_0$ and obtain uniform strong consistency of $\hat{\Lambda}_n$ on the whole support $[0, \tau_0]$. We believe that, at the price of additional technicalities, asymptotic distributional theory can be obtained also without imposing (19), as we did for the consistency in Theorem 2. This conjecture is supported by simulations but we leave the problem to be addressed by future research.

**Theorem 4.** Let the estimators $\hat{\beta}_n$ and $\hat{\Lambda}_n$ be defined as in Section 4. Assume that condition (19), (AN1)-(AN4) and (AC2), (AC5)-(AC7) hold. Then,

$$\left\langle \sqrt{n} \left( \hat{\Lambda}_n - \Lambda_0 \right), \sqrt{n} \left( \hat{\beta}_n - \beta_0 \right) \right\rangle \rightarrow G$$

weakly in $l^\infty(\mathcal{H}_m)$, where $\mathcal{H}_m$ is a functional space defined in Section 9.1, $l^\infty(\mathcal{H}_m)$ denotes the space of bounded real-valued functions on $\mathcal{H}_m$, $G$ is a tight Gaussian process in $l^\infty(\mathcal{H}_m)$ with mean zero and covariance process given in (A39) and for $h = (h_1, h_2) \in \mathcal{H}_m$

$$\langle \Lambda, \beta \rangle(h) = \int_0^{\tau_0} h_1(t) d\Lambda(t) + h_2' \beta.$$

The asymptotic variances of each component of $\hat{\beta}_n$ and of $\hat{\Lambda}_n(t)$ can be obtained from the covariance process in (A39) by taking $h_1(t) = 0$ for all $t$ and $h_2 = e_i$ (the $i$th unit vector) or $h_2 = 0$ and $h_1(s) = 1\{s \leq t\}$. We leave the details about these covariance matrices in the Supplementary Material because they have quite complicated expressions that require definitions of several other quantities. Even though it could be possible in principle to estimate the asymptotic standard errors through plug-in estimators and numerical inverse, we think that this is not feasible in practice and we do not intend to exploit it further. Instead, we use a bootstrap procedure for estimation of the standard errors in the application discussed in Section 7. However, the maximum likelihood estimators are not more favorable in this regard. For example, in the logistic/Cox model, the proposed estimators of the asymptotic variance in [18] also involve solving numerically complicated nonlinear equalitons. For this reason, bootstrap is used in practice to estimate the standard errors even for the maximum likelihood estimators.

By considering a two-step procedure, where estimation of the incidence parameters is performed independently of the latency model, we expect to loose efficiency of the estimators. However, this does not cause major concern because our purpose is to provide an alternative estimation method that performs better than the maximum likelihood estimation with sample sizes usually encountered in practice. Efficiency is a key concept for the asymptotics of the estimators, and in general there is no particular need for another method since the MLE would be the best choice. However, in many nonlinear models, like the mixture cure models, the asymptotic approximation is poor and the efficiency becomes a less relevant purpose for real data sample sizes. Hence, we choose to trade efficiency for better performance in a wider range of applications.
5.4. Verification of assumptions for $\hat{\pi}$

Next we show that our assumptions (AN1)-(AN4) of the asymptotic theory are satisfied for the nonparametric estimator $\hat{\pi}$ defined in (9) and the logistic model in (6). For reasons of simplicity, since we use results available in the literature only for a one-dimensional covariate, we consider only cases with one continuous covariate. In order for assumption (AN4) to be satisfied we need the following conditions:

(C1) The bandwidth $b$ is such that $nb^4 \to 0$ and $nb^{3+\xi}/(\log b^{-1}) \to \infty$ for some $\xi > 0$.

(C2) The support $X$ of $X$ is a compact subset of $\mathbb{R}$. The density $f_X(\cdot)$ of $X$ is bounded away from zero and twice differentiable with bounded second derivative.

(C3) The kernel $k$ is a twice continuously differentiable, symmetric probability density function with compact support and $\int uk(u)\,du = 0$.

(C4) (i) The functions $H([0,t]|x), H_1([0,t]|x)$ are twice differentiable with respect to $x$, with uniformly bounded derivatives for all $t \leq \tau_0, x \in \mathcal{X}$. Moreover, there exist continuous nondecreasing functions $L_1, L_2, L_3$ such that $L_i(0) = 0, L_i(\tau_0) < \infty$ and for all $t, s \in [0,\tau_0], x \in \mathcal{X}$,

$$|H_c(t|x) - H_c(s|x)| \leq |L_1(t) - L_1(s)|,$$

$$\left| \frac{\partial H_c(t|x)}{\partial x} - \frac{\partial H_c(s|x)}{\partial x} \right| \leq |L_2(t) - L_2(s)|,$$

$$\left| \frac{\partial H_1c(t|x)}{\partial x} - \frac{\partial H_1c(s|x)}{\partial x} \right| \leq |L_3(t) - L_3(s)|,$$

where the subscript $c$ denotes the continuous part of a function.

(ii) The jump points for the distribution function $G(t|x)$ of the censoring times given the covariate, are finite and the same for all $x$. The partial derivative of $G(t|x)$ with respect to $x$ exists and is uniformly bounded for all $t \leq \tau_0, x \in \mathcal{X}$. Moreover, the partial derivative with respect to $x$ of $F(t|x)$ (distribution function of the survival times $T$ given $X = x$) exists and is uniformly bounded for all $t \leq \tau_0, x \in \mathcal{X}$.

(C5) The survival time $T$ and the censoring time $C$ are independent given $X$.

(C1) to (C5) are conditions guaranteeing the rates of convergence and the i.i.d. representation [10]. In case of discrete covariates we also need to have only a finite number of atoms. Assumption (C5) is needed because we are dealing with the distribution of $T$ conditional only on the covariate $X$ (since the cure rate depends only on $X$).

**Theorem 5.** Under the conditions (C1)-(C5), the assumptions (AN1)-(AN4) hold true for the logistic model and the estimator $\hat{\pi}(x)$ defined in (9).
6. Simulation study

In this section we focus on the logistic/Cox mixture cure model and evaluate the finite sample performance of the proposed method. Comparison is made with the maximum likelihood estimator implemented in the package smcure.

We first illustrate through a brief example the convergence problems of the smcure estimator. We consider a model where the incidence depends on four independent covariates: \( X_1 \sim N(0, 2), X_2 \sim \text{Uniform}(-1, 1), X_3 \sim \text{Bernoulli}(0.8), X_4 \sim \text{Bernoulli}(0.2) \). The latency depends on \( Z_1 = X_1, Z_2 = X_3 \) and \( Z_3 = X_4 \). We generate the cure status \( B \) as a Bernoulli random variable with success probability \( \phi(\gamma, X) \) where \( \phi \) is the logistic function and \( \gamma = (0.6, -1, 1, 2.5, 1.2) \).

The survival times for the uncured observations are generated according to a Weibull proportional hazards model

\[
S_u(t | z) = \exp \left( -\mu t^\rho \exp(\beta' z) \right),
\]

and are truncated at \( \tau_0 = 14 \) for \( \rho = 1.75, \mu = 1.5, \beta = (-0.8, 0.9, 0.5) \). The censoring times are independent from \( X \) and \( T \). They are generated from the exponential distribution with parameter \( \lambda_C = 0.22 \) and are truncated at \( \tau = 16 \). We generate 1000 datasets according to this model with sample size \( n = 100 \), and we observe that smcure fails to converge in 43% of the cases. Convergence fails mainly in the \( \gamma \) parameter, with only 17% of the cases failing to converge also for the \( \beta \) parameter (because of the unreasonable \( \gamma \) estimators).

On the other hand, there was no convergence problem in the second step of the presmoothing approach. In addition, even among the cases where smcure converged, the presmoothing approach showed significantly better behavior, as can be seen in Table 1.

| Par. | presmoothing Bias | presmoothing Var. | presmoothing MSE | smcure Bias | smcure Var. | smcure MSE |
|------|-------------------|-------------------|-----------------|------------|-----------|----------|
| \( \gamma_1 \) | -0.113 | 0.620 | 0.633 | 0.200 | 8.318 | 8.358 |
| \( \gamma_2 \) | -0.073 | 0.156 | 0.162 | -0.388 | 3.085 | 3.236 |
| \( \gamma_3 \) | -0.071 | 0.546 | 0.551 | 0.280 | 1.957 | 2.035 |
| \( \gamma_4 \) | 0.037 | 1.326 | 1.327 | 0.704 | 14.395 | 14.891 |
| \( \gamma_5 \) | -0.250 | 8.398 | 8.461 | 1.621 | 36.456 | 36.945 |
| \( \beta_1 \) | -0.014 | 0.011 | 0.012 | -0.017 | 0.012 | 0.012 |
| \( \beta_2 \) | 0.024 | 0.064 | 0.065 | 0.026 | 0.065 | 0.065 |
| \( \beta_3 \) | -0.053 | 0.165 | 0.168 | -0.053 | 0.166 | 0.169 |

Hence, in the cases in which smcure exhibits very poor behavior, the presmoothing is obviously superior. Next, we focus on models for which smcure behaves reasonable (there are convergence problems in less than 3% of the cases) and show that, even in such scenarios presmoothing can lead to more accurate results.

We consider four different models and for each of them various choices of the parameters in order to cover a wide range of scenarios. The models are as follows.
Model 1. Both incidence and latency depend on one covariate $X$, which is uniform on $(-1, 1)$. We generate the cure status $B$ as a Bernoulli random variable with success probability $\phi(\gamma, X)$ where $\phi$ is the logistic function. The survival times for the uncured observations are generated according to a Weibull proportional hazards model

$$S_u(t|x) = \exp (-\mu t^\rho \exp(\beta x)),$$

and are truncated at $\tau_0$ for $\rho = 1.75$, $\mu = 1.5$, $\beta = 1$ and $\tau_0 = 4$. The censoring times are independent from $X$ and $T$. They are generated from the exponential distribution with parameter $\lambda_C$ and are truncated at $\tau = 6$.

Model 2. Both incidence and latency depend on one covariate $X$ with standard normal distribution. The cure status and the survival times for the uncured observations are generated as in Model 1 for $\rho = 1.75$, $\mu = 1.5$, $\beta = 1$ and $\tau_0 = 10$. The censoring times are generated according to a Weibull proportional hazards model

$$S_C(t|x) = \exp (-\nu \mu t^\rho \exp(\beta_C x)),$$

for $\beta_C = 1$ and various choices of $\nu$ and are truncated at $\tau = 15$.

Model 3. For the incidence we consider three independent covariates: $X_1$ is normal with mean zero and standard deviation 2, $X_2$ and $X_3$ are Bernoulli random variables with parameters 0.6 and 0.4 respectively. The latency also depends on three covariates: $Z_1 = X_1$, $Z_2$ is a uniform random variable on $(-3, 3)$ independent of the previous ones and $Z_3 = X_2$. The cure status and the survival times for the uncured observations are generated as in Model 1 for $\rho = 1.75$, $\mu = 1.5$ and different choices of the other parameters. The censoring times are generated independently of the previous variables from an exponential distribution with parameter $\lambda_C$ and are truncated at $\tau$, for given choices of $\lambda_C$ and $\tau$.

Model 4. This setting is obtained by adding an additional continuous covariate to the incidence component of Model 3. To be precise, $X_1$ is normal with mean zero and standard deviation 2, $X_2$ is uniform on $(-1, 1)$ independent of the other variables, $X_3$ and $X_4$ are Bernoulli random variables with parameters 0.6 and 0.4 respectively. As in Model 3, $Z_1 = X_1$, $Z_2$ is a uniform random variable on $(-3, 3)$ independent of the previous ones and $Z_3 = X_3$. The event and censoring times are generated as in the previous model.

For the four models we choose the values of the unspecified parameters in such a way that the cure rate is around 20%, 30%, 50% (corresponding respectively to scenarios 1, 2 and 3) and the censoring rate corresponds to three levels (with a difference of 5% between each other). The specification of the parameters and the corresponding censoring rate and percentage of the observations in the plateau are given Table 2. Note that, within each scenario, the fraction of the observations in the plateau decreases as the censoring rate increases because more cured observations are censored earlier and as a result are not observed in the plateau. This makes the estimation of the cure rate more difficult. The truncation of the survival and censoring times on $[0, \tau_0]$ and $[0, \tau]$ is made in such a way that $\tau_0 < \tau$ and condition (19) is satisfied but in practice it is
unlikely to observe event times at $\tau_0$. In this way, we try to find a compromise between theoretical assumptions and real-life scenarios.

For each setting we consider samples of size $n = 200, 400, 1000$. This leads to a total of 108 settings (4 models, 3 scenarios for the cure rate, 3 censoring levels and 3 sample sizes). In this way, we hope to address a number of issues such as the effect of the cure proportion, the sample size, amount and type of censoring, covariates (number, relation between $X$ and $Z$ and their distribution). For each configuration 1020 datasets were generated and the estimators of $\beta_0$ and $\gamma_0$ were computed through *smcure* and our method. We report the bias, variance and mean squared error (MSE) of the estimators, computed after omitting the lowest and the highest 1% of the estimators (for stability of the reported results) and rounded to three decimals. Tables 3-5 show some of the results, while the rest can be found in the online Supplementary Material. We aim to provide a ready-to-use method that works well in practice without needing to think about how to choose the kernel function or the bandwidth. Hence, we illustrate the performance of the method for some standard and commonly used choices. The kernel function $k$ is taken to be the Epanechnikov kernel $k(u) = (3/4)(1-u^2)1_{\{|u|\leq 1\}}$. We use the cross-validation bandwidth (implemented in the R package *np*) for kernel estimators of conditional distribution functions, in our case for estimation of $H = H_0 + H_1$ given the continuous covariates (affecting the incidence). In addition, we restrict to the interval $[0, Y(m)]$, where $Y(m)$ is the last observed event time since the estimator of the cure probability $\hat{\pi}$ in (9) is essentially a product over values of $t$ that are equal to the observed event times. This means that we use the cross-validation bandwidth for estimation of the conditional distribution $H(t|x)$ for $t \leq Y(m)$. This choice of bandwidth improves significantly the performance of the estimators, compared to the cross-validation bandwidth on the whole interval $[0, \tau]$, in situations with a large percentage of observations in the plateau, while it leads to little difference otherwise.

Simulations show that, for not large sample size, the new method performs better than *smcure* for estimation of $\gamma_0$, mostly because of a smaller variance. As the sample size increases, they tend to behave quite similarly. On the other hand, both methods give almost the same estimates for $\beta_0$ and $\Lambda$. The most favorable situation for our method is when there is little censoring among uncured observations and the censored uncured observations are in the region of covariates that corresponds to higher cure rate. This comes from the fact that the nonparametric estimator in (9) takes larger values when the product has more terms equal to one. This should not be a problem when we expect that subjects with high probability of being cured correspond to longer survival times, meaning that it is more probable for them to be censored compared to those with small cure probability and shorter survival times.

This is indeed the case in Model 1 and we observe that our approach outperforms *smcure* in all the scenarios. The difference between the two is more marked when $n$ is small and the absolute value of the $\gamma$ coefficient is larger. In Model 2, the situation is more difficult because censoring depends on the covariate in such a way that, the non-cured subjects have the same probability of being censored independently of their cure probability. However, for the first
Table 2
Parameter values and model characteristics for each scenario.

| Model Parameters | Scenario | Cens. level | Cens. parameters | Cens. rate | Plateau |
|------------------|----------|-------------|------------------|------------|---------|
| $\gamma = (1.75, 2)$ | 1        | $\lambda_C = 0.1$ | 25%               | 15%        |         |
|                  |          | $\lambda_C = 0.2$ | 30%               | 11%        |         |
|                  |          | $\lambda_C = 0.3$ | 35%               | 9%         |         |
| $\gamma = (1, 1.5)$ | 2        | $\lambda_C = 0.1$ | 34%               | 22%        |         |
|                  |          | $\lambda_C = 0.25$ | 45%               | 15%        |         |
|                  |          | $\lambda_C = 0.4$ | 46%               | 10%        |         |
| $\gamma = (0.1, 5)$ | 3        | $\lambda_C = 0.4$ | 45%               | 9%         |         |
|                  |          | $\lambda_C = 0.7$ | 65%               | 15%        |         |
| $\gamma = (1.5, 0.5)$ | 4        | $\nu = 1/15$ | 56%               | 30%        |         |
|                  |          | $\nu = 1/4$ | 35%               | 2%         |         |
| $\gamma = (1, 1)$ | 5        | $\nu = 1/13$ | 35%               | 14%        |         |
|                  |          | $\nu = 1/10$ | 40%               | 9%         |         |
|                  |          | $\nu = 5/18$ | 45%               | 6%         |         |
| $\gamma = (−0.1, 5)$ | 6        | $\nu = 1/9$ | 56%               | 30%        |         |
|                  |          | $\nu = 2/5$ | 65%               | 25%        |         |
| $\gamma = (0.5, −1, 2, 5, 1.2)$ | 7        | $\lambda_C = 0.12$ | 25%               | 10%        |         |
|                  |          | $\lambda_C = 0.25$ | 30%               | 6%         |         |
|                  |          | $\lambda_C = 0.45$ | 35%               | 4%         |         |
| $\gamma = (1, 2, 1.8, 0.5)$ | 8        | $\lambda_C = 0.2$ | 35%               | 16%        |         |
|                  |          | $\lambda_C = 0.5$ | 40%               | 9%         |         |
|                  |          | $\lambda_C = 0.8$ | 45%               | 6%         |         |
| $\gamma = (−0.8, 1.3, 1.5, −0.2)$ | 9        | $\lambda_C = 0.5$ | 55%               | 24%        |         |
|                  |          | $\lambda_C = 0.7$ | 59%               | 14%        |         |
| $\gamma = (0.6, −1, 1, 2, 5, 1.2)$ | 10       | $\lambda_C = 0.1$ | 25%               | 11%        |         |
|                  |          | $\lambda_C = 0.22$ | 30%               | 7%         |         |
|                  |          | $\lambda_C = 0.35$ | 35%               | 5%         |         |
| $\gamma = (0.45, 0.5, 2.1, 0.3)$ | 11       | $\lambda_C = 0.15$ | 35%               | 11%        |         |
|                  |          | $\lambda_C = 0.35$ | 40%               | 7%         |         |
| $\gamma = (−0.22, 0.3, −0.4, 0.5, −0.2)$ | 12       | $\lambda_C = 0.2$ | 55%               | 30%        |         |
|                  |          | $\lambda_C = 0.4$ | 59%               | 20%        |         |
| $\gamma = (0.4, −0.1, 0.5)$ | 13       | $\lambda_C = 0.7$ | 65%               | 12%        |         |
Table 3
Bias, variance and MSE of $\hat{\gamma}$ and $\hat{\beta}$ for smcure (second rows) and our approach (first rows)
in Model 1 and 2.

| Mod. | n  | scen. | Par. | Cens. level 1 Bias | Var. | MSE | Bias | Var. | MSE | Bias | Var. | MSE |
|------|----|-------|------|-------------------|------|-----|------|------|-----|------|------|-----|
| 1    | 200| 1     | $\gamma_1$ | 0.001 | 0.060 | 0.060 | 0.020 | 0.065 | 0.065 | 0.005 | 0.078 | 0.078 |
|      |    |       | $\gamma_2$ | -0.034 | 0.164 | 0.165 | -0.014 | 0.202 | 0.202 | -0.051 | 0.209 | 0.212 |
|      |    |       | $\beta$ | 0.008 | 0.028 | 0.028 | 0.015 | 0.029 | 0.029 | 0.013 | 0.034 | 0.035 |
|      |    |       | $\beta_2$ | 0.007 | 0.028 | 0.028 | 0.012 | 0.029 | 0.029 | 0.009 | 0.035 | 0.035 |
| 3    | 000| 1     | $\gamma_1$ | -0.004 | 0.059 | 0.059 | 0.009 | 0.065 | 0.065 | -0.014 | 0.091 | 0.092 |
|      |    |       | $\gamma_2$ | -0.034 | 0.536 | 0.537 | -0.111 | 0.595 | 0.608 | -0.085 | 0.809 | 0.816 |
|      |    |       | $\beta$ | 0.011 | 0.090 | 0.090 | 0.024 | 0.109 | 0.110 | 0.014 | 0.128 | 0.128 |
|      |    |       | $\beta_2$ | 0.007 | 0.091 | 0.091 | 0.014 | 0.110 | 0.110 | -0.001 | 0.120 | 0.120 |

| 400  | 1   |       | $\gamma_1$ | 0.001 | 0.028 | 0.028 | 0.007 | 0.032 | 0.032 | 0.001 | 0.037 | 0.037 |
|      |     |       | $\gamma_2$ | -0.024 | 0.083 | 0.084 | -0.004 | 0.088 | 0.088 | -0.018 | 0.107 | 0.107 |
|      |     |       | $\beta$ | 0.003 | 0.013 | 0.013 | 0.007 | 0.015 | 0.015 | 0.002 | 0.016 | 0.016 |
|      |     |       | $\beta_2$ | 0.002 | 0.013 | 0.013 | 0.005 | 0.015 | 0.015 | 0.000 | 0.016 | 0.016 |

| 2    | 200| 1     | $\gamma_1$ | 0.004 | 0.040 | 0.040 | 0.020 | 0.045 | 0.045 | -0.016 | 0.060 | 0.060 |
|      |    |       | $\gamma_2$ | 0.017 | 0.040 | 0.040 | 0.058 | 0.047 | 0.050 | 0.083 | 0.079 | 0.086 |
|      |    |       | $\beta$ | 0.016 | 0.040 | 0.040 | 0.008 | 0.047 | 0.047 | 0.029 | 0.072 | 0.073 |
|      |    |       | $\beta_2$ | 0.005 | 0.011 | 0.011 | 0.000 | 0.014 | 0.014 | 0.004 | 0.016 | 0.016 |
| 3    | 000| 1     | $\gamma_1$ | -0.016 | 0.071 | 0.071 | -0.057 | 0.065 | 0.068 | -0.139 | 0.083 | 0.102 |
|      |    |       | $\gamma_2$ | -0.468 | 0.723 | 0.942 | -0.943 | 0.823 | 1.713 | -1.348 | 0.829 | 2.646 |
|      |    |       | $\beta$ | 0.017 | 0.035 | 0.035 | 0.022 | 0.039 | 0.039 | 0.036 | 0.052 | 0.054 |
|      |    |       | $\beta_2$ | 0.014 | 0.035 | 0.035 | 0.017 | 0.040 | 0.040 | 0.025 | 0.053 | 0.054 |
| 400  | 1   |       | $\gamma_1$ | 0.011 | 0.019 | 0.019 | 0.019 | 0.023 | 0.023 | 0.002 | 0.032 | 0.032 |
|      |     |       | $\gamma_2$ | 0.018 | 0.019 | 0.019 | 0.037 | 0.023 | 0.025 | 0.047 | 0.034 | 0.036 |
|      |     |       | $\beta$ | 0.002 | 0.018 | 0.018 | -0.010 | 0.023 | 0.023 | -0.019 | 0.027 | 0.028 |
|      |     |       | $\beta_2$ | 0.009 | 0.018 | 0.018 | 0.007 | 0.025 | 0.025 | 0.008 | 0.032 | 0.032 |
| 3    | 000| 1     | $\gamma_1$ | -0.015 | 0.031 | 0.031 | -0.071 | 0.034 | 0.039 | -0.086 | 0.041 | 0.048 |
|      |    |       | $\gamma_2$ | -0.444 | 0.330 | 0.527 | -0.802 | 0.410 | 1.053 | -1.191 | 0.463 | 1.881 |
|      |    |       | $\beta$ | 0.007 | 0.016 | 0.016 | 0.015 | 0.019 | 0.020 | 0.017 | 0.024 | 0.024 |
|      |    |       | $\beta_2$ | 0.004 | 0.016 | 0.016 | 0.010 | 0.019 | 0.020 | 0.010 | 0.024 | 0.024 |
### Table 4
Bias, variance and MSE of $\hat{\gamma}$ for secure (second rows) and our approach (first rows) in Model 3.

| Mod. | n | scen. | Par. | Cens. level 1 | Cens. level 2 | Cens. level 3 |
|------|---|-------|------|---------------|---------------|---------------|
|      |   |       |      | Bias Var. MSE | Bias Var. MSE | Bias Var. MSE |
| 3    | 200 | 1     | $\gamma_1$ | 0.025 0.147 0.147 | 0.010 0.192 0.192 | $-0.008 0.243 0.243$ |
|      |    |       |      | 0.034 0.147 0.148 | 0.034 0.191 0.192 | $0.063 0.249 0.253$ |
|      |    |       |      | $-0.045 0.042 0.044$ | $-0.078 0.049 0.055$ | $-0.085 0.059 0.066$ |
|      |    |       |      | $-0.077 0.050 0.056$ | $-0.122 0.065 0.080$ | $-0.148 0.092 0.144$ |
|      |    |       |      | 0.081 0.366 0.374 | 0.074 0.485 0.491 | $0.029 0.536 0.537$ |
|      |    |       |      | 0.174 0.397 0.427 | 0.266 0.574 0.644 | $0.309 0.799 0.895$ |
|      |    |       |      | $-0.046 0.326 0.373$ | $-0.160 0.412 0.437$ | $-0.269 0.453 0.537$ |
|      |    |       |      | 0.087 0.366 0.374 | 0.089 0.528 0.535 | $0.186 0.908 0.943$ |
| 3    | 200 | 1     | $\gamma_2$ | $-0.059 0.161 0.164$ | $-0.091 0.258 0.266$ | $-0.223 0.419 0.468$ |
|      |    |       |      | $-0.053 0.163 0.166$ | $-0.071 0.261 0.266$ | $-0.138 0.524 0.543$ |
|      |    |       |      | 0.018 0.046 0.046 | 0.026 0.063 0.064 | $0.086 0.088 0.096$ |
|      |    |       |      | 0.080 0.052 0.058 | 0.121 0.080 0.095 | $0.252 0.170 0.233$ |
|      |    |       |      | 0.060 0.235 0.238 | 0.076 0.366 0.372 | $0.135 0.517 0.535$ |
|      |    |       |      | 0.091 0.242 0.251 | 0.135 0.375 0.393 | $0.228 0.642 0.694$ |
|      |    |       |      | $-0.030 0.202 0.203$ | $-0.040 0.292 0.293$ | $-0.081 0.479 0.486$ |
|      |    |       |      | $-0.027 0.205 0.205$ | $-0.017 0.277 0.277$ | $-0.037 0.534 0.535$ |
| 400  | 1   |       | $\gamma_1$ | 0.016 0.074 0.074 | 0.021 0.091 0.092 | 0.083 0.126 0.128 |
|      |    |       |      | 0.017 0.072 0.073 | 0.022 0.082 0.082 | 0.023 0.108 0.108 |
|      |    |       |      | $-0.026 0.019 0.019$ | $-0.039 0.023 0.025$ | $-0.070 0.032 0.037$ |
|      |    |       |      | $-0.042 0.020 0.021$ | $-0.049 0.025 0.027$ | $-0.084 0.035 0.041$ |
|      |    |       |      | 0.039 0.194 0.195 | 0.028 0.219 0.220 | $0.026 0.298 0.298$ |
|      |    |       |      | 0.093 0.190 0.198 | 0.097 0.206 0.215 | $0.158 0.297 0.322$ |
|      |    |       |      | 0.010 0.171 0.171 | $-0.091 0.193 0.201$ | $-0.178 0.276 0.307$ |
|      |    |       |      | 0.070 0.177 0.182 | 0.038 0.198 0.200 | $0.088 0.269 0.297$ |
| 3    | 400 | 1     | $\gamma_2$ | $-0.023 0.069 0.069$ | $-0.051 0.118 0.121$ | $-0.124 0.212 0.228$ |
|      |    |       |      | $-0.029 0.092 0.093$ | $-0.032 0.112 0.113$ | $-0.062 0.200 0.204$ |
|      |    |       |      | 0.003 0.023 0.023 | 0.006 0.033 0.033 | $0.042 0.048 0.050$ |
|      |    |       |      | 0.042 0.023 0.025 | 0.057 0.034 0.037 | 0.104 0.055 0.066 |
|      |    |       |      | 0.010 0.113 0.113 | 0.042 0.166 0.168 | 0.090 0.276 0.284 |
|      |    |       |      | 0.039 0.111 0.111 | 0.060 0.172 0.156 | 0.108 0.250 0.262 |
|      |    |       |      | 0.012 0.110 0.110 | $-0.021 0.131 0.131$ | $-0.047 0.220 0.223$ |
|      |    |       |      | 0.014 0.111 0.111 | $-0.018 0.117 0.118$ | $-0.020 0.183 0.183$ |
Bias, variance and MSE of $\hat{\gamma}$ for secure (second rows) and our approach (first rows) in Model 4.

| Mod. | n   | scen. | Par. | Cens. level 1 | Cens. level 2 | Cens. level 3 |
|------|-----|-------|------|---------------|---------------|---------------|
|      |     |       |      | Bias Var. MSE | Bias Var. MSE | Bias Var. MSE |
| 4    | 200 | 1     | $\gamma_1$ | 0.041 0.157 0.159 | 0.016 0.187 0.188 | -0.010 0.210 0.210 |
|      |     |       |      | 0.077 0.178 0.184 | 0.096 0.228 0.238 | 0.127 0.285 0.301 |
|      |     |       | $\gamma_2$ | -0.017 0.039 0.039 | -0.019 0.042 0.042 | -0.015 0.049 0.049 |
|      |     |       |      | -0.090 0.052 0.060 | -0.125 0.069 0.085 | -0.164 0.108 0.135 |
|      |     |       | $\gamma_3$ | -0.245 0.159 0.219 | -0.281 0.165 0.244 | -0.355 0.179 0.305 |
|      |     |       |      | 0.064 0.244 0.249 | 0.084 0.304 0.311 | 0.114 0.395 0.408 |
|      |     |       | $\gamma_4$ | -0.068 0.331 0.336 | -0.162 0.385 0.411 | -0.285 0.443 0.524 |
|      |     |       |      | 0.171 0.401 0.430 | 0.241 0.561 0.619 | 0.314 0.842 0.941 |
|      |     |       | $\gamma_5$ | -0.095 0.301 0.310 | -0.234 0.349 0.404 | -0.366 0.371 0.505 |
|      |     |       |      | 0.106 0.363 0.375 | 0.143 0.509 0.529 | 0.177 0.693 0.724 |
| 3    | 1   | 1     | $\gamma_1$ | -0.044 0.079 0.081 | -0.079 0.095 0.101 | -0.148 0.132 0.154 |
|      |     |       |      | 0.000 0.079 0.079 | 0.003 0.096 0.096 | 0.009 0.141 0.141 |
|      |     |       | $\gamma_2$ | 0.018 0.007 0.008 | 0.024 0.008 0.009 | 0.041 0.010 0.012 |
|      |     |       |      | 0.015 0.008 0.008 | 0.017 0.009 0.010 | 0.028 0.013 0.014 |
|      |     |       | $\gamma_3$ | 0.034 0.066 0.067 | 0.046 0.073 0.075 | 0.067 0.087 0.091 |
|      |     |       |      | -0.025 0.080 0.080 | -0.033 0.091 0.092 | -0.041 0.120 0.122 |
|      |     |       | $\gamma_4$ | 0.041 0.102 0.104 | 0.054 0.125 0.128 | 0.082 0.166 0.173 |
|      |     |       |      | 0.022 0.100 0.101 | 0.023 0.126 0.126 | 0.026 0.179 0.180 |
|      |     |       | $\gamma_5$ | -0.031 0.103 0.104 | -0.034 0.120 0.121 | -0.054 0.159 0.162 |
|      |     |       |      | -0.016 0.099 0.099 | -0.013 0.115 0.115 | -0.018 0.159 0.151 |
| 400  | 1   | 1     | $\gamma_1$ | 0.013 0.067 0.067 | 0.015 0.079 0.080 | 0.005 0.097 0.097 |
|      |     |       |      | 0.024 0.067 0.068 | 0.037 0.080 0.082 | 0.043 0.101 0.103 |
|      |     |       | $\gamma_2$ | -0.001 0.017 0.017 | -0.003 0.020 0.020 | -0.007 0.023 0.023 |
|      |     |       |      | -0.042 0.020 0.021 | -0.055 0.025 0.028 | -0.079 0.034 0.041 |
|      |     |       | $\gamma_3$ | -0.229 0.089 0.141 | -0.207 0.090 0.133 | -0.275 0.102 0.178 |
|      |     |       |      | 0.046 0.107 0.109 | 0.061 0.137 0.141 | 0.066 0.162 0.166 |
|      |     |       | $\gamma_4$ | -0.063 0.161 0.165 | -0.143 0.175 0.196 | -0.222 0.215 0.265 |
|      |     |       |      | 0.085 0.176 0.183 | 0.107 0.222 0.234 | 0.145 0.318 0.339 |
|      |     |       | $\gamma_5$ | -0.075 0.146 0.151 | -0.192 0.177 0.214 | -0.299 0.199 0.269 |
|      |     |       |      | 0.043 0.157 0.159 | 0.049 0.194 0.196 | 0.060 0.253 0.257 |
| 3    | 1   | 1     | $\gamma_1$ | -0.024 0.038 0.039 | -0.038 0.047 0.048 | -0.092 0.064 0.073 |
|      |     |       |      | -0.003 0.036 0.036 | 0.002 0.044 0.044 | 0.004 0.060 0.060 |
|      |     |       | $\gamma_2$ | 0.006 0.003 0.003 | 0.010 0.004 0.004 | 0.019 0.005 0.006 |
|      |     |       |      | 0.005 0.004 0.004 | 0.005 0.004 0.004 | 0.006 0.006 0.006 |
|      |     |       | $\gamma_3$ | 0.028 0.033 0.034 | 0.045 0.038 0.040 | 0.065 0.045 0.049 |
|      |     |       |      | -0.010 0.036 0.036 | -0.008 0.042 0.042 | -0.008 0.052 0.052 |
|      |     |       | $\gamma_4$ | 0.021 0.052 0.053 | 0.032 0.062 0.063 | 0.060 0.088 0.092 |
|      |     |       |      | 0.015 0.050 0.050 | 0.016 0.060 0.060 | 0.019 0.083 0.083 |
|      |     |       | $\gamma_5$ | -0.024 0.049 0.050 | -0.041 0.059 0.061 | -0.048 0.077 0.079 |
|      |     |       |      | -0.017 0.049 0.049 | -0.022 0.056 0.057 | -0.022 0.069 0.069 |
two scenarios the new method is still superior. The third scenario is more problematic because the cure probability drops very fast from almost one to almost zero, resulting in a large fraction of uncured observations with almost zero cure probability. The presence of censoring in this region leads to overestimation of the cure rate. If we would take $\beta_C = 0.1$ (meaning larger probability of being censored for higher cure rate), then the new approach is significantly superior (see Table 6 for $n = 400$ and scenario 3). In Model 3, complications arise because of the presence of different covariates for the incidence and latency. Hence, subjects with higher cure rate might correspond to shorter survival times. As a result, the previous problem might still happen and its effects are more visible for large sample size and large censoring rate. Finally, Model 4 suggests that, even though the assumptions in Section 5 were shown to be satisfied only for one continuous covariate, the method could be applied in more general cases. We noticed that, when a continuous covariate affects only the incidence and not the latency, the bandwidth selected by the np package is often very large, meaning that it fails to capture the effect of this covariate on the conditional distribution function. In those cases, we truncate the selected bandwidth from above at 2. Note that the bandwidth is chosen for standardized covariates so the truncation level can be fixed regardless of the distribution of the covariate. We decided to truncate at 2 since it seems to be a kind of boundary for a ‘reasonable’ bandwidth with standardized covariates (we do not want to externally affect chosen bandwidths smaller than 2 but we only replace extremely large values by 2). However, even when reasonable, the np bandwidth for $X_2$ seems to be larger than it should, resulting in more bias in the estimator of $\gamma_3$. Nevertheless, in terms of mean squared error, the method performs well for not large sample size. If $X_2$ would affect also the latency, the selected bandwidth would be more adequate and there would be no bias problems.

To conclude, the new approach seems to perform significantly better than smcure when the sample size is not large and the fraction of censored observations is not much higher than the expected cure proportion. In other situations, both methods are comparable. However, one has to be more careful when there is no reason to expect that the censored subjects correspond to higher cure probabilities.

In the previous settings, we truncated the event times at $\tau_0$ in such a way that condition (19) is satisfied but in practice it is unlikely to observe event times at $\tau_0$. Next, we consider one additional model for which condition (19) is not satisfied. The covariates and the parameters are as in Model 3 described.
above, but the event times are generated from a Weibull distribution on $[0, \tau_0]$ with $\tau_0 = 15$, i.e.,

$$S_u(t|z) = \frac{\exp\{-\mu t^\rho \exp(\beta'z)\} - \exp\{-\mu \tau_0^\rho \exp(\beta'z)\}}{1 - \exp\{-\mu \tau_0^\rho \exp(\beta'z)\}}$$

The censoring times are exponentially distributed as in Model 3 and truncated at $\tau = 20$. Results for sample size $n = 200$ and three censoring levels are shown in Table 7. Compared to Model 3 above, we observe that, when condition (19) is not satisfied, presmoothing is even more superior than the smcure estimator.

| Par. | Cens. level 1 | Cens. level 2 | Cens. level 3 |
|------|---------------|---------------|---------------|
|      | Bias | Var. | MSE | Bias | Var. | MSE | Bias | Var. | MSE |
| $\gamma_1$ | 0.015 | 0.152 | 0.152 | 0.000 | 0.196 | 0.196 | -0.032 | 0.246 | 0.247 |
|       | 0.017 | 0.150 | 0.151 | 0.027 | 0.193 | 0.194 | 0.035 | 0.260 | 0.262 |
| $\gamma_2$ | -0.054 | 0.044 | 0.047 | -0.077 | 0.052 | 0.058 | -0.109 | 0.064 | 0.076 |
|       | -0.085 | 0.050 | 0.057 | -0.119 | 0.069 | 0.083 | -0.171 | 0.101 | 0.130 |
| $\gamma_3$ | 0.087 | 0.379 | 0.386 | 0.073 | 0.450 | 0.456 | 0.045 | 0.578 | 0.580 |
|       | 0.197 | 0.423 | 0.462 | 0.249 | 0.561 | 0.623 | 0.343 | 0.885 | 1.002 |
| $\gamma_4$ | -0.010 | 0.339 | 0.339 | -0.106 | 0.373 | 0.385 | -0.228 | 0.498 | 0.550 |
|       | 0.125 | 0.364 | 0.380 | 0.156 | 0.523 | 0.548 | 0.260 | 1.513 | 1.581 |

Finally we conclude with a remark about the computational aspect. The proposed approach is computationally more intensive than the MLE mainly because of the bandwidth selection through a cross-validation procedure. For example, for one iteration in Model 3 with sample size 200 and 400, smcure computes the estimates in 0.7 and 0.8 seconds respectively, while the new approach requires 4.1 and 23.5 seconds (with a Core i7-8665U CPU desktop). However, this seems still reasonable since the method is not meant for much larger sample sizes.

7. Application: Melanoma study

To illustrate the practical performance, we apply the proposed estimation procedure to two medical datasets for patients with melanoma and compare the results with smcure. Melanoma is the third most common skin cancer type with overall incidence rate 21.8 out of 100,000 people in the US (Cancer statistics from the Center for Disease Control and Prevention) and according to the American Cancer Society, 6850 people are expected to die of melanoma in 2020. However, in the recent years, the chances of survival for melanoma patients have increased due to earlier diagnosis and improvement of treatment and surgical techniques. The 5-year survival rates based on the stage of the cancer when it was first diagnosed are 92% for localized, 65% for regional and 25% for distant stage. It is also known that this disease is more common among white people and the death rate is higher for men than women. Even though most melanoma patients are cured by their initial treatment, it is not possible to distinguish them from the
uncured patients. Hence, accurately estimating the probability of being cured is important in order to plan further treatment and prevent recurrence of uncured patients.

7.1. Eastern Cooperative Oncology Group (ECOG) Data

We use the melanoma data (ECOG phase III clinical trial e1684) from the smcure package [7] in order to compare our results with those of smcure. The purpose of this study was to evaluate the effect of treatment (high dose interferon alpha-2b regimen) as the postoperative adjuvant therapy. The event time is the time from initial treatment to recurrence of melanoma and three covariates have been considered: age (continuous variable centered to the mean), gender (0=male and 1=female) and treatment (0=control and 1=treatment). The data consists of 284 observations (after deleting missing data) out of which 196 had recurrence of the melanoma cancer (around 30% censoring). The Kaplan-Meier curve is shown in Figure 1. The parameter estimates, standard errors and corresponding p-values for the Wald test using our method and the smcure package are given in Table 8. Standard errors are computed through 500 naive bootstrap samples.

We observe that, for both methods, the effects of the covariates have the same direction. Only the intercept was found significant for the incidence with
Table 9
Results for the incidence (logistic component) and the latency (Cox PH component) from the ECOG data.

| Covariates | Model 1 | | | Model 2 | | | Model 3 | | |
|------------|---------|---|---|--------|---|---|--------|---|---|
|            | Estimates | SE | p-value | Estimates | SE | p-value | Estimates | SE | p-value |
| **incidence** | | | | | | | | | |
| Intercept   | 1.307    | 0.309 | 7·10^{-6} | 1.414    | 0.321 | 10^{-5} | 1.418    | 0.307 | 4·10^{-6} |
| Age         | 0.0164   | 0.0125 | 0.1905 | 0.0205   | 0.0154 | 0.1803 | 0.0209   | 0.0146 | 0.1528 |
| Gender      | -0.0265  | 0.3113 | 0.9320 | -0.0673  | 0.3352 | 0.8407 | -0.0222  | 0.3130 | 0.9432 |
| Treatment   | -0.6060  | 0.3509 | 0.0842 | -0.6773  | 0.3223 | 0.0415 | -0.6913  | 0.3439 | 0.0444 |
| **latency** | | | | | | | | | |
| Age         | -0.0074  | 0.0066 | 0.2568 | -0.0795  | 0.1863 | 0.0719 | -0.0073  | 0.0064 | 0.2579 |

smcure, while our method concludes that also age and treatment are significant. In particular, the probability of recurring melanoma is higher for the control group compared to the treatment group. This seems to be indeed the case if we look at the Kaplan Meier survival curves for the two groups in Figure 1. On the other hand, both methods agree that none of the covariates is significant for the latency.

To illustrate another advantage of the new approach, we also compute the maximum likelihood estimator with the smcure package for different choices of the latency model. We see in Table 9 that the estimators of the incidence component (and their significance) change depending on which variables are included in the latency. On the other hand, the new method does not suffer from this problem because it estimates the incidence independently of the latency.

7.2. Surveillance, Epidemiology and End Results (SEER) database

The SEER database collects cancer incidence data from population-based cancer registries in US. These data consist of patient demographic characteristics, primary tumor site, tumor morphology, stage at diagnosis, length of follow up and vital status. We select the database ‘Incidence - SEER 18 Regs Research Data’ and extract the melanoma cancer data for the county of San Francisco in California during the period 2004 – 2015. We consider only patients with stage at diagnosis: localized, regional and distant and exclude those with unknown or zero follow-up time and restrict the study to white people because of the very small number of cases from other races. The event time is death because of melanoma. This cohort consists of 1445 melanoma cases out of which 596 are female and 849 male. The age ranges from 11 to 101 years old, the follow-up from 1 to 155 months. For most of the patients the cancer has been diagnosed at early stage (localized), while for 101 of them the stage at diagnosis is ‘regional’ and only for 42 it is ‘distant’. We aim at evaluating how age, gender and stage at diagnosis affect the survival of melanoma patients in this cohort. The use of cure models is justified from the presence of a long plateau containing around 20% of the observations (see the Kaplan-Meier curve in Figure 2). Moreover, the Kaplan-Meier curves depending on gender and stage at diagnosis in Figure 2 confirm that gender and stage affect the cure rate.
Fig 2. Upper panel: Kaplan-Meier survival curves for SEER data. Left panel: group division based on gender, females (solid) and males (dotted). Right panel: group division based on cancer stage at diagnosis, localized (solid), regional (dashed) and distant (dotted).
the prediction error in the test set given by logistic/Cox model and the single-index/Cox model. Afterwards, we compute the test set of size 964 and 481 respectively. Using the training set, we estimate the incidence. More precisely, as in [2], we divide the data into a training set and a index mixture cure model proposed in [2] through the prediction error of the methods agree that all the considered covariates are significant for the incidence variable is equal to zero for females and one for males. We observe that both S
indicates the regional stage and S
2
is 98
98
53, whereas for the single-index model it is 156
156
0.53.

We checked the fit of the logistic model by comparing it with the single-index mixture cure model proposed in [2] through the prediction error of the logistic model performs better. The parameter estimates, standard errors and corresponding p-values for the \( \hat{\beta} \) weight for the \( j \)-th observation in the test set, computed based on the parameter estimates (and the link function for the single-index model) in the training set. More precisely, for the logistic/Cox model we have \( \hat{\pi}(X_{j}^{\text{test}}) = \phi(\hat{\gamma}_{n}, X_{j}^{\text{test}}) \) and \( \hat{W}_{j} = \Delta_{j}^{\text{test}} + (1 - \Delta_{j}^{\text{test}}) \frac{\hat{\pi}(X_{j}^{\text{test}}) \exp \left( -\hat{\Lambda}_{n}(Y_{j}^{\text{test}}) e^{\hat{\gamma}_{n} Z_{j}^{\text{test}}} \right)}{1 - \hat{\pi}(X_{j}^{\text{test}}) + \hat{\pi}(X_{j}^{\text{test}}) \exp \left( -\hat{\Lambda}_{n}(Y_{j}^{\text{test}}) e^{\hat{\gamma}_{n} Z_{j}^{\text{test}}} \right)} \), where \( \hat{\gamma}_{n}, \hat{\beta}_{n} \) and \( \hat{\Lambda}_{n} \) are the estimated parameters and the estimated hazard function in the training set. For the single-index/Cox model, the only difference is that \( \hat{\pi}(X_{j}^{\text{test}}) = \hat{g}_{n}(\hat{\gamma}_{n}, X_{j}^{\text{test}}) \) where \( \hat{g}_{n} \) is the estimated link function as in [2]. The weights \( W_{j} \) correspond to the conditional expectation of the cure status \( B \) given the observations. We find that the prediction error for the logistic model is 98.53, whereas for the single-index model it is 156.55. This means that the logistic model performs better.

The parameter estimates, standard errors and corresponding p-values for the Wald test using our method and the smcure package are given in Table 10. Standard errors are computed with 500 naive bootstrap samples. The covariate stage is classified using two dummy Bernoulli variables \( S_{1} \) and \( S_{2} \), where \( S_{1} = 1 \) indicates the regional stage and \( S_{2} = 1 \) indicates the distant stage. The gender variable is equal to zero for females and one for males. We observe that both methods agree that all the considered covariates are significant for the incidence

| Covariates | smcure package Estimates | SE | p-value | Our approach Estimates | SE | p-value |
|------------|--------------------------|----|---------|------------------------|----|---------|
| Intercept  | -4.2071                  | 0.3817 | 0       | -4.2436                | 0.3980 | 0       |
| Age        | 0.0304                   | 0.0122 | 0.0124  | 0.0328                 | 0.0172 | 0.0565  |
| Gender     | 1.1318                   | 0.4211 | 0.0072  | 1.2341                 | 0.4792 | 0.010   |
| \( S_{1} \) | 2.6738                   | 0.3702 | 5 \( 10^{-13} \) | 2.4474                 | 0.4247 | 8 \( 10^{-8} \) |
| \( S_{2} \) | 4.8763                   | 0.5067 | 8 \( 10^{-16} \) | 3.9426                 | 0.4536 | 0       |

| Covariates | smcure package Estimates | SE | p-value | Our approach Estimates | SE | p-value |
|------------|--------------------------|----|---------|------------------------|----|---------|
| Age        | -0.0139                  | 0.0098 | 0.1577  | -0.0143                | 0.0106 | 0.1756  |
| Gender     | -0.0549                  | 0.4065 | 0.8925  | -0.0871                | 0.3687 | 0.8131  |
| \( S_{1} \) | 0.5176                   | 0.3993 | 0.1949  | 0.6130                 | 0.3971 | 0.1226  |
| \( S_{2} \) | 1.8039                   | 0.4529 | 7 \( 10^{-5} \) | 1.8623                 | 0.5072 | 0.0002  |

Table 10: Results for the incidence (logistic component) and the latency (Cox PH component) from the SEER data.
(with age being a borderline case for our approach). For the latency, only being in the distant stage is found significant with both methods. Moreover, again the effects of all the covariates on the latency and incidence have the same direction for both methods.

8. Discussion

In this paper we proposed a new estimation procedure for the mixture cure model with a parametric form of the incidence (for example logistic) and any semiparametric model for the latency. We investigated more in detail the logistic/Cox model given its practical relevance. Instead of using an iterative algorithm for dealing with the unknown cure status, this method relies on a preliminary nonparametric estimator of the cure probabilities. We showed through simulations that the new approach improves upon the classical maximum likelihood estimator implemented in the package smcure, mainly for smaller sample sizes. For the latency, both methods behave similarly. Hence, it is of particular interest in situations in which the focus is on the estimation of cure probabilities. The real data application on the ECOG clinical trial also showed that the improvement in estimation can be meaningful in practice and help detecting significant effects.

The proposed method has the advantage of direct estimation of the incidence component, without relying on the latency, which makes it robust to latency model misspecification. On the contrary, the smcure estimator strongly depends on the choice of the variables for the latency and could be biased for a misspecified Cox model. Hence, for practical reason, confronting the estimators obtained with the two methods is valuable for confirming the results or obtaining new insights. From the theoretical point of view, unlike the standard maximum likelihood estimation, presmoothing allows us to obtain consistency and asymptotic normality without requiring the ‘unrealistic’ assumption that the distribution of uncured subjects has a positive mass at the end point of the support.

It might be argued that since the proposed method relies on smoothing, it is more complex and the results can be affected by the choice of the kernel function or the bandwidth. Our purpose was to show that the user doesn’t have to think about this because the standard choices proposed in this paper perform well in practice. In addition, since the final estimator is a parametric one and the kernel estimator is only a preliminary step of the procedure, the results would anyway be more stable with respect to these choices than in a nonparametric setting. The main challenge this method faces is extension to many continuous covariates for the incidence. We did not deeply investigate such situations since, in that case, multiple bandwidths have to be chosen, which can be more problematic and computationally intensive. However, our approach based on presmoothing allows to efficiently handle these situations if the estimator \( \hat{\pi} \) is constructed in a more adequate way. One possibility would be to construct the estimator assuming a single-index model for the latency, which is reasonable since the final goal is a
parametric estimator. With this approach one can avoid the choice of multiple bandwidths and perform the estimation as in the one dimensional case. However, this problem will be addressed by future research. In this regard, even though considering only one continuous covariate might seem restrictive in practice, the proposed procedure constitutes the basis for further developments of new estimators for general dimension scenarios that do not require multidimensional smoothing.

9. Appendix

9.1. Proof of Theorem 4

We obtain the asymptotic normality of $\hat{\Lambda}_n$, $\hat{\beta}_n$ following the proof of Theorem 3 in [18]. In order to work with a one-dimensional submodel, for $d$ in a neighbourhood of the origin, let $\hat{\Lambda}_n(s) = \sum_{i=1}^n \Delta_i I_{\{Y_i < \tau_0\}} (h_1(Y_i) + h'_2 Z_i)$

$$\sum_{i=1}^n \{\Delta_i + (1 - \Delta_i) I_{\{Y_i \leq \tau_0\}} g_i(Y_i, \hat{\Lambda}_n, \hat{\beta}_n, \hat{\gamma}_n)\}$$

$$\times \left\{e^{\beta' Z_i} \int_0^Y h_1(s) d\hat{\Lambda}_n(s) + e^{\beta' Z_i} \hat{\Lambda}_n(Y_i) h'_2 Z_i\right\},$$

where $g_j$ is defined in (17) and $\hat{\gamma}_n$ is the maximizer of (10). Let $\Upsilon_n = (\hat{\Lambda}_n, \hat{\beta}_n)$ and $\Upsilon_0 = (\Lambda_0, \beta_0)$. Furthermore, denote by $S$ the asymptotic version of $S_n$:

$$S(\Lambda, \beta)(h_1, h_2) = E \left[\Delta I_{\{Y < \tau_0\}} \{h_1(Y) + h'_2 Z\} - \{\Delta + (1 - \Delta) I_{\{Y \leq \tau_0\}} g(Y, \Lambda, \beta, \gamma_0)\}\right]$$

$$\times \left\{e^{\beta' Z} \int_0^Y h_1(s) d\Lambda(s) + e^{\beta' Z} \Lambda(Y) h'_2 Z\right\}. $$

We have $\hat{S}_n(\Upsilon_n) = 0$ and $S(\Upsilon_0) = 0$. The score function $S_n$ and $S$ are respectively a random and a deterministic map from $\Xi$ to $l^\infty(\mathcal{H}_m)$ (the space of bounded real-valued functions on $\mathcal{H}_m$), where

$$\Xi = \{\Lambda, \beta : \sup_{h \in \mathcal{H}_m} \left|\int_0^{\tau_0} h_1(s) d\Lambda(s) + h'_2 \beta \right| < \infty\}$$

and $\mathcal{H}_m = \{h \in \mathcal{H} : \|h\|_H \leq m\}$. Here $\|h\|_H = ||h_1||_v + \|h_2\|_{L_1}$, $\|h_2\|_{L_1} = \sum_{j=1}^q |h_{2,j}|$, $\|h_1\|_v = |h_1(0)| + V_0^{\tau_0}(h_1)$ and $V_0^{\tau_0}(h_1)$ denotes the total variation
of \( h_1 \) on \([0, \tau_0] \). This means that \( S_n \) is a random variable defined in the abstract probability space \((\Omega, \mathcal{F}, \mathbb{P})\) (where the random vector \((B, T_0, C, X, Z)\) is defined) with values in the space of bounded functions \( \Xi \to L^\infty(\mathcal{H}_m) \) with respect to the supremum norm. The latter one is a Banach space equipped with the Borel \( \sigma \)-field.

We need to show that conditions 1-4 of Theorem 4 in [18] (or Theorem 3.3.1 in [26]) are satisfied. The main difference of the function \( S \) from the one in [18] is that here \( \gamma = \gamma_0 \) fixed. We are only considering variation with respect to \( \beta \) and not \( \gamma \), so the components of \( h \) that correspond to \( \gamma \) are set to zero. However, conditions 2 and 3 of Theorem 4 in [18] for \( S \) can be shown in the same way as in [18]. Details about conditions 1 and 4 can be found in the online Supplementary Material.

9.2. Proof of Theorem 5

The logistic model for the cure probability obviously satisfies assumptions (AN1) and (AN3). Let \( \Pi \) be the space of continuously differentiable functions \( f \) from \( \mathcal{X} \) to \([0, 1]\) such that

\[
\sup_{x_1, x_2 \in \mathcal{X}} \frac{|f'(x_1) - f'(x_2)|}{|x_1 - x_2|^{\xi}} \leq M
\]

for some \( M > 0 \) and \( \xi \in (0, 1] \). If such space is equipped with the supremum norm, the covering numbers satisfy

\[
\log N(\epsilon, \Pi, \| \cdot \|_\infty) \leq K \frac{1}{\epsilon^{1/(1+\xi)}}
\]

for some constant \( K > 0 \) independent of \( \epsilon \) (see Theorem 2.7.1 in [26]). Obviously, for \( \epsilon > 1 \), \( \log N(\epsilon, \Pi, \| \cdot \|_\infty) = 0 \). Hence, assumption (AN2) is satisfied. It remains to check (AN4). Recall that the estimator of the cure probability \( \hat{\pi}(x) \) is the value at time \( \tau_0 \) of the Beran estimator \( \hat{S}(t|x) \), while \( \pi_0(x) = S(\tau_0|x) \). Moreover, by assumption (4), we have \( \inf_x H((\tau_0, \infty)|x) > 0 \). From Proposition 4.1 and 4.2 in [27] it follows that

\[
\sup_x |\hat{\pi}(x) - \pi_0(x)| = O\left((nb)^{-1/2}(\log b^{-1})^{1/2}\right) \quad a.s.,
\]

\[
\sup_x |\hat{\pi'}(x) - \pi'_0(x)| = O\left((nb^3)^{-1/2}(\log b^{-1})^{1/2}\right) \quad a.s.
\]

and

\[
\sup_{x_1, x_2 \in \mathcal{X}} \frac{|\hat{\pi'}(x_1) - \pi'_0(x_1) - \hat{\pi'}(x_2) + \pi'_0(x_2)|}{|x_1 - x_2|^{\xi/2}} = O\left((nb^3+\xi)^{-1/2}(\log b^{-1})^{1/2}\right) \quad a.s.,
\]

where \( \xi \) is as in assumption (C1). Since \( \pi_0 \) is twice continuously differentiable, from assumption (C1) it follows that \( \hat{\pi} \) satisfies (i,ii) of (AN4). From Theorem
3.2 of [10] (with \( T = \tau_0 \)) we have \( \hat{\pi}(x) - \pi_0(x) = \frac{1}{n} \sum_{i=1}^{n} A_i(x) + R_n(x) \), where

\[
A_i(x) = -\frac{1 - \phi(\gamma_0, x)}{f_X(x)} \frac{1}{b} \left( x - X_i \right) - \left\{ \frac{\Delta_i \mathbf{1}_{\{Y_i \leq \tau_0\}}}{H([Y_i, \infty)|x]} - \int_{0}^{Y_i \wedge \tau_0} \frac{H_1(ds|x)}{H^2([s, \infty)|x]} \right\}
\]

and \( \sup_x |R_n(x)| = O\left((nb)^{-3/4}(\log n)^{3/4}\right) \) a.s.. Hence

\[
\mathbb{E}^* \left[ (\hat{\pi}(X) - \pi_0(X)) \left( \frac{1}{\phi(\gamma_0, X)} + \frac{1}{1 - \phi(\gamma_0, X)} \right) \nabla_{\gamma} \phi(\gamma, X) \right] = \frac{1}{n} \sum_{i=1}^{n} \mathbb{E}^* \left[ A_i(x) \left( \frac{1}{\phi(\gamma_0, X)} + \frac{1}{1 - \phi(\gamma_0, X)} \right) \nabla_{\gamma} \phi(\gamma, X) \right] + \mathbb{E}^* \left[ R_n(X) \left( \frac{1}{\phi(\gamma_0, X)} + \frac{1}{1 - \phi(\gamma_0, X)} \right) \nabla_{\gamma} \phi(\gamma, X) \right].
\]

The second term on the right hand side of the previous display is bounded by \( c \sup_x |R_n(x)| = o(n^{-1/2}) \) for some \( c > 0 \) because of assumptions (C1) and (AN1). Furthermore, from (AN1) and (AC4) and a Taylor expansion, it follows that the generic element of the sum in the first term is equal to

\[
- \int x b \left\{ \frac{\Delta_i \mathbf{1}_{\{Y_i \leq \tau_0\}}}{H([Y_i, \infty)|x]} - \int_{0}^{Y_i \wedge \tau_0} \frac{H_1(ds|x)}{H^2([s, \infty)|x]} \right\} \frac{1}{\phi(\gamma_0, x)} \nabla_{\gamma} \phi(\gamma_0, x) dx
\]

\[
= - \left\{ \frac{\Delta_i \mathbf{1}_{\{Y_i \leq \tau_0\}}}{H([Y_i, \infty)|X_i]} - \int_{0}^{Y_i \wedge \tau_0} \frac{H_1(ds|X_i)}{H^2([s, \infty)|X_i]} \right\} \frac{1}{\phi(\gamma_0, X_i)} \nabla_{\gamma} \phi(\gamma_0, X_i) + O(b^2).
\]

Since because of (C1) we have \( O(b^2) = o(n^{-1/2}) \), (AN4-iii) holds with

\[
\Psi(Y, \Delta, X) = - \left\{ \frac{\Delta_i \mathbf{1}_{\{Y_i \leq \tau_0\}}}{H([Y, \infty)|X]} - \int_{0}^{Y \wedge \tau_0} \frac{H_1(ds|X)}{H^2([s, \infty)|X]} \right\} \frac{1}{\phi(\gamma_0, X)} \nabla_{\gamma} \phi(\gamma_0, X).
\]

\( \square \)

Acknowledgements

I. Van Keilegom and E. Musta acknowledge financial support from the European Research Council (2016-2021, Horizon 2020) and grant agreement 694409. For the simulations we used the infrastructure of the Flemish Supercomputer Center (VSC).

Supporting information may be found in the online appendix. It contains the proofs of Theorems 1, 2 and 3 in Section 5 and additional simulation results.
References

[1] AERTS, M., HENS, N. and SIMONOFF, J. S. (2010). Model selection in regression based on pre-smoothing. *J. Appl. Stat.* 37 1455–1472.

[2] AMICO, M., VAN KEILEGOM, I. and LEGRAND, C. (2019). The single-index/Cox mixture cure model. *Biometrics* 75 452–462.

[3] ANDERSEN, P. K. and GILL, R. D. (1982). Cox’s Regression Model for Counting Processes: A Large Sample Study. *Ann. Stat.* 10 1100–1120.

[4] BERKSON, J. and GAGE, R. P. (1952). Survival curve for cancer patients following treatment. *J. Am. Stat. Assoc.* 47 501–515.

[5] BOAG, J. W. (1949). Maximum likelihood estimates of the proportion of patients cured by cancer therapy. *J. R. Stat. Soc. B* 11 15–53.

[6] BURKE, K. and PATILEA, V. (2020). A likelihood-based approach for cure regression models. *TEST* 1–20.

[7] CAI, C., ZOU, Y., PENG, Y. and ZHANG, J. (2012). smcure: An R-Package for estimating semiparametric mixture cure models. *Comput. Meth. Prog. Bio.* 108 1255–1260.

[8] CHEN, X., LINTON, O. and VAN KEILEGOM, I. (2003). Estimation of semiparametric models when the criterion function is not smooth. *Econometrica* 71 1591–1608.

[9] CRISTOBAL, J. C., ROCA, P. F. and MANTEIGA, W. G. (1987). A class of linear regression parameter estimators constructed by nonparametric estimation. *Ann. Stat.* 603–609.

[10] DU, Y. and AKRITAS, M. (2002). Uniform strong representation of the conditional Kaplan-Meier process. *Math. Methods Stat.* 11 152–182.

[11] FAREWELL, V. T. (1982). The use of mixture models for the analysis of survival data with long-term survivors. *Biometrics* 1041–1046.

[12] FERRATY, F., GONZÁLEZ-MANTEIGA, W., MARTÍNEZ-CALVO, A. and VIEU, P. (2012). Presmoothing in functional linear regression. *Stat. Sin.* 69–94.

[13] FLEMING, T. R. and HARRINGTON, D. P. (2011). *Counting Processes and Survival Analysis* 169. John Wiley & Sons.

[14] HAN, X. (2017). Statistical Methods for Analysis of Genetic and Survival Data with Latent Heterogeneity, PhD thesis, New York University.

[15] KUK, A. Y. and CHEN, C.-H. (1992). A mixture model combining logistic regression with proportional hazards regression. *Biometrika* 79 531–541.

[16] LEE, T. E., FISHER, D. O., BLOMBERG, S. P. and WINTLE, B. A. (2017). Extinct or still out there? Disentangling influences on extinction and rediscovery helps to clarify the fate of species on the edge. *Global Change Biol.* 23 621–634.

[17] LI, C.-S. and TAYLOR, J. M. (2002). A semi-parametric accelerated failure time cure model. *Stat. Med.* 21 3235–3247.

[18] LU, W. (2008). Maximum likelihood estimation in the proportional hazards cure model. *Ann. I. Stat. Math.* 60 545–574.

[19] MÜLLER, U. U. and VAN KEILEGOM, I. (2019). Goodness-of-fit tests for the cure rate in a mixture cure model. *Biometrika* 106 211–227.
[20] Patilea, V. and Van Keilegom, I. (2020). A general approach for cure models in survival analysis. *Annals of Statistics* **48** 2323–2346.
[21] Peng, Y. and Dear, K. B. (2000). A nonparametric mixture model for cure rate estimation. *Biometrics* **56** 237–243.
[22] Sposto, R. (2002). Cure model analysis in cancer: an application to data from the Children’s Cancer Group. *Statistics in medicine* **21** 293–312.
[23] Stringer, S., Denys, D., Kahn, R. S. and Derks, E. M. (2016). What cure models can teach us about genome-wide survival analysis. *Behav. Genet.* **46** 269–280.
[24] Sy, J. P. and Taylor, J. M. (2000). Estimation in a Cox proportional hazards cure model. *Biometrics* **56** 227–236.
[25] Taylor, J. M. (1995). Semi-parametric estimation in failure time mixture models. *Biometrics* 899–907.
[26] Van der Vaart, A. W. and Wellner, J. A. (1996). *Weak Convergence and Empirical Processes, with Applications to Statistics*. Springer Series in Statistics. Springer-Verlag, New York.
[27] Van Keilegom, I. and Akritas, M. G. (1999). Transfer of tail information in censored regression models. *Ann. Stat.* **27** 1745–1784.
[28] Wellner, J. A. (1978). Limit theorems for the ratio of the empirical distribution function to the true distribution function. *Z. Wahrsch. Verw. Gebiete* **45** 73–88.
[29] Wycinka, E. and Jurkiewicz, T. (2017). Mixture cure models in prediction of time to default: comparison with logit and Cox models. In *Contemporary Trends and Challenges in Finance* 221–231. Springer.
[30] Xu, J. and Peng, Y. (2014). Nonparametric cure rate estimation with covariates. *Can. J. Stat.* **42** 1–17.
[31] Yamaguchi, K. (1992). Accelerated failure-time regression models with a regression model of surviving fraction: an application to the analysis of “permanent employment” in Japan. *J. Amer. Stat. Assoc.* **87** 284–292.
[32] Zhang, J. and Peng, Y. (2007). A new estimation method for the semi-parametric accelerated failure time mixture cure model. *Stat. Med.* **26** 3157–3171.
A presmoothing approach for estimation in semiparametric mixture cure models

Supplementary Material

Eni Musta*, Valentin Patilea† and Ingrid Van Keilegom∗

∗KU Leuven, †Ensai

This supplement is organized as follows. Appendix A contains technical lemmas and proofs. Appendix B collects additional simulation results, that were omitted from the main paper due to page limits.

Appendix A: Technical lemmas and proofs

Lemma 1. Let $B$ be a Bernoulli random variable, $T_0$ a nonnegative random variable and let $T = T_0$ if $B = 1$ and $T = \infty$ if $B = 0$. Let $X$ and $Z$ be two real-valued random vectors. Then

$T_0 \perp (C, X) \mid Z \quad \text{and} \quad B \perp (C, T_0, Z) \mid X \quad \Rightarrow \quad T \perp C \mid (X, Z)$

Proof. This lemma is similar to Lemma 8.1 in [2]. We provide the proof for completeness. By elementary properties of conditional independence we have

$B \perp (C, T_0, Z) \mid X \quad \iff \quad B \perp C \mid (X, Z, T_0) \quad \text{and} \quad B \perp T_0 \mid (X, Z) \quad \text{and} \quad B \perp Z \mid X$

and

$T_0 \perp (C, X) \mid Z \quad \iff \quad T_0 \perp C \mid (X, Z) \quad \text{and} \quad T_0 \perp X \mid Z$.

Then,

$C \perp B \mid (X, Z, T_0) \quad \text{and} \quad C \perp T_0 \mid (X, Z) \quad \iff \quad (B, T_0) \perp C \mid (X, Z)$

The result follows from the fact that $T$ is completely determined by $B$ and $T_0$.

A.1. Identifiability with restricted survival times

For any $0 < \tau^* \leq \tau_0$, let

$T_0^* = \min(T_0, \tau^*), \quad T^* = BT_0^* + (1 - B)\infty \quad \text{and} \quad C^* = \min(C, \tau^*)$.

Moreover, let

$Y^* = \min(T^*, C^*) \quad \text{and} \quad \Delta^* = I\{T^* \leq C^*\}$. 

1
A first aspect to study is the identifiability of the true values of the parameter when \((Y, \Delta)\) is replaced by \((Y^*, \Delta^*)\). Here, identifiability means that the true values \(\beta_0\) and \(\Lambda_0\) of the parameters maximize the expectation of the criterion maximized to obtain the estimators. This issue is addressed in Lemma 2. Let us introduce some additional notation: for any \(0 < \tau^* \leq \tau_0\) and \(\Lambda \in \mathcal{H}\), \(\Lambda_{|\tau^*}\) is defined as

\[
\Lambda_{|\tau^*}(t) = \Lambda(t), \quad \forall t \in [0, \tau^*) \quad \text{and} \quad \Delta\Lambda_{|\tau^*}(\tau^*) = \Lambda_{|\tau^*}(\{\tau^*\}) = 1. \tag{A1}
\]

The dominating measure for the model of \(T_0\) changes with such a stopped cumulative hazard measure to allow for a positive mass at \(\tau^*\). Then, \(\ell\) defined in (13) becomes

\[
\ell(y, d, x, z; \beta, \Lambda_{|\tau^*}, \gamma) = \mathbb{1}_{\{y < \tau^*\}} \left[ d \log f_u(y|z; \beta, \Lambda) + (1 - d) \log \left\{ 1 - \phi(\gamma, x) + \phi(\gamma, x)S_u(y|z; \beta, \Lambda) \right\} \right] + \mathbb{1}_{\{y \geq \tau^*\}} \left[ d \log S_u(\tau^*|z; \beta, \Lambda) + (1 - d) \log \left\{ 1 - \phi(\gamma, x) \right\} \right]. \tag{A2}
\]

**Lemma 2.** Let \(0 < \tau^* \leq \tau_0\). Assume that for any \(\tilde{\beta} \in B\) and \(\tilde{\Lambda} \in \mathcal{H}\),

\[
S_u(t|z; \tilde{\beta}, \tilde{\Lambda}_{|\tau^*}) = S_u(t|z; \beta_0, \Lambda_{0|\tau^*}), \quad \forall t \in [0, \tau^*) \quad \implies \quad \tilde{\beta} = \beta_0 \quad \text{and} \quad \tilde{\Lambda}_{|\tau^*} = \Lambda_{0|\tau^*}. \tag{A3}
\]

Then \((\beta_0, \Lambda_{0|\tau^*})\) is the unique solution of

\[
\max_{\beta \in B, \Lambda \in \mathcal{H}} \mathbb{E} \left[ \ell(Y^*, \Delta^*, X, Z; \beta, \Lambda_{|\tau^*}, \gamma_0) \right]. \tag{A4}
\]

Condition (A3) is a minimal requirement of identification of the true value of the parameters in the model for the uncured subjects if the variable \(T_0 \wedge C\) was observed and only the events in a subset of the support of \(T_0\) are considered. In the Cox PH model (A3) is guaranteed by the requirement that \(Var(Z)\) has full rank.

**Proof of Lemma 2.** First, let

\[
H_k([0, t]|x, z) = \mathbb{P}(Y \leq t, \Delta = k|X = x, Z = z), \quad k \in \{0, 1\}, \quad t \in [0, \infty),
\]

and let \(H_k(dt|x, z)\) be the associated conditional measures. These conditional measures characterize the distribution of \((Y, \Delta)\) given \(X = x\) and \(Z = z\). By the model and independence assumptions, for any \(t \geq 0\),

\[
H_1(dt|x, z) = \phi(\gamma_0, x)F_C([t, \infty)|x, z)f_u(t|z; \beta_0, \Lambda_0)dt, \tag{A5}
\]

and

\[
H_0(dt|x, z) = \{1 - \phi(\gamma_0, x) + \phi(\gamma_0, x)S_u(t|z; \beta_0, \Lambda_0)\}F_C(dt|x, z). \tag{A6}
\]

Following an usual notation abuse, herein we treat \(dt\) not just as the length of a small interval but also as the name of the interval itself. Note that up to additive terms which do not depend on the parameters \(\beta, \Lambda,\)

\((y, d) \mapsto d \log f_u(y|z; \beta_0, \Lambda_0) + (1 - d) \log \{1 - \phi(\gamma_0, x) + \phi(\gamma_0, x)S_u(y|z; \beta_0, \Lambda_0)\},\)

\((y, d) \mapsto d \log f_u(y|z; \beta_0, \Lambda_0) + (1 - d) \log \{1 - \phi(\gamma_0, x) + \phi(\gamma_0, x)S_u(y|z; \beta_0, \Lambda_0)\},\)
is the conditional log-density of \((Y, \Delta)\) given \(X = x\) and \(Z = z\). From this and Kullback information inequality one can deduce that the expectation of \(\ell\) defined in (13) is maximized by \(\beta_0, \Lambda_0\) and \(\gamma_0\).

Let \(0 < \tau^* \leq \tau_0\). Note that

\[
H_1([\tau^*, \tau_0]|x, z) = H_1([\tau^*, \infty]|x, z) = \phi(\gamma_0, x) \int_{[\tau^*, \tau_0]} F_C([t, \infty]|x, z)f_u(t|z; \beta_0, \Lambda_0)dt,
\]

and

\[
H_0([\tau^*, \infty]|x, z) = \phi(\gamma_0, x) \int_{[\tau^*, \tau_0]} S_u(t|z; \beta_0, \Lambda_0)F_C(dt|x, z)
+ \{1 - \phi(\gamma_0, x)\}F_C([\tau^*, \infty]|x, z).
\]

Moreover,

\[
d(x, z; \tau^*) := \phi(\gamma_0, x) \int_{[\tau^*, \tau_0]} F_C([t, \infty]|x, z)f_u(t|z; \beta_0, \Lambda_0)dt
+ \phi(\gamma_0, x) \int_{[\tau^*, \tau_0]} S_u(t|z; \beta_0, \Lambda_0)F_C(dt|x, z)
= \phi(\gamma_0, x)F_C([\tau^*, \infty]|x, z)S_u(\tau^*|z; \beta_0, \Lambda_0)
= \mathbb{P}(T_0 \wedge C \geq \tau^*, B = 1).
\]

In the limit case of no cure, \(d(x, z; \tau^*) = H_1([\tau^*, \infty]|x, z) + H_0([\tau^*, \infty]|x, z)\). By construction we have \(Y^* = \min(Y, \tau^*)\), and

\[
\mathbb{P}(Y^* = \tau^*, \Delta^* = 1|X = x, Z = z) = d(x, z; \tau^*).
\]

Next, let

\[
H_k^*(\{0, t]|x, z) = \mathbb{P}(Y^* \leq t, \Delta^* = k|X = x, Z = z), \quad k \in \{0, 1\}, \quad t \in [0, \infty),
\]

and let \(H_k^*(dt|x, z)\) be the associated conditional measures. This means for any \(t \in [0, \tau^*)\),

\[
H_k^*(dt|x, z) = H_1^*(dt|x, z) \quad \text{and} \quad H_k^*(dt|x, z) = H_0^*(dt|x, z).
\]

Moreover,

\[
H_1^*(\{\tau^*\}|x, z) = H_1^*(\{\tau^*, \infty\}|x, z) = d(x, z; \tau^*),
\]

and

\[
H_0^*(\{\tau^*\}|x, z) = H_0^*(\{\tau^*, \tau_0\}|x, z) = \{1 - \phi(\gamma_0, x)\}F_C([\tau^*, \infty]|x, z).
\]

Now, according to the inversion formulae of [6], without any reference to a model, one can solve the set of equations

\[
\begin{align*}
H_1^*(dt|x, z) &= \phi^*(x, z)F_C^*(\{t, \infty\}|x, z)F_u^*(dt|x, z), \\
H_0^*(dt|x, z) &= \{1 - \phi^*(x, z)\} + \phi^*(x, z)S_u^*(t|x, z)\}F_C^*(dt|x, z),
\end{align*}
\]  

(A7)
where \( F_u^* = 1 - S_u^* \). Solving (A7) for \( F_C^*, S_u^* \) and \( \phi^* \), the functional \( S_u^* \) is a proper survival function which puts mass only on sets where \( H_1 \) does. Note that solving the similar system with \( H_1, H_0 \) instead of \( H_1^0, H_0^0 \), one gets the true \( F_C, S_u \) and \( \phi \). If \( \Lambda^*_C \) denotes the cumulative hazard function associated to the solution \( F_C^* \), then

\[
\Lambda^*_C(dt|x, z) = \frac{H_0^*(dt|x, z)}{H_1^*((t, \infty)|x, z) + H_0^*((t, \infty)|x, z)}, \quad t \geq 0,
\]

and thus, by construction, we have \( F_C(dt|x, z) = F_C^*(dt|x, z) \) on \([0, \tau^*)\), for any \( x, z \). Then, by (A6) and the second equation in (A7) we deduce

\[
\phi^*(x, z)F_u^*(t|x, z) = \phi(\gamma_0, x)F_u(t|z; \beta_0, \Lambda_0), \quad \forall t \in [0, \tau^*), \forall x, z.
\]

Next, taking into account that \( S_u^*(t|x, z) = 0 \), \( \forall t \geq \tau^* \), \( \forall x, z \), and integrating the second equation (A7) on \([\tau^*, \infty)\), we obtain

\[
\{1 - \phi^*(x, z)\}F_u^*([\tau^*, \infty)|x, z) = H_0^*((\{\tau^*\}|x, z) = \{1 - \phi(x, z)\}F_C([\tau^*, \infty)|x, z).
\]

Since \( F_C^*([0, \tau^*)|x, z) = F_C([0, \tau^*)|x, z) \), we deduce that \( \phi^*(x, z) = \phi(\gamma_0, x) \) and thus

\[
F_u^*(t|x, z) = F_u(t|z; \beta_0, \Lambda_0) = F_u(t|z; \beta_0, \Lambda_0|_{\tau^*}), \quad \forall t \in [0, \tau^*), \forall x, z. \quad (A8)
\]

The second equality in the last display is by the construction of the survival function from the cumulative hazard function: only the values of \( \Lambda_0 \) on \([0, t]\) contribute to obtain \( F_u(t|z; \beta_0, \Lambda_0) \). Since the inversion formula necessarily yields \( F_u^*([0, \tau^*)|x, z) \equiv 1 \), we deduce

\[
F_u^*([\tau^*]|x, z) = S_u(\tau^*|z; \beta_0, \Lambda_0) = S_u(\tau^*|z; \beta_0, \Lambda_0|_{\tau^*}). \quad (A9)
\]

Finally, we can write

\[
E \left[ \ell(Y^*, \Delta^*, X, Z; \beta, \Lambda_{[\tau^*]}, \gamma_0) \right]
= \iiint \log \ell(t, 1, x, z; \beta, \Lambda_{[\tau^*]}, \gamma_0)H_1^*(dt|x, z)G(dx, dz)
+ \iiint \log \ell(t, 0, x, z; \beta, \Lambda_{[\tau^*]}, \gamma_0)H_0^*(dt|x, z)G(dx, dz).
\]

To obtain the identifiability result it remains to apply Kullback information inequality. More precisely, it suffices to notice that here, up to additive terms which do not depend on the parameters, \( \ell \) defined in (A2) considered with \( \beta_0, \Lambda_0|_{\tau^*} \) corresponds to the log-density of the conditional law of \((Y^*, \Delta^*)\) given \(X = x\) and \(Z = z\). (Note that the dominated measure changed as we introduce jumps at \( \tau^* \).) This follows from (A8) and (A9). Thus \( \beta_0, \Lambda_0|_{\tau^*} \) is solution of the problem (A4). The unicity of the solution is guaranteed by (A3). \( \Box \)
A.2. Consistency

Proof of Theorem 1. We follow the idea of [7]. Since we are interested in almost sure convergence, we work with fixed realizations of the data, \( \omega \) that will lie in a set of probability one. Let \( \Omega \) be the abstract probability space where the random vector \((B, T_0, C, X, Z)\) is defined (for example we can take \( \Omega = \{0, 1\} \times [0, \tau_0] \times X \times Z \) and \((B, T_0, C, X, Z)(\omega) = \omega \). Let \( N \subset \Omega \) be a set of probability one \( \mathbb{P}(N) = 1 \) and fix \( \omega \in N \). We will show that each subsequence \( \hat{\gamma}_{mk} \) has a subsequence that converges to \( \gamma_0 \). As a bounded sequence in \( \mathbb{R}^p \), \( \hat{\gamma}_{mk} \) has a convergent subsequence \( \hat{\gamma}_{mk} \to \gamma^* \). It suffices to show that \( \gamma^* = \gamma_0 \). Since \( \hat{\gamma}_{mk} \) maximizes \( \log \hat{L}_{mk,1} \), we have

\[
0 \leq \frac{1}{m_k} \log \hat{L}_{mk,1}(\hat{\gamma}_{mk}) - \frac{1}{m_k} \log \hat{L}_{mk,1}(\gamma_0)
\]

\[
= \frac{1}{m_k} \sum_{i=1}^{m_k} \left\{ \left[ 1 - \hat{\pi}(X_i) \right] \log \frac{\phi(\hat{\gamma}_{mk}, X_i)}{\phi(\gamma_0, X_i)} + \hat{\pi}(X_i) \log \frac{1 - \phi(\hat{\gamma}_{mk}, X_i)}{1 - \phi(\gamma_0, X_i)} \right\}
\]

\[
= \frac{1}{m_k} \sum_{i=1}^{m_k} \left\{ \left[ 1 - \pi_0(X_i) \right] \log \frac{\phi(\gamma^*, X_i)}{\phi(\gamma_0, X_i)} + \pi_0(X_i) \log \frac{1 - \phi(\gamma^*, X_i)}{1 - \phi(\gamma_0, X_i)} \right\} + o(1)
\]

(A10)

if \( N \subset \{ \omega : \sup_{x} |\hat{\pi}(x) - \pi_0(x)| \to 0 \} \). Note that the remainder term \( o(1) \) in the previous display depends on \( \omega \) and converges to zero as \( \hat{\pi} \) converges to \( \pi_0 \). Next we will show that, for an appropriate choice of \( N \), the first term converges to

\[
\mathbb{E} \left\{ \left[ 1 - \pi_0(X) \right] \log \frac{\phi(\gamma^*, X)}{\phi(\gamma_0, X)} + \pi_0(X) \log \frac{1 - \phi(\gamma^*, X)}{1 - \phi(\gamma_0, X)} \right\}
\]

(A11)

where the expectation is taken with respect to \( X \) and \( \gamma^* \in \mathbb{R}^p \) (for a fixed \( \omega \)). Since here we are dealing with a simple parametric model, this convergence follows easily from the uniform law of large numbers. However, we follow a longer argument to explain the idea that will be used also in the proof of Theorem 2 (where the model is semiparametric). It is obvious, by the law of large numbers, that

\[
\frac{1}{m_k} \sum_{i=1}^{m_k} \left\{ \left[ 1 - \pi_0(X_i) \right] \log \phi(\gamma_0, X_i) + \pi_0(X_i) \log (1 - \phi(\gamma_0, X_i)) \right\}
\]

\[
\to \mathbb{E} \left\{ \left[ 1 - \pi_0(X) \right] \log \phi(\gamma_0, X) + \pi_0(X) \log (1 - \phi(\gamma_0, X)) \right\} \text{ a.s.}
\]

and, at first sight it seems that the same holds when \( \gamma_0 \) is replaced by \( \gamma^* \). However, the proof is more delicate because \( \gamma^* \) depends on \( \omega \) and thus also the event of probability one where the strong law of large numbers holds for this average. To avoid this we consider a countable dense subset of \( G \), \( \{ \hat{\gamma}_l \}_{l \geq 1} \) (for example the subset for which all components of \( \gamma \) are rational numbers). Now,
consider the countable collection of the probability one sets \( \{N_i\}_{i \geq 1} \) where
\[
\frac{1}{m_k} \sum_{i=1}^{m_k} \left\{ (1 - \pi_0(X_i)) \log \phi(\tilde{\gamma}_i, X_i) + \pi_0(X_i) \log (1 - \phi(\tilde{\gamma}_i, X_i)) \right\}
\to E \left\{ (1 - \pi_0(X)) \log \phi(\tilde{\gamma}_i, X) + \pi_0(x) \log (1 - \phi(\tilde{\gamma}_i, X)) \right\} \quad \forall l \geq 1.
\]

If \( N \subseteq (\cap_{i \geq 1} N_i) \), we can write
\[
\frac{1}{m_k} \sum_{i=1}^{m_k} \left\{ (1 - \pi_0(X_i)) \log \phi(\gamma^*, X_i) + \pi_0(X_i) \log (1 - \phi(\gamma^*, X_i)) \right\}
- E \left\{ (1 - \pi_0(X)) \log \phi(\gamma^*, X) + \pi_0(x) \log (1 - \phi(\gamma^*, X)) \right\}
\leq \left| \frac{1}{m_k} \sum_{i=1}^{m_k} \left\{ (1 - \pi_0(X_i)) \log \frac{\phi(\gamma^*, X_i)}{\phi(\tilde{\gamma}_i, X_i)} + \pi_0(X_i) \log \frac{1 - \phi(\gamma^*, X_i)}{1 - \phi(\tilde{\gamma}_i, X_i)} \right\} \right|
+ \left| \frac{1}{m_k} \sum_{i=1}^{m_k} \left\{ (1 - \pi_0(X_i)) \log \phi(\tilde{\gamma}_i, X_i) + \pi_0(X_i) \log (1 - \phi(\tilde{\gamma}_i, X_i)) \right\} \right|
- E \left\{ (1 - \pi_0(X)) \log \phi(\tilde{\gamma}_i, X) + \pi_0(x) \log (1 - \phi(\tilde{\gamma}_i, X)) \right\}
+ \left| E \left\{ (1 - \pi_0(X)) \log \frac{\phi(\gamma^*, X)}{\phi(\tilde{\gamma}_i, X)} + \pi_0(x) \log \frac{1 - \phi(\gamma^*, X)}{1 - \phi(\tilde{\gamma}_i, X)} \right\} \right|.
\]

Since \( \tilde{\gamma}_i \) can be taken arbitrarily close to \( \gamma^* \), by properties of \( \phi \) in assumptions (AC3)-(AC4), it can be easily derived that, for an appropriate choice of \( \tilde{\gamma}_i \), the first and the third term on the right hand side in the previous equation converge to zero. Moreover, the second term also converges to zero in the set of probability one that we are considering. As a result, we can conclude that
\[
0 \leq \frac{\log \hat{L}_{m_k,1}(\gamma_{m_k}) - \log \hat{L}_{m_k,1}(\gamma_0)}{m_k}
= E \left\{ (1 - \pi_0(X)) \log \frac{\phi(\gamma^*, X)}{\phi(\gamma_0, X)} + \pi_0(x) \log \frac{1 - \phi(\gamma^*, X)}{1 - \phi(\gamma_0, X)} \right\} + o(1)
\]

For each \( x \in X \), consider the function
\[
g_x(z) = \phi(\gamma_0, x) \log \frac{z}{\phi(\gamma_0, x)} + (1 - \phi(\gamma_0, x)) \log \frac{1 - z}{1 - \phi(\gamma_0, x)}, \quad z \in (0, 1).
\]
It is easy to check that \( g_x(z) \leq 0 \) and the equality holds only if \( z = \phi(\gamma_0, x) \). Hence, the expectation in (A11) is smaller or equal to zero. Due to the inequality in (A10), it must be equal to zero, which means that \( \phi(\gamma^*, X) = \phi(\gamma_0, X) \). By the identifiability assumption (5), this is possible only if \( \gamma^* = \gamma_0 \).

\[\Box\]

**Lemma 3.** Assume (AC2),(AC5) hold and \( \tau^* \) is such that (20) is satisfied. Then \( \sup_n A_n(\tau^*) < \infty \) almost surely.
Proof. By definition
\[
\hat{\Lambda}_n(\tau^*) = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i 1\{Y_i < \tau^*\}}{\sum_{j=1}^{n} \Delta_j 1\{Y_i < \tau^*_j\} \exp(\hat{\beta}_n^t Z_j) \left\{ \Delta_j + (1 - \Delta_j)g_j(Y_j, \hat{\Lambda}_n, \hat{\beta}_n, \hat{\gamma}_n) \right\}}.
\]

From assumptions (AC2) and (AC5) we have
\[
\frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i 1\{r^*_i \leq Y_i \leq \tau^*_i\} \exp(\hat{\beta}_n^t Z_i) \left\{ \Delta_j + (1 - \Delta_j)g_j(Y_j, \hat{\Lambda}_n, \hat{\beta}_n, \hat{\gamma}_n) \right\}}{\sum_{j=1}^{n} \Delta_j 1\{r^*_i \leq Y_i \leq \tau^*_i\} \exp(\hat{\beta}_n^t Z_j)} \geq \frac{1}{n} \sum_{i=1}^{n} \Delta_j 1\{r^*_i \leq Y_i \leq \tau^*_i\} \exp(\hat{\beta}_n^t Z_j)
\]
for some \(c > 0\). Since \(\frac{1}{n} \sum_{i=1}^{n} \Delta_j 1\{r^*_i \leq Y_i \leq \tau^*_i\} \xrightarrow{a.s.} P \{Y \geq \tau^*, \Delta = 1\} > 0\), it follows that \(\frac{1}{n} \sum_{i=1}^{n} \Delta_j 1\{r^*_i \leq Y_i \leq \tau^*_i\}\) is bounded from below away from zero almost everywhere. As a result
\[
\sup_n \hat{\Lambda}_n(\tau^*) \leq \sup_n \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i 1\{Y_i < \tau^*\}}{\sum_{j=1}^{n} \Delta_j 1\{Y_i < \tau^*_j\} \exp(\hat{\beta}_n^t Z_j) \left\{ \Delta_j + (1 - \Delta_j)g_j(Y_j, \hat{\Lambda}_n, \hat{\beta}_n, \hat{\gamma}_n) \right\}} \leq \sup_n \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i 1\{Y_i < \tau^*_i\}}{\sum_{j=1}^{n} \Delta_j 1\{r^*_i \leq Y_i \leq \tau^*_i\}} \leq \frac{1}{c} \left( \inf_n \frac{1}{n} \sum_{i=1}^{n} \Delta_j 1\{r^*_i \leq Y_i \leq \tau^*_i\} \right)^{-1}
\]
is bounded almost surely. Note that, if (19) is satisfied, then we can take \(\tau^* = \tau_0\).

**Proof of Theorem 2.** Let \(0 < \tau^* \leq \tau_0\) and
\[
\hat{\ell}_n(\beta, \Lambda_{1|\tau^*}, \hat{\gamma}_n) = \frac{1}{n} \sum_{i=1}^{n} \ell(Y_i^*, \Lambda_{1|\tau^*}, X_i, Z_i; \beta, \Lambda_{1|\tau^*}, \hat{\gamma}_n),
\]
with \(\ell\) defined in (A2). If we consider the Cox PH model for the conditional law of \(T_0\), then
\[
\hat{\ell}_n(\beta, \Lambda_{1|\tau^*}, \hat{\gamma}_n) = \frac{1}{n} \sum_{i=1}^{n} \Delta_i \left[ 1\{Y_i < \tau^*\} \log \Delta \Lambda(Y_i) + \beta^t Z_i - \Lambda(Y_i) e^{\beta^t Z_i} \right] \\
+ \frac{1}{n} \sum_{i=1}^{n} (1 - \Delta_i) 1\{Y_i < \tau^*\} \log \left\{ 1 - \phi(\hat{\gamma}_n, X_i) + \phi(\hat{\gamma}_n, X_i) \exp \left( -\Lambda(Y_i) e^{\beta^t Z_i} \right) \right\} \\
- \frac{\Lambda(\tau^*)}{n} \sum_{i=1}^{n} 1\{Y_i \geq \tau^*\} 1\{B_i = 1\} e^{\beta^t Z_i} + \frac{1}{n} \sum_{i=1}^{n} 1\{Y_i \geq \tau^*\} 1\{B_i = 0\} 1\{1 - \phi(\hat{\gamma}_n, X_i)\},
\]
and has to be maximized with respect to $\beta$ and $\Lambda$ in the class of step functions $\Lambda$ with jumps of size $\Delta \Lambda$ at the event times in $[0, \tau^*)$. As in [5], it can be shown that the maximizer $(\hat{\Lambda}_n^*, \hat{\beta}_n^*)$ of $\hat{I}_n^*$ exists and it is finite. Moreover, for $t \in [0, \tau_0]$, 

$$\hat{\Lambda}_n^* = \Lambda_{n, 0, \tau_0, \hat{\beta}_n^*, \hat{\gamma}_n}$$

where

$$\Lambda_{n, 0, \tau_0, \hat{\beta}_n^*, \hat{\gamma}_n}(t) = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i \mathbb{1}_{\{Y_i \leq t, Y_i < \tau^*\}}}{\sum_{j=1}^{n} \mathbb{1}_{\{Y_i \geq Y_j, \bar{Y}_j \leq \bar{Y}_i\}} \exp(\beta_j Z_j) \{\Delta_j^* + (1 - \Delta_j) \mathbb{1}_{\{Y_j < \tau^*\}} g_j(Y_j, \Lambda_{n, 0, \tau_0, \hat{\beta}_n^*, \hat{\gamma}_n})\}}.$$ 

$$\Delta^* = \mathbb{1}_{\{T^*_n \leq \tau^*\}} = \Delta \mathbb{1}_{\{Y_j < \tau^*\}} + \mathbb{1}_{\{Y_j \geq \tau^*\}} \mathbb{1}_{\{|B_i| = 1\}}$$ and $g_j(t, \Lambda, \beta, \gamma)$ defined in (17). 

Let

$$\hat{\Lambda}_0, n(t) = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i \mathbb{1}_{\{Y_i \leq t, Y_i < \tau_0\}}}{\sum_{j=1}^{n} \mathbb{1}_{\{Y_i \geq Y_j, \bar{Y}_j \leq \bar{Y}_i\}} \exp(\beta_j Z_j) \{\Delta_j^* + (1 - \Delta_j) g_j(Y_j, \Lambda_0, \beta_0, \gamma_0)\}}.$$ 

(12) 

We want to prove that $\hat{\beta}_n \xrightarrow{a.s.} \beta_0$, and $\sup_{t \in [0, \bar{\tau}]} |\hat{\Lambda}_n(t) - \Lambda_0(t)| \xrightarrow{a.s.} 0$ for any $\bar{\tau} < \tau_0$. We suppose that the previous statement is false, i.e $\hat{\beta}_n$ does not converge almost surely to $\beta_0$ or there exists $\bar{\tau}$ such that $\sup_{t \in [0, \bar{\tau}]} |\hat{\Lambda}_n(t) - \Lambda_0(t)|$ does not converge to zero almost surely. This means that, there exist $\epsilon > 0$ and $\bar{\tau} < \tau_0$ such that

$$\mathbb{P}[A_1(\bar{\tau}, \epsilon)] > 0,$$ 

with $A_1(\bar{\tau}, \epsilon) = \left\{ \limsup_{n \to \infty} \left[ \frac{1}{n} \sum_{i=1}^{n} \|\hat{\beta}_n - \beta_0\| + \sup_{t \in [0, \bar{\tau}]} \left| \hat{\Lambda}_n(t) - \Lambda_0(t) \right| \right] > \epsilon \right\}.$$

On the other hand, since $(\hat{\Lambda}_n, \hat{\beta}_n)$ maximizes $\hat{I}_n(\Lambda, \beta, \hat{\gamma}_n)$, for any realization $\omega$ of the data we have

$$\hat{I}_n(\hat{\beta}_n, \hat{\Lambda}_n, \hat{\gamma}_n) - \hat{I}_n(\beta_0, \hat{\Lambda}_0, \hat{\gamma}_n) \geq 0.$$ (13)

Then the idea for creating the contradiction is to show that the previous inequality is not satisfied for any $\omega$ in some sets of positive probability. We argue for a fixed realization $\omega$ of the data. As a bounded sequence in $\mathbb{R}^q$, $\hat{\beta}_n$ has a convergent subsequence $\hat{\beta}_{n_k} \to \beta$. Let $(\tau_i)_{i \geq 1}$ be an increasing sequence such that $\lim_{i \to \infty} \tau_i = \tau_0$. Since for all $\tau < \tau_0$, $\Lambda_n(\tau) < \infty$ almost surely (see Lemma 3), by Helly’s selection theorem ([1]), there exists a subsequence $\Lambda_{n_k}$ of $\Lambda_{n_k}$, converging pointwise to a function $\Lambda$ on $[0, \tau_1]$. Repeating the same argument, we can extract a further subsequence converging pointwise to a function $\Lambda$ on $[0, \tau_2]$ and so on. Hence, there exist a subsequence $\Lambda_{n_k}$ converging pointwise to a function $\Lambda$ on all compacts of $[0, \tau_0]$ that do not include $\tau_0$. This defines a monotone function $\Lambda$ on $[0, \tau_0]$, which could be extended at $\tau_0$ by taking the limit. As in Lemma 2 of [5], it can be shown that $\Lambda$ is absolutely continuous and pointwise convergence of monotone functions to a continuous monotone function implies uniform convergence on compacts. Note that the chosen subsequence and the limits $\beta$ and $\Lambda$ depend on $\omega$. To keep the notation simple, in what follows we
use the index $n$ instead of the chosen subsequence $r_k$. For any $\tau^* < \tau_0$, we can write

$$0 \leq \hat{t}_n(\hat{\beta}_n, \hat{\Lambda}_n, \gamma_n) - \hat{t}_n(\hat{\beta}_0, \hat{\Lambda}_{0,n}, \gamma_n) = \hat{t}_n(\hat{\beta}_n, \hat{\Lambda}_{n|\tau^*}, \gamma_n) + D_{1n} - \hat{t}_n(\hat{\beta}_0, \hat{\Lambda}_{0,n|\tau^*}, \gamma_n) - D_{2n} = \mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \hat{\beta}, \hat{\Lambda}_{1|\tau^*}, \gamma_0)] + D_{1n} + R_{1n} - \mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \hat{\beta}_0, \hat{\Lambda}_{0|\tau^*}, \gamma_0)] - D_{2n} - R_{2n}, \quad (A14)$$

where

$$D_{1n} = \hat{t}_n(\hat{\beta}_n, \hat{\Lambda}_n, \gamma_n) - \hat{t}_n(\hat{\beta}_0, \hat{\Lambda}_{0,n}, \gamma_n), \quad (A15)$$

$$D_{2n} = \hat{t}_n(\hat{\beta}_n, \hat{\Lambda}_{0,n}, \gamma_n) - \hat{t}_n(\hat{\beta}_0, \hat{\Lambda}_{0,n|\tau^*}, \gamma_n), \quad (A16)$$

$$R_{1n} = \hat{t}_n(\hat{\beta}_n, \hat{\Lambda}_{n|\tau^*}, \gamma_n) - \mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \hat{\beta}, \hat{\Lambda}_{1|\tau^*}, \gamma_0)], \quad (A17)$$

$$R_{2n} = \hat{t}_n(\hat{\beta}_n, \hat{\Lambda}_{0,n|\tau^*}, \gamma_n) - \mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \hat{\beta}_0, \hat{\Lambda}_{0|\tau^*}, \gamma_0)]. \quad (A18)$$

Note that the limit of $(\hat{\beta}_n, \hat{\Lambda}_n)$ depends on $\omega$, but here the expectation is taken with respect to $(Y^*, \Delta^*, X, Z)$ for fixed $(\hat{\beta}, \hat{\Lambda})$. We now define the event $A_3(\tau^*) = \{|R_{1n} - R_{2n}| \to 0\}$. By Lemma 4, for any $\tau^* < \tau_0$, we have $\mathbb{P}[A_3(\tau^*)] = \mathbb{P}[A_1(\bar{\tau}, \epsilon)]$. Next, for $\bar{\tau} < \tau_0$ and $\epsilon > 0$ such that $\mathbb{P}[A_1(\bar{\tau}, \epsilon)] > 0$, by Lemma 6 there exist $0 < c_1 < 1$ and $\delta > 0$ such that we have

$$c = \inf \left\{ \mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \beta_0, \Lambda_{0|\tau^*}, \gamma_0)] - \mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \beta, \Lambda_{1|\tau^*}, \gamma_0)] : \forall \bar{\tau} + \delta \leq \tau^* < \tau_0, \quad \|\beta - \beta_0\| \geq c_1 \epsilon/2 \quad \text{or} \quad \sup_{t \in [0, \bar{\tau}]} |\Lambda(t) - \Lambda_0(t)| \geq (1 - c_1) \epsilon/2 \right\} > 0.$$

Note that if $\omega \in A_1(\bar{\tau}, \epsilon)$ and $\hat{\beta}$ and $\hat{\Lambda}$ are the limits for $\hat{\beta}_n$ and $\hat{\Lambda}_n$, respectively, then necessarily, either $\|\beta - \beta_0\| \geq c_1 \epsilon/2$, or $\sup_{t \in [0, \bar{\tau}]} |\Lambda(t) - \Lambda_0(t)| \geq (1 - c_1) \epsilon/2$, and consequently

$$\mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \hat{\beta}, \hat{\Lambda}_{1|\tau^*}, \gamma_0)] - \mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \beta_0, \Lambda_{0|\tau^*}, \gamma_0)] \geq c, \quad \forall \bar{\tau} + \delta \leq \tau^* < \tau_0.$$

Finally, we define

$$A_2(\tau^*) = \left\{ \limsup_{n \to \infty} |D_{1n} - D_{2n}| \leq c/2 \right\};$$

with $D_{1n}$ and $D_{2n}$ defined in (A15) and (A16), and choose $\tau^* \in [\bar{\tau} + \delta, \tau_0)$ such that

$$c_0 \{ \mathbb{P}(T_0 \geq \tau^*) \log\{1/\mathbb{P}(T_0 \geq \tau^*)\} + \mathbb{P}(C \in [\tau^*, \tau_0)) \} < c/2,$$

with $c_0$ the constant from Lemma 5. Then we have $\mathbb{P}[A_2(\tau^*)] = 1$. Gathering facts, we deduce that by a suitable choice of $\tau^* \in [\bar{\tau} + \delta, \tau_0)$, we necessarily have
\(\mathbb{P}[A_1(\bar{r}, \epsilon) \cap A_2(\tau^*) \cap A_3(\tau^*)] > 0\). Moreover, with such a suitable \(\tau^*\), for any \(\omega \in A_1(\bar{r}, \epsilon) \cap A_2(\tau^*) \cap A_3(\tau^*)\), we have
\[
\lim_{n \to \infty} \sup \left| \hat{I}_n(\hat{\beta}_n, \hat{\Lambda}_n, \tilde{\gamma}_n) - \hat{I}_n(\beta_0, \hat{\Lambda}_0, \hat{\gamma}_n) \right| \leq -c/2 < 0.
\]

We deduce that (A13) is violated on an event of positive probability, which by definition is impossible. Thus \(\hat{\beta}_n \xrightarrow{a.s.} \beta_0\), and \(\sup_{t \in [0, \bar{r}]} |\hat{\Lambda}_n(t) - \Lambda_0(t)| \xrightarrow{a.s.} 0\) for any \(\bar{r} < \tau_0\).

If condition (19) is satisfied, we want to show in addition that \(\hat{\Lambda}_n(t) - \Lambda_0(t) \xrightarrow{a.s.} 0\) for any \(t < \tau_0\) and \(\Lambda_0(\tau_0) = \lim_{t \uparrow \tau_0} \Lambda_0(t)\), we necessarily have \(\hat{\Lambda} = \Lambda_0\) on the whole interval \([0, \tau_0]\). This concludes the proof of the Theorem.

**Lemma 4.** Consider a realization of the data \(\omega\) and assume that \(\hat{\beta}_n(\omega) \to \bar{\beta}\) and \(\hat{\Lambda}_n(\omega)(t) \to \bar{\Lambda}(t)\) for any \(t \in [0, \tau_0]\), for some absolutely continuous function \(\bar{\Lambda}\). Let \(0 < \tau^* < \tau_0\) and let \(R_{1n}, R_{2n}\) be defined as in (A17) and (A18), respectively. There exists an event \(A_3(\tau^*)\) of probability one such that, for any \(\omega \in A_3(\tau^*)\),
\[
R_{1n}(\omega) - R_{2n}(\omega) \to 0.
\]

**Proof.** Let us consider some \(0 < \tau^* < \tau_0\). From Theorem 1 and Lemma 2 in [5] it follows that the event
\[
A_3^1(\tau^*) = \left\{ \tilde{\gamma}_n \to \gamma_0 \text{ and } \sup_{t \in [0, \tau^*]} |\hat{\Lambda}_{0,n}(t) - \Lambda_0(t)| \to 0 \right\}
\]
has probability one. Next we argue for the given realization of the data \(\omega \in A_3^1(\tau^*)\) and will determine the event \(A_3(\tau^*)\) appropriately. By the triangular inequality we can write
\[
|R_{1n} - R_{2n}| \leq \left| \left\{ \hat{I}^*_n(\hat{\beta}_n, \hat{\Lambda}_{0,n|\tau^*}, \hat{\gamma}_n) - \hat{I}^*_n(\beta_0, \hat{\Lambda}_{0,0|\tau^*}, \hat{\gamma}_0) \right\} - \left\{ \hat{I}^*_n(\hat{\beta}, \hat{\Lambda}_{1|\tau^*}, \gamma_0) - \hat{I}^*_n(\beta_0, \hat{\Lambda}_{0|\tau^*}, \gamma_0) \right\} \right|
+ \left| \hat{I}^*_n(\beta_0, \Lambda_{0|\tau^*}, \gamma_0) - E \left[ I(Y^*, \Delta^*, X, Z; \beta_0, \Lambda_{0|\tau^*}, \gamma_0) \right] \right|
+ \left| \hat{I}^*_n(\hat{\beta}, \hat{\Lambda}_{1|\tau^*}, \gamma_0) - E \left[ I(Y^*, \Delta^*, X, Z; \hat{\beta}, \hat{\Lambda}_{1|\tau^*}, \gamma_0) \right] \right|. \tag{A19}
\]

Since \(\hat{\Lambda}\) is absolutely continuous, it is differentiable almost everywhere. Let
\[ \hat{\lambda}(t) = d\hat{\Lambda}(t)/dt. \] By definition we have
\[
\hat{t}_n^*(\hat{\beta}_n, \hat{\Lambda}_n|_{\tau^*}, \hat{\gamma}_n) - \hat{t}_n^*(\beta_0, \hat{\Lambda}_0|_{\tau^*}, \hat{\gamma}_n)
= \frac{1}{n} \sum_{i=1}^{n} \Delta_i \mathbb{I}_{\{Y_i < \tau^*\}} \left\{ \log \frac{\hat{\Lambda}_n(Y_i)}{\hat{\Lambda}_0(Y_i)} + (\hat{\beta}_n - \beta_0)'Z_i - \hat{\Lambda}_n(Y_i)e^{\beta_n'Z_i} + \hat{\Lambda}_0(Y_i)e^{\beta_0'Z_i} \right\}
+ \frac{1}{n} \sum_{i=1}^{n} (1 - \Delta_i) \mathbb{I}_{\{Y_i < \tau^*\}} \log \frac{1 - \phi(\hat{\gamma}_n, X_i) + \phi(\hat{\gamma}_n, X_i)}{1 - \phi(\gamma_0, X_i) + \phi(\gamma_0, X_i)} \exp \left\{ -\hat{\Lambda}_n(Y_i)e^{\beta_n'Z_i} \right\}
- \frac{1}{n} \sum_{i=1}^{n} \mathbb{I}_{\{Y_i \geq \tau^*\}} \mathbb{I}_{\{B_i=1\}} \left\{ \hat{\Lambda}_n(\tau^*)e^{\beta_n'Z_i} - \hat{\Lambda}_0(\tau^*)e^{\beta_0'Z_i} \right\}.
\]

If \( \omega \in A_3^k(\tau^*) \), we obtain
\[
\hat{t}_n^*(\hat{\beta}_n, \hat{\Lambda}_n|_{\tau^*}, \hat{\gamma}_n) - \hat{t}_n^*(\beta_0, \hat{\Lambda}_0|_{\tau^*}, \hat{\gamma}_n)
= \frac{1}{n} \sum_{i=1}^{n} \Delta_i \mathbb{I}_{\{Y_i < \tau^*\}} \left\{ \log \frac{\hat{\Lambda}(Y_i)}{\Lambda_0(Y_i)} + (\hat{\beta} - \beta_0)'Z_i - \hat{\Lambda}(Y_i)e^{\beta'Z_i} + \Lambda_0(Y_i)e^{\beta_0'Z_i} \right\}
+ \frac{1}{n} \sum_{i=1}^{n} (1 - \Delta_i) \mathbb{I}_{\{Y_i < \tau^*\}} \log \frac{1 - \phi(\gamma_0, X_i) + \phi(\gamma_0, X_i)}{1 - \phi(\gamma_0, X_i) + \phi(\gamma_0, X_i)} \exp \left\{ -\hat{\Lambda}(Y_i)e^{\beta'Z_i} \right\}
- \frac{1}{n} \sum_{i=1}^{n} \mathbb{I}_{\{Y_i \geq \tau^*\}} \mathbb{I}_{\{B_i=1\}} \left\{ \hat{\Lambda}(\tau^*)e^{\beta'Z_i} - \Lambda_0(\tau^*)e^{\beta_0'Z_i} \right\} + o(1)
= \hat{t}_n^*(\hat{\beta}, \hat{\Lambda}|_{\tau^*}, \gamma_0) - \hat{t}_n^*(\beta_0, \Lambda_0|_{\tau^*}, \gamma_0) + o(1),
\]
where the remainder term depends on \( \omega \) and converges to zero. Hence, the first term on the right hand side of (A19) converges to zero. Let \( A_2^k(\tau^*) \) be the event where
\[ \hat{t}_n^*(\beta_0, \Lambda_0|_{\tau^*}, \gamma_0) \rightarrow \mathbb{E} \left[ I(Y^*, \Delta^*, X, Z; \beta_0, \Lambda_0|_{\tau^*}, \gamma_0) \right] \quad \text{as } n \rightarrow \infty. \]

By the law of large numbers \( \mathbb{P}[A_2^k(\tau^*)] = 1 \), implying that also the second term on the right hand side of (A19) converges to zero if \( \omega \in A_2^k(\tau^*) \). It remains to deal with the third term. Note that here \( (\hat{\beta}, \hat{\Lambda}) \) depend on \( \omega \) and the expectation is taken with respect to \( (Y, \Delta, X, Z) \) for fixed \( (\hat{\beta}, \hat{\Lambda}) \). We have the same issue as in the proof of Theorem 1 when dealing with the terms involving \( \hat{\beta} \) and \( \hat{\Lambda} \), so we need to consider approximations by elements of a countable dense subset of \( B \) and of the space of bounded, absolutely continuous, increasing functions in \([0, \tau^*] \) (is separable, so such subset exists). The same reasoning is used also in [4, 5, 7]. Hence, there exists a countable collection of probability one sets \( \{N_i\}_{i \geq 1} \) where
\[ \hat{t}_n^*(\beta_i, \Lambda_i, \gamma_0) \rightarrow \mathbb{E} \left[ I(Y^*, \Delta^*, X, Z; \beta_i, \Lambda_i, \gamma_0) \right] \quad \text{as } n \rightarrow \infty. \]
Lemma 5. Let \( P \) for some \( \tau \) and \((\gamma, Z)\) supposed bounded, there exist constants \( 0 \leq \omega \leq 1 \). Then the largest jump of any of the cumulative hazard functions we need to consider (\( \Lambda \)) is necessarily of order \( 1/n \). However, no meaningful lower bound could be derived for these jumps. More precisely, such a bound is necessarily of order \( 1/n \), so that the sequence

\[
\left| l_n^*(\beta, \Lambda_{\tau_n}, \gamma_0) - \mathbb{E} \left[ l(Y^*, \Delta^*, X, Z; \beta, \Lambda_{\tau^*}, \gamma_0) \right] \right| \to 0.
\]

To conclude, we define \( A_3(\tau^*) = A_3^1(\tau^*) \cap A_3^2(\tau^*) \cap A_3^3(\tau^*) \) and we have \( \mathbb{P}(A_3(\tau^*)) = 1 \). \( \Box \)

**Lemma 5.** Let \( D_{1,n} \) and \( D_{2,n} \) be defined as in (A15) and (A16), respectively, for some \( \tau^* < \tau_0 \). Then there exists a constant \( c_0 \) independent of \( \tau^* \) such that

\[
\mathbb{P} \left[ \limsup_{n \to \infty} |D_{1,n} - D_{2,n}| > c_0 \left\{ \mathbb{P}(T_0 \geq \tau^*) \log \left( 1/\mathbb{P}(T_0 \geq \tau^*) \right) + \mathbb{P}(C \in [\tau^*, \tau_0]) \right\} \right] = 0.
\]

**Proof.** By definition, for any \( \gamma, \beta \) and cumulative hazard function \( \Lambda \) piecewise constant with jumps at the observed events

\[
l_n(\beta, \Lambda, \gamma) - \hat{l}_n(\beta, \Lambda_{|\tau^*}, \gamma)
\]

\[
= \frac{1}{n} \sum_{i=1}^{n} \mathbb{I}_{\{\tau^* \leq Y_i < \tau_0\}} \Delta_i \log \Lambda(\{Y_i\})
\]

\[
+ \frac{1}{n} \sum_{i=1}^{n} \mathbb{I}_{\{\tau^* \leq Y_i < \tau_0\}} \Delta_i \beta^T \mathbb{Z}_i
\]

\[
- \frac{1}{n} \sum_{i=1}^{n} \mathbb{I}_{\{Y_i \geq \tau^*\}} \exp(\beta^T \mathbb{Z}_i) \{\Delta_i \Lambda(Y_i) - \mathbb{I}_{\{B_{i,1}=1\}} \Lambda(\tau^*-\}) \}
\]

\[
+ \frac{1}{n} \sum_{i=1}^{n} \mathbb{I}_{\{\tau_0 \leq Y_i \geq \tau^*\}} \left[ (1-\Delta_i) \log \left\{ 1 - \phi_i(\gamma) + \phi_i(\gamma) \exp \left( -\Lambda(Y_i)e^{\beta^T \mathbb{Z}_i} \right) \right\} \right]
\]

\[
- \mathbb{I}_{\{B_{i,1}=0\}} \log \left\{ 1 - \phi_i(\gamma) \right\} \}
\]

\[
r_{1,n}(\Lambda; \tau^*) + r_{2,n}(\beta; \tau^*) - r_{3,n}(\Lambda, \beta; \tau^*) + r_{4,n}(\Lambda, \beta, \gamma; \tau^*)
\]

where \( \phi_i(\gamma) \) is a short notation for \( \phi(\gamma, X_i) \). For proving the Lemma, we have to suitably bound \( r_{1,n}, \ldots, r_{4,n} \). For this purpose, let us notice that, by definition, all the cumulative hazard functions we have to consider (\( \Lambda_n, \hat{\Lambda}_{0,n}, \ldots \)) have bounded jumps at the event times. More precisely, because the parameter space \( \mathcal{B} \) and \( Z \) are supposed bounded, there exist constants \( 0 < c_l < c_u \) such that

\[
c_l \leq \exp(\beta^T Z) \leq c_u.
\]

Then the largest jump of any of the cumulative hazard functions we need to consider is bounded by \( 1/c_l \) (which is located at the last uncensored observation), the second largest one (and is located at the before last uncensored observation) is bounded by \( 1/2c_l \), ...

To control \( r_{1,n}(\Lambda; \tau^*) \), one would look for a suitable lower bound for the jumps of \( \Lambda \). However, no meaningful lower bound could be derived for these jumps. More precisely, such a bound is necessarily of order \( 1/n \), so that the sequence
of the logarithm of the jumps is unbounded. Fortunately, for our purposes it suffices to find a bound for

$$\left| r_n(A; \tau^*) - r_n(\hat{A}_{0,n}; \tau^*) \right| = \frac{1}{n} \sum_{i=1}^{n} \mathbb{I}_{\{\tau^* \leq Y_i < \tau_0\}} \Delta_i \log \frac{\hat{A}_n(\{Y_i\})}{\hat{A}_{0,n}(\{Y_i\})},$$

where

$$\frac{\hat{A}_n(\{Y_i\})}{\hat{A}_{0,n}(\{Y_i\})} = \frac{\sum_{j=1}^{n} \mathbb{I}_{\{\tau_0 \geq Y_j \geq Y_i\}} \exp(\beta U_j) \{\Delta_j + (1 - \Delta_j) g_j(Y_j, A_0, \beta, \gamma)\}}{\sum_{j=1}^{n} \mathbb{I}_{\{\tau_0 \geq Y_j \geq Y_i\}} \exp(\beta U_j) \{\Delta_j + (1 - \Delta_j) g_j(Y_j, A_0, \beta, \gamma)\}}.$$ 

Since all $g_j$’s are between 0 and 1, it is easy to see that for any uncensored $Y_i \geq \tau^*$,

$$\frac{1}{\rho_n(Y_i)} \leq \frac{\hat{A}_n(\{Y_i\})}{\hat{A}_{0,n}(\{Y_i\})} \leq \frac{c_n}{c_l} \rho_n(Y_i),$$

where

$$\rho_n(t) = \frac{\sum_{j=1}^{n} \mathbb{I}_{\{\tau_0 \geq Y_j \geq t \geq \tau^*\}} \Delta_j \mathbb{I}_{\{\tau_0 \geq Y_j \geq t \geq \tau^*\}}}{\sum_{j=1}^{n} \Delta_j \mathbb{I}_{\{\tau_0 \geq Y_j \geq \tau^*\}}}, \quad t \in [\tau^*, \tau_0].$$

Thus, since all $\rho_n(Y_i)$’s are larger than 1, it suffices to suitably bound

$$0 \leq A_n = \frac{1}{n} \sum_{i=1}^{n} \mathbb{I}_{\{Y_i \geq \tau^*\}} \Delta_i \log(\rho_n(Y_i)),$$

which we decompose as

$$A_n = \frac{1}{n} \sum_{i=1}^{n} \mathbb{I}_{\{Y_i \in [\tau^*, \tau_0 - a_n]\}} \Delta_i \log(\rho_n(Y_i)) + \frac{1}{n} \sum_{i=1}^{n} \mathbb{I}_{\{Y_i \in [\tau_0 - a_n, \tau_0]\}} \Delta_i \log(\rho_n(Y_i)) =: A_{1n} + A_{2n},$$

for some sequence of real numbers $a_n$, $n \geq 1$, decreasing to zero. The rate of $a_n$ should be taken such that, on one hand, for any constant $C > 0$,

$$\mathbb{P}(\limsup_{n \to \infty} A_{2n} > C) = 0, \quad (A20)$$

and, on the other hand, the lim sup of $A_{1n}$ could be controlled by a function of $\tau^*$ almost surely. More precisely, since

$$A_{2n} \leq \frac{\log n}{n} \sum_{i=1}^{n} \mathbb{I}_{\{Y_i \in [\tau_0 - a_n, \tau_0]\}} \Delta_i,$$

we take $a_n$ such that $p_n \log n \to 0$ and $p_n \log^2 n \to \infty$, where

$$p_n = \mathbb{P}(Y \in [\tau_0 - a_n, \tau_0], \Delta = 1) = \mathbb{E} \left[ \phi(\gamma_0, X) \int_{[\tau_0 - a_n, \tau_0]} F_C([t, \infty]|X, Z) F_u(dt|Z) \right].$$
Then, by Theorem 1(i) from [9], we have

\[
\lim_{n \to \infty} \frac{1}{n} \sum_{i=1}^{n} \mathbb{1}_{\{Y_i \in [\tau_0-a_n,\tau_0]\}} \Delta_i = 1, \quad \text{a.s.,}
\]

which implies (A20). On the other hand, we have

\[
A_{1n} \leq \log \left( \sup_{t \in [\tau^*,\tau_0-a_n]} \rho_n(t) \right) \times \frac{1}{n} \sum_{i=1}^{n} \mathbb{1}_{\{Y_i \in [\tau^*,\tau_0]\}} \Delta_i.
\]

By the same Theorem 1(i) from [9],

\[
\lim_{n \to \infty} \sup_{t \in [\tau^*,\tau_0-a_n]} \left[ \rho_n(t) \frac{\mathbb{P}(Y \in [t,\tau_0-a_n], \Delta = 1)}{\mathbb{P}(Y \in [t,\tau_0-a_n])} \right] = 1, \quad \text{a.s.}
\]

By our assumptions, there exists a constant \(C_r\), independent of \(\tau^*, \beta, \gamma\) and \(\Lambda\), such that

\[
1 < \inf_{t \in [\tau^*,\tau_0-a_n]} \frac{\mathbb{P}(Y \in [t,\tau_0-a_n])}{\mathbb{P}(Y \in [t,\tau_0-a_n], \Delta = 1)} \leq C_r.
\]

Gathering facts, deduce with probability 1, for sufficiently large \(n\),

\[
\left| r_{1n}(\hat{\Lambda}_n; \tau^*) - r_{1n}(\hat{\Lambda}_{0,n}; \tau^*) \right| \leq c \frac{N^*}{n},
\]

where \(N^*\) be the number of uncensored observations in \([\tau^*, \tau_0]\) and \(c\) is some constant (independent of \(\tau^*, \beta, \gamma\) and \(\Lambda\)). Here, \(N^*\) is a binomial random variable with \(n\) trials and success probability

\[
p^* = \mathbb{P}(Y \geq \tau^*, \Delta = 1) = \mathbb{E} \left[ \phi(\gamma_0, X) \int_{[\tau^*,\tau_0]} F_C(\cdot | X, Z) F_u(\cdot | Z) \right] \leq \sup_x \phi(\gamma_0, x) \mathbb{P}(Y \geq \tau^*).
\]

To bound \(r_{3n} = r_{3n}(\Lambda, \beta; \tau^*)\), we note that \(\mathbb{1}_{\{B_i=1\}} = \Delta_i + (1-\Delta_i) \mathbb{1}_{\{B_i=1\}}\) and rewrite

\[
r_{3n} = \frac{1}{n} \sum_{i=1}^{n} \mathbb{1}_{\{Y_i \geq \tau^*\}} e^{\phi Z_i} \Delta_i \{\Lambda(Y_i) - \Lambda(\tau^*-\)}
\]

\[
- \frac{\Lambda(\tau^*)}{n} \sum_{i=1}^{n} \mathbb{1}_{\{Y_i \geq \tau^*\}} e^{\phi Z_i} \mathbb{1}_{\{B_i=1\}} (1-\Delta_i) = r_{3an} - r_{3bn}.
\]

On one hand,

\[
r_{3an} \leq \frac{c u}{ c_t} \times \frac{N^*}{n}.
\]
The last inequality is obtained by bounding the jumps of Λ and using the following identity: for any integer $M \geq 1$,

$$
\sum_{k=1}^{M} \sum_{j=k}^{M} \frac{1}{j} = \sum_{j,k=1}^{M} \frac{1}{j} = M.
$$

To bound $r_{3bn}$, let us note that

$$
\Lambda(\tau^* -) \leq \frac{1}{c_1} \sum_{j=N^*+1}^{\infty} \frac{1}{j} \leq c_1 \log \frac{N}{N^*},
$$

with $c_1$ some constant depending only on $c_1$ and the maximal value of the convergent sequence

$$
\sum_{j=1}^{m} \frac{1}{j} = \log m, \quad m \geq 1.
$$

Here, $N = \sum_{i=1}^{n} \Delta_i$ is a binomial random variable with $n$ trials and success probability

$$
p = P(\Delta = 1) = E \left[ \phi(\gamma_0, X) \int_{[0, \tau_0]} F_C([t, \infty]|X,Z)F_u(dt|Z) \right].
$$

Thus

$$
r_{3bn} \leq c \log \frac{N}{N^*} \times \frac{1}{n} \sum_{i=1}^{n} \mathbb{1}_{\{Y_i \geq \tau^*\}} \mathbb{1}_{\{B_i = 1\}} (1 - \Delta_i) = c \log \frac{N/n}{N^*/n} \times \frac{Q^*}{n},
$$

where $Q^*$ is a binomial variable with $n$ trials and success probability

$$
q^* = E \left[ \phi(\gamma_0, X) \int_{[\tau^*, \tau_0]} F_u([t, \tau_0]|X,Z)F_C(dt,X,Z) \right]
$$

$$
\leq E \left[ \phi(\gamma_0, X)F_C([\tau^*, \tau_0]|X,Z)F_u([\tau^*, \tau_0]|Z) \right]
$$

$$
\leq \left[ \sup_x \phi(\gamma_0, x) \right] \left[ \sup_{x,z} \frac{F_C([\tau^*, \tau_0]|X=x, Z=z)}{\tau_0 - \tau^*} \right] \times (\tau^* - \tau_0) \times P(T_0 \geq \tau^*)
$$

$$
\leq c(\tau^* - \tau_0) \times P(T_0 \geq \tau^*),
$$

and $c$ is some constant. By the strong Law of Large Numbers,

$$
\lim_{n \to \infty} \log \frac{N}{N^*} = \log \frac{p}{p^*}, \ a.s.
$$

Next, to bound $r_{2n} = r_{2n}(\beta; \tau^*)$, we write

$$
r_{2n} = \frac{1}{n} \sum_{i=1}^{n} \mathbb{1}_{\{\tau^* \leq T_i < \tau_0\}} e^{\beta Z_i} \Delta_i \leq c_n \frac{N^*}{n}.
$$
Finally, to control $r_{4n} = r_{4n}(\Lambda, \beta, \gamma; \tau^*)$, since $I\{B_i=0\} = (1-\Delta_i)I\{B_i=0\}$ and $\log(1+u) \leq u$, $\forall u \geq 0$, we have

$$r_{4n} = \frac{1}{n} \sum_{i=1}^{n} I\{Y_i \geq \tau^*\}I\{B_i=0\} \log \left\{ 1 + \frac{\phi_i(\gamma) \exp \left( -\Lambda(Y_i)e^{\beta Z_i} \right)}{1 - \phi_i(\gamma)} \right\}$$

$$\quad + \frac{1}{n} \sum_{i=1}^{n} I\{Y_i \geq \tau^*\}(1-\Delta_i)I\{B_i=1\} \log \left\{ 1 - \phi_i(\gamma) + \phi_i(\gamma) \exp \left( -\Lambda(Y_i)e^{\beta Z_i} \right) \right\}.$$ 

Thus

$$|r_{4n}| \leq \sup_{\gamma,x} \left| \frac{\phi(\gamma, x)}{1 - \phi(\gamma, x)} \right| \exp \left( -c_1\Lambda(\tau^*) - \frac{1}{n} \sum_{i=1}^{n} I\{Y_i \geq \tau^*\}I\{B_i=0\} \right)$$

$$\quad + \sup_{\gamma,x} |\log(1 - \phi(\gamma, x))| - \frac{1}{n} \sum_{i=1}^{n} I\{Y_i \geq \tau^*\}(1-\Delta_i)I\{B_i=1\}$$

$$= c_1 \exp \left( -c_1\Lambda(\tau^*) \right) \frac{R^*}{n} + c_2 \frac{Q^*}{n},$$

where $R^*$ is a binomial variable with $n$ trials and success probability

$$r^* = \mathbb{E}\left[ (1 - \phi(\gamma_0, X))F_C([\tau^*, \tau_0]|X, Z) \right],$$

and $c_1$ and $c_2$ are some constants. Deduce that there exists a constant $c_3$ such that

$$|r_{4n}| \leq c_3 \left( \frac{R^*}{n} + \frac{Q^*}{n} \right).$$

Gathering facts, there exists a constants $C^*$ and $c^*$, independent of $\tau^*$, $\beta$, $\gamma$ and $\Lambda$, such that

$$\left| \hat{\nu}_n(\beta, \Lambda, \gamma) - \hat{\nu}(\beta, \Lambda|\tau^*, \gamma) \right| \leq C^* \left\{ \frac{N^*}{n} + \frac{Q^*}{n} \left[ 1 + \log \frac{n}{N^*} \right] + \frac{R^*}{n} \right\} + o_{a.s.}(1),$$

where $N^*$, $Q^*$ and $R^*$ are binomial with $n$ trials and success probabilities $p^*$, $q^*$ and $r^*$, respectively, and

$$p^* + q^* \leq c^*P(T_0 \geq \tau^*) \quad \text{and} \quad r^* \leq c^*P(C \in [\tau^*, \tau_0]).$$

**Lemma 6.** Assume that for any $x$ and $z$, the conditional distribution of the censoring times given $X = x$ and $Z = z$ is such that there exists a constant $C > 0$ such that

$$\inf_{[t_1, t_2] \subset [0, \tau_0]} \inf_{x, z} \{ F_C(t_2|x, z) - F_C(t_1|x, z) \} > C(t_2 - t_1), \quad \forall \delta > 0.$$
Let $0 < \bar{\tau} < \tau_0$ and $\epsilon > 0$. There exist $c_1, c_2 > 0$, $\delta > 0$ such that $c_1 + c_2 = 1$ and

$$\inf \left\{ \mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \beta, \Lambda_{0|\tau^*, \gamma_0})] - \mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \beta, \Lambda_{|\tau^*, \gamma_0})] : \tau + \delta \leq \tau^* < \tau_0, \quad ||\beta - \beta_0|| \geq c_1 \epsilon \quad \text{or} \quad \sup_{t \in [0, \bar{\tau}]} |\Lambda(t) - \Lambda_0(t)| \geq c_2 \epsilon \right\} > 0$$

**Proof.** Note that, for any $\tau^* \in (\bar{\tau}, \tau_0)$,

$$\mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \beta, \Lambda_{0|\tau^*, \gamma_0})] - \mathbb{E}[\ell(Y^*, \Delta^*, X, Z; \beta, \Lambda_{|\tau^*, \gamma_0})]$$

is the Kullback-Leibler divergence $KL(\mathbb{P}|Q)$, where $\mathbb{P}$ and $Q$ are the probability measures of $(Y^*, \Delta^*, X, Z)$ when the true parameters are $(\Lambda_0, \beta_0, \gamma_0)$ and $(\Lambda, \beta, \gamma_0)$ respectively. By Pinsker's inequality, we have

$$KL(\mathbb{P}|Q) \geq 2\delta(\mathbb{P}, Q)^2,$$

where $\delta(\mathbb{P}, Q)$ is the total variation distance between the two probability measures, defined as

$$\delta(\mathbb{P}, Q) = \sup_A |\mathbb{P}(A) - Q(A)|,$$

where the supremum is taken over all measurable sets $A$. We want to find a positive lower bound for $\delta(\mathbb{P}, Q)$ independent of $\tau^*$ and $Q$, for all $Q$ such that $||\beta - \beta_0|| \geq c_1 \epsilon$ or $\sup_{t \in [0, \bar{\tau}]} |\Lambda(t) - \Lambda_0(t)| \geq c_2 \epsilon$. Hence, it is sufficient to find $k > 0$ and for each such $Q$ an event $A$, which could depend on $Q$, for which $|\mathbb{P}(A) - Q(A)| > k$. Without loss of generality we can assume that the covariate vector $Z$ has mean zero.

**Case 1.** If $\sup_{t \in [0, \bar{\tau}]} |\Lambda(t) - \Lambda_0(t)| \geq c_2 \epsilon$, there exists $\check{t} \in [0, \bar{\tau}]$ such that either

$$\Lambda(\check{t}) \geq \Lambda_0(\check{t}) + c_2 \epsilon \quad (A21)$$

or

$$\Lambda(\check{t}) \leq \Lambda_0(\check{t}) - c_2 \epsilon. \quad (A22)$$

We first consider (A21) and define

$$\delta = \min \left\{ \frac{\tau_0 - \bar{\tau}}{2}, \frac{c_2 \epsilon}{2 \sup_{t \in [0, (\bar{\tau} + \tau_0)/2]} \lambda_0(t)} \right\}.$$

It follows that for all $t \in [\check{t}, \check{t} + \delta] \subset [0, (\bar{\tau} + \tau_0)/2] \subset [0, \tau_0]$ we have $\Lambda(t) \geq \Lambda_0(t) + \frac{1}{2} c_2 \epsilon$. Indeed, we can write

$$\Lambda(t) \geq \Lambda(\check{t}) \geq \Lambda_0(\check{t}) + c_2 \epsilon \geq \Lambda_0(t) - \delta \sup_{u \in [0, (\bar{\tau} + \tau_0)/2]} \lambda_0(u) + c_2 \epsilon \geq \Lambda_0(t) + \frac{1}{2} c_2 \epsilon, \quad \forall t \in [\check{t}, \check{t} + \delta].$$
Since \( Z \) has mean zero, \( (\beta - \beta_0)'Z \) also has zero mean. Moreover, since \( B \) is compact and \( Z \) is bounded non degenerated variance, we have

\[
\inf_{\beta \in B} \mathbb{P}((\beta - \beta_0)'Z \geq 0) > 0 \quad \text{and} \quad \inf_{\beta \in B} \mathbb{P}((\beta - \beta_0)'Z \leq 0) > 0 \quad (A23)
\]

(see proof below). Let \( A_\beta \) be the event \( \{\Delta^* = 0, Y^* \in [\bar{t}, \bar{t} + \delta], (\beta - \beta_0)'Z \geq 0\} \), which depends on \( \beta \) and thus on \( Q \). However, by (A23) and the construction of the model, the event \( A_\beta \) has positive probability which stays bounded away from zero. Moreover, we have

\[
\mathbb{P}(A_\beta) - Q(A_\beta) = \int_{(\beta - \beta_0)'z \geq 0} \int_{\bar{t}}^{\bar{t} + \delta} \phi(\gamma_0, x) \times \left\{ \exp \left( -\Lambda_0(t)e^{\beta_0'z} \right) - \exp \left( -\Lambda(t)e^{\beta'z} \right) \right\} F_C(dt|x, z)G(dx, dz).
\]

Whenever \( (\beta - \beta_0)'z \geq 0 \), by the mean value theorem, we obtain

\[
\exp \left( -\Lambda_0(t)e^{\beta_0'z} \right) - \exp \left( -\Lambda(t)e^{\beta'z} \right) = \left\{ \Lambda(t)e^{\beta'z} - \Lambda_0(t)e^{\beta_0'z} \right\} e^{-\xi} = \left\{ \Lambda(t) - \Lambda_0(t) \right\} e^{\beta_0'z} e^{-\xi} \geq \Lambda(t) - \Lambda_0(t) \geq \xi > 0
\]

for some \( \xi > 0 \) such that \( |\xi - \Lambda_0(t)e^{\beta_0'z}| \leq |\Lambda(t)e^{\beta'z} - \Lambda_0(t)e^{\beta_0'z}|, t \in [\bar{t}, \bar{t} + \delta] \).

Now, let

\[
M(t) = \Lambda_0(t) \sup_{\beta, z} e^{\beta'z} \inf_{\beta, z} e^{\beta_0'z} + \log \frac{2}{\inf_{\beta, z} e^{\beta_0'z}}, \quad t \in [\bar{t}, \bar{t} + \delta],
\]

Then, for \( (\beta - \beta_0)'z \geq 0 \) and \( t \in [\bar{t}, \bar{t} + \delta] \), such that \( \Lambda(t) \leq M(t) \) we simply use (A21) and write

\[
\exp \left( -\Lambda_0(t)e^{\beta_0'z} \right) - \exp \left( -\Lambda(t)e^{\beta'z} \right) \geq \frac{1}{2} e^{\xi} e^{\beta_0'z} e^{-\xi} \geq k_1 e,
\]

for some constant \( k_1 > 0 \) independent of \( \Lambda, \beta \) and the event \( A_\beta \), because \( M(t) \) is uniformly bounded on \([0, (\bar{t} + \tau_0)/2]\) and thus \( e^{-\xi} \) is bounded away from zero. On the other hand, for \( t \in [\bar{t}, \bar{t} + \delta] \) such that \( M(t) > M(t) \), we have

\[
\exp \left( -\Lambda(t)e^{\beta'z} \right) \leq \exp \left( -M(t) \inf_{\beta, z} e^{\beta_0'z} \right) \leq \frac{1}{2} \exp \left( -\Lambda_0(t)e^{\beta_0'z} \right).
\]

Consequently,

\[
\exp \left( -\Lambda_0(t)e^{\beta_0'z} \right) - \exp \left( -\Lambda(t)e^{\beta'z} \right) \geq \frac{1}{2} \exp \left( -\Lambda_0(t)e^{\beta_0'z} \right) \geq \frac{1}{2} \exp \left( -\Lambda_0((\bar{t} + \tau_0)/2) \sup_{\beta, z} e^{\beta_0'z} \right) = k_2(\tau) > 0.
\]
We conclude that, for any \( t \in [ar{t}, \bar{t} + \delta] \),
\[
\exp(-\Lambda_0(t)e^{\beta \epsilon z}) - \exp(-\Lambda(t)e^{\beta \epsilon z}) \geq \min\{k_1\epsilon, k_2(\tau)\} > 0.
\]

It follows that
\[
|P(A_\beta) - Q(A_\beta)| \geq \min\{k_1\epsilon, k_2(\tau)\} \inf_x \phi(\gamma_0, x)
\times \iint_{(\beta - \beta_0)z \geq 0} \{F_C(\bar{t} + \delta|x, z) - F_C(\bar{t}|x, z)\} G(dx, dz).
\]

By assumption we have
\[
\inf_{x,z} F_C(\bar{t} + \delta|x, z) - F_C(\bar{t}|x, z) \geq C\delta,
\]
yielding that there exist another constant \( k_3 > 0 \) independent of \( \Lambda, \beta \) and the event \( A_\beta \) (but depending on \( \epsilon \) and \( \tau \)) such that
\[
\forall \beta \in B, \quad |P(A_\beta) - Q(A_\beta)| \geq k_3 \inf_{\beta \in B} P((\beta - \beta_0)'Z \geq 0) > 0.
\]

Note that the uniform lower bound holds for any choice of the constants \( c_1 \) and \( c_2 \) in the statement of the Lemma.

We next consider (A22). Let
\[
\tilde{\delta} = \min\left\{ \frac{\bar{t} - \bar{t}}{2}, \frac{c_2\epsilon}{2\sup_{t \in [0, \bar{t}]} \lambda_0(t)} \right\}.
\]

It follows that for all \( t \in [\bar{t} - \tilde{\delta}, \bar{t}] \) we have \( \Lambda(t) \leq \Lambda_0(t) - \frac{1}{2}c_2\epsilon \). Indeed, we can write
\[
\Lambda(t) \leq \Lambda(\bar{t}) \leq \{\Lambda_0(\bar{t}) - \Lambda_0(t)\} + \Lambda_0(t) - c_2\epsilon
\leq \tilde{\delta} \sup_{u \in [0, \bar{t}]} \lambda_0(u) + \Lambda_0(t) - c_2\epsilon \leq \Lambda_0(t) - \frac{1}{2}c_2\epsilon, \quad \forall t \in [\bar{t} - \tilde{\delta}, \bar{t}].
\]

Next we redefine \( A_\beta \) as the event \( \{\Delta^* = 0, Y^* \in [\bar{t} - \tilde{\delta}, \bar{t}], (\beta - \beta_0)'Z \leq 0\} \), which depends on \( \beta \) and thus on \( Q \). However, by (A23) and the construction of the model, the event \( A_\beta \) has positive probability which stays bounded away from zero. Moreover, we have
\[
P(A_\beta) - Q(A_\beta) = \iint_{(\beta - \beta_0)z \leq 0} \int_{\bar{t} - \tilde{\delta}}^{\bar{t}} \phi(\gamma_0, x)
\times \left\{ \exp\left(-\Lambda_0(t)e^{\beta \epsilon z}\right) - \exp\left(-\Lambda(t)e^{\beta \epsilon z}\right) \right\} F_C(dt|x, z)G(dx, dz).
\]

Whenever \( (\beta - \beta_0)'z \leq 0 \), by the mean value theorem, we obtain
\[
\exp\left(-\Lambda_0(t)e^{\beta \epsilon z}\right) - \exp\left(-\Lambda(t)e^{\beta \epsilon z}\right) \leq \{\Lambda(t) - \Lambda_0(t)\}e^{\beta \epsilon z}e^{-\epsilon} \leq -\frac{1}{2}c_2\epsilon e^{\beta \epsilon z}e^{-\epsilon},
\]
boundedness of $t$ for some $\xi > 0$ such that $|\xi - \Lambda_0(t)e^{\beta_0 z}| \leq |\Lambda(t)e^{\beta' z} - \Lambda_0(t)e^{\beta_0 z}| \leq 2\Lambda_0(t)e^{\beta_0 z}, t \in [\bar{t} - \delta, \bar{t}]$. Thus necessarily $0 < \xi \leq 2\Lambda_0(\bar{t})e^{\beta_0 z}$, and thus $e^{-\xi}$ stays away from zero. Using arguments as we used for the case (A22), we deduce that $\mathbb{P}(A_\beta) - Q(A_\beta)$ is negative and away from zero. Thus we obtain the result with $\bar{\tau} \leq \tau^* < \tau_0$ instead of $\bar{\tau} + \delta \leq \tau^* < \tau_0$. Finally, it remains to recall that inf is a decreasing function of nested sets. Now the arguments for Case 1 are complete for any choice of the constants $c_1$ and $c_2$ in the statement of the Lemma.

**Case 2.** If $\sup_{t \in [0, \bar{t}]} |\Lambda(t) - \Lambda_0(t)| \leq c_2 \epsilon$, then necessarily $\|\beta - \beta_0\| \geq c_1 \epsilon$. In particular we also have that $\Lambda(\bar{\tau}) \leq \Lambda_0(\bar{\tau}) + c_2 \epsilon$, so all such functions $\Lambda$ are uniformly bounded on $[0, \bar{\tau}]$. Without loss of generality we can also assume that $\Lambda_0(\bar{\tau}/2) \geq 1$ (otherwise we can take a larger $\bar{\tau}$). Note that

$$
\text{Var}((\beta - \beta_0)'Z) = (\beta - \beta_0)'\text{Var}(Z)(\beta - \beta_0) \geq (c_1 \epsilon)^2 \lambda_{\text{min}},
$$

with $\lambda_{\text{min}}$ the smallest eigenvalue of $\text{Var}(Z)$. From this lower bound for the variance of $(\beta - \beta_0)'Z$, and since $Z$ is centered and has a bounded support, we have

$$
\inf_{|\beta - \beta_0| \geq c_1 \epsilon} \mathbb{P}( (\beta - \beta_0)'Z \geq z_0 ) > \frac{(c_1 \epsilon)^2 \lambda_{\text{min}}}{2 \sup \|Z\|^2}, \quad (A24)
$$

for $z_0 = c_1 \epsilon \lambda_{\text{min}}^{1/2}/2$ (see proof below). If

$$
\inf_{|\beta - \beta_0| \geq c_1 \epsilon} \mathbb{P}( (\beta - \beta_0)'Z \geq z_0 ) > \frac{(c_1 \epsilon)^2 \lambda_{\text{min}}}{2 \sup \|Z\|^2},
$$

let $A_\beta$ be the event $\{\Delta^* = 0, Y^* \in [\bar{\tau}/2, \bar{\tau}], (\beta - \beta_0)'Z \geq z_0\}$. By (A24) and the construction of the model, the event $A_\beta$ has positive probability which stays bounded away from zero. Next, as in Case 1, we write

$$
\mathbb{P}(A_\beta) - Q(A_\beta) = \int_{(\beta - \beta_0)'Z \geq z_0} \int_{[\bar{\tau}/2, \bar{\tau}]} \phi(z_0, x)\left\{ \mathbb{P}(Q_{\beta}(\tau)/x, z) - \mathbb{P}(Q_{\beta}(\tau)/x, z) \right\} F_G(\tau|/x, z) G(dx, dz),
$$

and

$$
\exp \left( -\Lambda_0(t)e^{\beta_0 z} \right) - \exp \left( -\Lambda(t)e^{\beta' z} \right) = \left( \{\Lambda(t) - \Lambda_0(t)\} e^{\beta_0 z} + \Lambda(t) \{e^{\beta' z} - e^{\beta_0 z}\} \right) e^{-\xi},
$$

for some $\xi > 0$ such that $|\xi - \Lambda_0(t)e^{\beta_0 z}| \leq |\Lambda(t)e^{\beta' z} - \Lambda_0(t)e^{\beta_0 z}|$. From the boundedness of $\beta$, $z$, $\Lambda$ and $\Lambda_0$ on $[0, \bar{\tau}]$, it follows that $e^{-\xi} \geq k_4 > 0$ for some $k_4$ independent of $\Lambda$, $\beta$ and the event $A_\beta$ (but depending on $\bar{\tau}$). Moreover, since for $t \in [\bar{\tau}/2, \bar{\tau}]$, $(\beta - \beta_0)'z \geq z_0$,

$$
|\Lambda(t) - \Lambda_0(t)| e^{\beta_0 z} \leq c_2 \epsilon e^{\beta_0 z},
$$
and

\[ \Lambda(t) \left\{ e^{\beta^T z} - e^{\beta_0^T z} \right\} \geq \Lambda_0(\bar{\tau}/2) e^{\beta_0^T z} \left\{ e^{(\beta - \beta_0)^T z} - 1 \right\} \geq e^{\beta_0^T z} z_0 = e^{\beta_0^T z} \lambda_{\min}^{1/2} c_1 \epsilon / 2, \]

we obtain

\[ \exp \left( -\Lambda_0(t) e^{\beta_0^T z} \right) - \exp \left( -\Lambda(t) e^{\beta^T z} \right) \geq \epsilon \left[ \lambda_{\min}^{1/2} c_1 / 2 - c_2 \right] e^{\beta_0^T z} e^{-\epsilon}. \]

Define

\[ c_1 = \frac{4}{\lambda_{\min}^{1/2}} \quad \text{and} \quad c_2 = \frac{\lambda_{\min}^{1/2}}{\lambda_{\min}^{1/2} + 4}, \]

such that \( 0 < c_1, c_2 < 1 \) and \( c_1 + c_2 = 1 \), and deduce that

\[ \exp \left( -\Lambda_0(t) e^{\beta_0^T z} \right) - \exp \left( -\Lambda(t) e^{\beta^T z} \right) \geq e^{\lambda_{\min}^{1/2} e^{\beta_0^T z} k_4 \left\{ \lambda_{\min}^{1/2} + 4 \right\}^{-1}}. \]

Deduce that, for any \( \| \beta - \beta_0 \| \geq c_1 \epsilon, \)

\[ P(A_\beta) - Q(A_\beta) \geq \epsilon \left[ \lambda_{\min}^{1/2} e^{\beta_0^T z} k_4 \left\{ \lambda_{\min}^{1/2} + 4 \right\}^{-1} \right] \inf_z e^{\beta_0^T z} \inf_x \phi(\gamma_0, x) \times \inf_{|\beta - \beta_0| \geq c_1 \epsilon} P(C \in [\bar{\tau}/2, \bar{\tau}], (\beta - \beta_0)^T Z \geq z_0) > 0. \]

Note that this bound does not depend on \( \delta \) in the statement of the Lemma. Finally it is easy to see that similar arguments apply when \( \inf_{|\beta - \beta_0| \geq c_1 \epsilon} P((\beta - \beta_0)^T Z \leq -z_0) > (c_1 \epsilon)^2 \lambda_{\min} / \{4 \sup \| Z \|^2 \}, \) for the same expression of \( z_0 \). In this case, we define \( A_\beta = \{ \Delta^* = 0, Y^* \in [\bar{\tau}/2, \bar{\tau}], (\beta - \beta_0)^T Z \leq -z_0 \} \) and follow the same steps as above to show that

\[ \exp \left( -\Lambda_0(t) e^{\beta_0^T z} \right) - \exp \left( -\Lambda(t) e^{\beta^T z} \right) < 0, \]

and the difference of exponentials stays away from zero. Now, the proof of Lemma 6 is complete. \( \square \)

**Proof of Equation (A.23)**. For \( \beta = \beta_0 \) we have \( P((\beta - \beta_0)^T Z \geq 0) = 1 \) and thus we only have to study \( \beta \neq \beta_0 \). Since \( Var(Z) \) is non degenerated, \( P((\beta - \beta_0)^T Z = 0) < 1 \) for any \( \beta \neq \beta_0 \). Next, we could write

\[
0 = \mathbb{E} \left( \frac{(\beta - \beta_0)^T Z}{\| \beta - \beta_0 \|} \right) = \mathbb{E} \left( \frac{(\beta - \beta_0)^T Z}{\| \beta - \beta_0 \|} 1_{\{ (\beta - \beta_0)^T Z \geq 0 \}} \right) + \mathbb{E} \left( \frac{(\beta - \beta_0)^T Z}{\| \beta - \beta_0 \|} 1_{\{ (\beta - \beta_0)^T Z < 0 \}} \right) \\
\leq \| Z \| P((\beta - \beta_0)^T Z \geq 0) + \mathbb{E} \left( \frac{(\beta - \beta_0)^T Z}{\| \beta - \beta_0 \|} 1_{\{ (\beta - \beta_0)^T Z < 0 \}} \right). \\
\]

It remains to notice that

\[
\sup_{\| \beta \| = 1} \mathbb{E} \left( \frac{\beta^T Z 1_{\{ \beta^T Z < 0 \}}}{\| \beta \|} \right) < 0. 
\]
Indeed, if \( \mathbb{E}\left(\begin{array}{c}
abla'Z_1\{\hat{\beta}'Z < 0\}\end{array}\right) \), which is negative, could be arbitrarily close to zero, and since \( \mathbb{E}\left(\begin{array}{c}
abla'Z_1\{\hat{\beta}'Z < 0\}\end{array}\right) = -\mathbb{E}\left(\begin{array}{c}
abla'Z_1\{\hat{\beta}'Z \geq 0\}\end{array}\right) \), we deduce that \( \mathbb{E}(|\hat{\beta}'Z|) \) could be arbitrarily close to zero, for suitable \( \hat{\beta} \) with unit norm. Since the support of \( Z \) is bounded and
\[
\lambda_{\text{min}}(\text{Var}(Z)) \leq \mathbb{E}(|\hat{\beta}'Z|) \leq \mathbb{E}(|\hat{\beta}'Z|) \sup \|Z\|, \quad \forall \|\hat{\beta}\| = 1,
\]
we thus get a contradiction with the assumption that \( \lambda_{\text{min}} \), the smallest eigenvalue of \( \text{Var}(Z) \), is positive. Deduce that (A23) holds true. \( \square \)

**Proof of Equation (A24).** It suffices to prove the following property. Let \( U \) be a centered variable such that \( |U| \leq M \) for some constant \( M \) and \( \text{Var}(U) \) is bounded from below by some constant \( 0 < C < M^2 \). Then there exists \( z_0 > 0 \) such that \( \mathbb{P}(|U| \geq z_0) > C/2M^2 \) with \( z_0 \) depending on \( M \) and \( C \) but independent of the law of \( U \).

For any \( 0 < z_0 < M \) we can write
\[
C \leq \mathbb{E}(U^2) = \mathbb{E}\left(U^2\mathbb{1}_{\{|U| \geq z_0\}}\right) + \mathbb{E}\left(U^2\mathbb{1}_{\{|U| < z_0\}}\right) \leq M^2\mathbb{P}(|U| \geq z_0) + z_0^2\{1 - \mathbb{P}(|U| \geq z_0)\}.
\]
Deduce that
\[
\mathbb{P}(|U| \geq z_0) \geq \frac{C - z_0^2}{M^2 - z_0^2}.
\]
Finally, it suffices to take \( z_0^2 \leq C M^2/(2M^2 - C) \) in order to obtain
\[
\mathbb{P}(|U| \geq z_0) \geq \frac{C}{2M^2}.
\]
Since \( C \) could be arbitrarily small, we could take \( z_0^2 = C/4 \). \( \square \)

**A.3. Asymptotic normality**

**Proof of Theorem 3.** Let \( m \) be as in (21) and define \( M_n(\gamma, \pi) = \frac{1}{n} \sum_{i=1}^{n} m(X_i; \gamma, \pi) \) and \( M(\gamma, \pi) = \mathbb{E}[m(X; \gamma, \pi)] \). Note that \( m(x; \gamma_0, \pi_0) = 0 \) and \( M(\gamma_0, \pi_0) = 0 \). If we take partial derivatives with respect to \( \gamma \) of the vector \( M(\gamma, \pi) \) evaluated at \( (\gamma_0, \pi_0) \) we obtain a matrix \( \nabla_\gamma M(\gamma_0, \pi_0) \) with elements
\[
\nabla_\gamma M(\gamma_0, \pi_0)_{kl} = \mathbb{E}\left[ \frac{\partial}{\partial \gamma_k} \left\{ \frac{1 - \pi(X)}{\phi(\gamma, X)} - \frac{\pi(X)}{1 - \phi(\gamma, X)} \right\} \frac{\partial}{\partial \gamma_l} \phi(\gamma, X) \right]_{\gamma_0, \pi_0},
\]
for \( k, l \in \{1, \ldots, p\} \), because
\[
\frac{1 - \pi_0(x)}{\phi(\gamma_0, x)} - \frac{\pi_0(x)}{1 - \phi(\gamma_0, x)} = 0 \quad \forall x \in \mathcal{X}.
\]
Hence,\[
\Gamma_1 := \nabla_\gamma M(\gamma, \pi_0) = -E[W(X)\nabla_\gamma \phi(\gamma_0, X)\nabla_\gamma \phi(\gamma_0, X)']
\] (A25)
where\[
W(X) = \frac{1 - \pi_0(X)}{\phi(\gamma_0, X)^2} + \frac{\pi_0(X)}{(1 - \phi(\gamma_0, X))^2} = \frac{1}{\phi(\gamma_0, X)} + \frac{1}{1 - \phi(\gamma_0, X)} > 0.
\]
We will also use the Gateaux derivative of $M(\gamma, \pi_0)$ in a direction $[\pi - \pi_0]$ given by\[
\Gamma_2(\gamma, \pi_0)[\pi - \pi_0] := \nabla_\pi M(\gamma, \pi_0)[\pi - \pi_0]
= \lim_{h \to 0} \frac{1}{h} [M(\gamma, \pi_0 + h(\pi - \pi_0)) - M(\gamma, \pi_0)]
= -\lim_{h \to 0} \frac{1}{h} E \left[ \left\{ \frac{h(\pi(X) - \pi_0(X))}{\phi(\gamma, X)} + \frac{h(\pi(X) - \pi_0(X))}{1 - \phi(\gamma, X)} \right\} \nabla_\gamma \phi(\gamma, X) \right]
= -E \left[ \{\pi(X) - \pi_0(X)\} \left\{ \frac{1}{\phi(\gamma, X)} + \frac{1}{1 - \phi(\gamma, X)} \right\} \nabla_\gamma \phi(\gamma, X) \right].
\] (A26)

We apply Theorem 2 in [3] so we need to verify its conditions. Consistency of $\hat{\gamma}_n$ is shown in Theorem 1, while condition (2.1) in [3] is satisfied by construction since\[
\|M_n(\hat{\gamma}_n, \hat{\pi}_n)\| = 0 = \inf_{\gamma \in G} \|M_n(\gamma, \hat{\pi}_n)\|.
\]
Note that assumption (AC1) was needed in Theorem 1 in order to obtain almost sure convergence. However, here we only need convergence in probability for which (AN4)-(ii) suffices. For condition (2.2) in [3], the derivative of $M$ with respect to $\gamma$ is computed in (A25) and the matrix is negative definite (as a result also full rank) because of our assumption (AN3). Moreover the directional derivative was computed in (A26) and for $[\gamma, \pi] \in G_{\delta_n} \times \Pi_{\delta_n}$ with $G_{\delta_n} = \{ \gamma \in G : |\gamma - \gamma_0| \leq \delta_n \}$, $\Pi_{\delta_n} = \{ \pi \in \Pi : \|\pi - \pi_0\|_\infty \leq \delta_n \}$, $\delta_n = o(1)$, we have\[
\|M(\gamma, \pi) - M(\gamma, \pi_0) - \Gamma_2(\gamma, \pi_0)[\pi - \pi_0]\|
= \left\| E \left[ \left\{ \frac{\pi_0(X) - \pi(X)}{\phi(\gamma, X)} + \frac{\pi_0(X) - \pi(X)}{1 - \phi(\gamma, X)} \right\} \nabla_\gamma \phi(\gamma, X) \right] \right\| + E \left[ \{\pi(X) - \pi_0(X)\} \left\{ \frac{1}{\phi(\gamma, X)} + \frac{1}{1 - \phi(\gamma, X)} \right\} \nabla_\gamma \phi(\gamma, X) \right]\| = 0,
\]
which means that condition (2.3i) is satisfied. For condition (2.3ii), we have\[
\Gamma_2(\gamma, \pi_0)[\pi - \pi_0] - \Gamma_2(\gamma_0, \pi_0)[\pi - \pi_0]
= -E \left[ \{\pi(X) - \pi_0(X)\} \left\{ \left( \frac{1}{\phi(\gamma, X)} + \frac{1}{1 - \phi(\gamma, X)} \right) \nabla_\gamma \phi(\gamma, X) \right. \right.
\left. - \left( \frac{1}{\phi(\gamma_0, X)} + \frac{1}{1 - \phi(\gamma_0, X)} \right) \nabla_\gamma \phi(\gamma_0, X) \right\} \right].
Then, from $\sup_x |\pi(x) - \pi_0(x)| \leq \delta_n$, $|\gamma - \gamma_0| \leq \delta_n \to 0$ and (AN1), it follows that

$$
\|\Gamma_2(\gamma, \pi_0)[\pi - \pi_0] - \Gamma_2(\gamma_0, \pi_0)[\pi - \pi_0]\| \leq o(1)\delta_n.
$$

Conditions (2.4) and (2.6) in [3] are satisfied thanks to our assumption (AN4) because from (AN1) we have

$$
\|\Gamma_2(\gamma_0, \pi_0)[\pi - \pi_0] - \Gamma_2(\gamma_0, \pi_0)[\pi - \pi_0]\| \leq o(1)\delta_n.
$$

Then we conclude by central limit theorem that

$$
\sqrt{n}(M_n(\gamma_0, \pi_0) + \Gamma_2(\gamma_0, \pi_0)[\hat{\pi} - \pi_0]) \xrightarrow{d} N(0, V)
$$

where $V = \text{Var}(\Psi(Y, \Delta, X, Z))$. It remains to deal with condition (2.5), which is a consequence of Theorem 3 in [3] and assumption (AN2) because from (AN1) we have

$$
\|m(x; \gamma_1, \pi_1) - m(x; \gamma_2, \pi_2)\| \leq \left\| \left( \frac{1 - \pi_1(x)}{\phi(\gamma_1, x)} + \frac{\pi_1(x)}{1 - \phi(\gamma_1, x)} \right) \nabla_\gamma \phi(\gamma_1, X) \\
- \left( \frac{1 - \pi_2(x)}{\phi(\gamma_2, x)} + \frac{\pi_2(x)}{1 - \phi(\gamma_2, X)} \right) \nabla_\gamma \phi(\gamma_2, X) \right\|
\leq C_1\|\gamma_1 - \gamma_2\| + C_2\|\pi_1 - \pi_2\|_\infty.
$$

Finally, the asymptotic normality follows from Theorem 2 in [3] and the asymptotic covariance matrix is given by

$$
\Sigma_\gamma = (\Gamma_1 \Gamma_1)^{-1} \Gamma_1 V \Gamma_1 \Gamma_1^{-1} = \Gamma_1^{-1} V \Gamma_1^{-1} \tag{A28}
$$

\[\square\]

PROOF OF THEOREM 4. We show that conditions 1 and 4 of Theorem 4 in [5] are satisfied. Define $S_n$ as the version of $\hat{S}_n$ where $\hat{\gamma}_n$ is replaced by $\gamma_0$

$$
S_n(\hat{\Lambda}_n, \hat{\beta}_n)(h_1, h_2) = \frac{1}{n} \sum_{i=1}^{n} \Delta_i I_{\{\gamma_i < \gamma_0\}} [h_1(Y_i) + h_2'Z_i] \\
- \frac{1}{n} \sum_{i=1}^{n} \left\{ \Delta_i + (1 - \Delta_i) I_{\{\gamma_i \leq \gamma_0\}} g_i(Y_i, \hat{\Lambda}_n, \hat{\beta}_n, \gamma_0) \right\} \\
\times \left\{ e^{\hat{\beta}_i Z_i} \int_{0}^{Y_i} h_1(s) d\hat{\Lambda}_n(s) + e^{\hat{\beta}_i Z_i^2} \hat{\Lambda}_n(Y_i) h_2'Z_i \right\}
$$
Condition 1. We start by writing
\[
\hat{S}_n(\Lambda_0, \beta_0)(h_1, h_2) - S(\Lambda_0, \beta_0)(h_1, h_2) = \left[ \hat{S}_n(\Lambda_0, \beta_0)(h_1, h_2) - S_n(\Lambda_0, \beta_0)(h_1, h_2) \right] \\
+ [S_n(\Lambda_0, \beta_0)(h_1, h_2) - S(\Lambda_0, \beta_0)(h_1, h_2)].
\] (A29)

For the second term on the right hand side we have
\[
S_n(\Lambda_0, \beta_0)(h_1, h_2) - S(\Lambda_0, \beta_0)(h_1, h_2) = \int f_h(y, \delta, x, z) \, d(\mathbb{P}_n - \mathbb{P})(y, \delta, x, z)
\] (A30)
where
\[
f_h(y, \delta, x, z) = h_2 z \left\{ \delta 1_{\{y < \tau_0\}} - \left[ \delta - (1 - \delta) 1_{\{y \leq \tau_0\}} g(y, \Lambda_0, \beta_0, \gamma_0) \right] e^{\beta_0 z} \Lambda_0(y) \right\} \\
+ \delta 1_{\{y < \tau_0\}} h_1(y) - \left[ \delta - (1 - \delta) 1_{\{y \leq \tau_0\}} g(y, \Lambda_0, \beta_0, \gamma_0) \right] e^{\beta_0 z} \int_0^y h_1(s) \, d\Lambda_0(s).
\]
The classes \( \{h_2 \in \mathbb{R}^q, \|h_2\| \leq m\} \), \( \{h_1 \in BV[0, \tau_0], \|h_1\|_v \leq m\} \) and
\[
\left\{ \int_0^y h_1(t) \, d\Lambda_0(t), h_1 \in BV[0, \tau_0], \|h_1\|_v \leq m \right\}
\]
are Donsker classes (the last one because it consists of monotone bounded functions). As in [5], because of the boundedness of the covariates and \( \Lambda_0 \), it follows that \( \{f_h(y, \delta, x, z), h \in \mathcal{H}_m\} \) is also a Donsker class since it is sum of products of Donsker classes with fixed uniformly bounded functions.

On the other hand, for the first term on the right hand side of (A29), we have
\[
\left[ \hat{S}_n(\Lambda_0, \beta_0)(h_1, h_2) - S_n(\Lambda_0, \beta_0)(h_1, h_2) \right] \\
= -\frac{1}{n} \sum_{i=1}^n (1 - \Delta_i) 1_{\{Y_i \leq \tau_0\}} \left\{ e^{\beta_0 Z_i} \int_0^{Y_i} h_1(s) \, d\Lambda_0(s) + e^{\delta_0 Z_i} \Lambda_0(Y_i) h'_2 Z_i \right\} \\
\times \{g_i(Y_i, \Lambda_0, \beta_0, \gamma_0) - g_i(Y_i, \Lambda_0, \beta_0, \gamma_0)\}
\]
\[
= -\frac{1}{n} \sum_{i=1}^n (1 - \Delta_i) 1_{\{Y_i \leq \tau_0\}} e^{\beta_0 Z_i} \left\{ \int_0^{Y_i} h_1(s) \, d\Lambda_0(s) + \Lambda_0(Y_i) h'_2 Z_i \right\} \\
\times \frac{\partial g_i}{\partial \phi}(Y_i, \Lambda_0, \beta_0, \gamma_0) \left\{ \phi(\gamma_0, X_i) - \hat{\phi}(\gamma_0, X_i) \right\} + o_P(n^{-1/2}),
\] (A31)
where
\[
\frac{\partial g_i}{\partial \phi}(Y_i, \Lambda_0, \beta_0, \gamma_0) = \frac{\exp\left(-\Lambda(Y_i)e^{\beta Z_i}\right)}{1 - \phi(\gamma, X_j) + \phi(\gamma, X_j) \exp(-\Lambda(Y_i)e^{\beta Z_i})} \\
+ \frac{\phi(\gamma, X_j) \exp\left(-\Lambda(Y_i)e^{\beta Z_i}\right)}{[1 - \phi(\gamma, X_j) + \phi(\gamma, X_j) \exp(-\Lambda(Y_i)e^{\beta Z_i})]^2}.
\]
In order to conclude that the remainder term is of order \(o_P(n^{-1/2})\) we use
\[
\sup_x |\phi(\tilde{\gamma}_n, x) - \phi(\gamma_0, x)| \leq \sup_{\gamma \in G, x \in X} \|\nabla_\gamma \phi(\gamma, x)\| |\tilde{\gamma}_n - \gamma_0| = O_P(n^{-1/2})
\]
and the fact that \(\frac{\partial^2 g}{\partial \gamma^2}(Y_i, \Lambda_0, \beta_0, \gamma)\) and
\[
(1 - \Delta_i) I_{\{Y_i \leq \tau_0\}} e^{\beta_0 Z_i} \left\{ \int_0^{Y_i} h_1(s) d\Lambda_0(s) + \Lambda_0(Y_i) h_2' Z_i \right\}
\]
are uniformly bounded functions thanks to our assumptions on \(Z, \Lambda, \Phi\) and \(h\). From the same assumptions we also obtain
\[
\frac{1}{n} \sum_{i=1}^n (1 - \Delta_i) I_{\{Y_i \leq \tau_0\}} e^{\beta_0 Z_i} \left\{ \int_0^{Y_i} h_1(s) d\Lambda_0(s) + \Lambda_0(Y_i) h_2' Z_i \right\}
\]
\[
\times \frac{\partial g_i}{\partial \phi}(Y_i, \Lambda_0, \beta_0, \gamma) \{\phi(\tilde{\gamma}_n, X_i) - \phi(\gamma_0, X_i)\}
\]
\[
= \frac{1}{n} \sum_{i=1}^n (1 - \Delta_i) e^{\beta_0 Z_i} \left\{ \int_0^{Y_i} h_1(s) d\Lambda_0(s) + \Lambda_0(Y_i) h_2' Z_i \right\}
\]
\[
\times \frac{\partial g_i}{\partial \phi}(Y_i, \Lambda_0, \beta_0, \gamma) \nabla_\gamma \phi(\gamma_0, X_i)' \{\tilde{\gamma}_n - \gamma_0\} + o_P(n^{-1/2})
\]
\[
= \mathbb{E} \left[ (1 - \Delta) I_{\{Y \leq \tau_0\}} e^{\beta_0 Z} \left\{ \int_0^Y h_1(s) d\Lambda_0(s) + \Lambda_0(Y) h_2' Z \right\}
\]
\[
\times \frac{\partial g}{\partial \phi}(Y, \Lambda_0, \beta_0, \gamma) \nabla_\gamma \phi(\gamma_0, X)' \{\tilde{\gamma}_n - \gamma_0\} + o_P(n^{-1/2}) \right].
\]
(A32)

and the expectation term is uniformly bounded. To prove the asymptotic normality of \(\tilde{\gamma}_n - \gamma_0\) in Theorem 3 we used Theorem 2 in [3]. Going through the proof of Theorem 2 in [3], we actually have
\[
(\tilde{\gamma}_n - \gamma_0) = -(\Gamma_1' \Gamma_1)^{-1} \Gamma_1' \{M_n(\gamma_0, \pi_0) + \Gamma_2(\gamma_0, \pi_0)[\hat{\pi} - \pi_0]\} + o_P(n^{-1/2})
\]
where \(\Gamma_1\) is defined in (A25) and \(\Gamma_2\) in (A26). From Assumption (AN4-iii) and (A27), it follows that
\[
(\tilde{\gamma}_n - \gamma_0) = -(\Gamma_1' \Gamma_1)^{-1} \Gamma_1 \int \Psi(y, \delta, x) (P_n - P)(y, \delta, x, z) + o_P(n^{-1/2}). \quad (A33)
\]

Putting together (A29)-(A33), we have
\[
\hat{S}_n(\Lambda_0, \beta_0)(h_1, h_2) - S(\Lambda_0, \beta_0)(h_1, h_2)
\]
\[
= \int \left\{ f_h(y, \delta, x, z) - Q_h \Gamma_1^{-1} \Psi(y, \delta, x) \right\} d(P_n - P)(y, \delta, x, z) + o_P(n^{-1/2})
\]
We can write the Donsker class of functions (since sum of bounded Donsker classes is also Donsker).

In order to conclude the convergence of \( \sqrt{n}(S_n(T_0) - S(T_0)) \) to a Gaussian process \( G^* \), we need to have that \( \{Q_h \Gamma^{-1}_1 \Psi(y, \delta, x), h \in \mathcal{H}_m \} \) is a bounded Donsker class of functions (since sum of bounded Donsker classes is also Donsker). We can write

\[
Q_h \Gamma^{-1}_1 \Psi(y, \delta, x) = h_2^2 \mathbb{E} \left[ (1 - \Delta) I_{\{Y \leq \tau_0\}} e^{\beta_0 Z} \Lambda_0(Y) \frac{\partial g}{\partial \phi}(Y, \Lambda_0, \beta_0, \gamma_0) \nabla \gamma \phi(\gamma_0, X)' \right] \Gamma^{-1}_1 \Psi(y, \delta, x)
\]

By assumption (AN1) and \( \inf H((\tau_0, \infty) | x) > 0 \), \( \Lambda_0(\tau_0) < \infty \) and the boundedness of the covariates, we have that

\[
\mathbb{E} \left[ (1 - \Delta) I_{\{Y \leq \tau_0\}} e^{\beta_0 Z} \Lambda_0(Y) \frac{\partial g}{\partial \phi}(Y, \Lambda_0, \beta_0, \gamma_0) \nabla \gamma \phi(\gamma_0, X)' \right] \Gamma^{-1}_1 \Psi(y, \delta, x)
\]

is uniformly bounded. Hence

\[
\left\{ h_2^2 \mathbb{E} \left[ (1 - \Delta) I_{\{Y \leq \tau_0\}} e^{\beta_0 Z} \Lambda_0(Y) \frac{\partial g}{\partial \phi}(Y, \Lambda_0, \beta_0, \gamma_0) \nabla \gamma \phi(\gamma_0, X)' \right] \Gamma^{-1}_1 \Psi(y, \delta, x) : h_2 \in \mathbb{R}^q, \|h_2\|_{L_1} \leq m \right\}
\]

is a Donsker class (see Example 2.10.10 in [8]). It can also be shown that, since \( h_1 \) belongs to the class of bounded functions with bounded variation and all the other terms are uniformly bounded, that

\[
\left\{ \int_0^{\tau_0} \mathbb{E} \left[ (1 - \Delta) I_{\{Y \leq \tau_0\}} e^{\beta_0 Z} \frac{\partial g}{\partial \phi}(Y, \Lambda_0, \beta_0, \gamma_0) \nabla \gamma \phi(\gamma_0, X)' \right] h_1(s) d\Lambda_0(s) \Gamma^{-1}_1 \Psi(y, \delta, x), \right. \]

\[
\left. h_1 \in BV[0, \tau_0], \|h_1\|_v \leq m \right\}
\]

is also a bounded Donsker class (covering numbers of order \( \epsilon \) of \( \{h_1 \in BV[0, \tau_0], \|h_1\|_v \leq m \} \) correspond to covering numbers of order \( \epsilon \) for some constant \( c > 0 \).

The limit process \( G^* \) has mean zero because

\[
\mathbb{E}[f_h(y, \delta, x, z)] = S(T_0)(h) = 0 \quad \text{and} \quad \mathbb{E}[\Psi(Y, \Delta, X)] = 0.
\]
The covariance process of $G^*$ is
\[
\text{Cov}(G^*(h), G^*(\tilde{h})) \equiv E \left[ \left\{ f_h(Y, \Delta, X, Z) - Q_h \Gamma_1^{-1} \Psi(Y, \Delta, X) \right\} \left\{ f_{\tilde{h}}(Y, \Delta, X, Z) - Q_{\tilde{h}} \Gamma_1^{-1} \Psi(Y, \Delta, X) \right\} \right] \\
= E\left[f_h(Y, \Delta, X, Z) f_{\tilde{h}}(Y, \Delta, X, Z) \Psi(Y, \Delta, X) \right] - Q_h \Gamma_1^{-1} E[f_h(Y, \Delta, X, Z) \Psi(Y, \Delta, X)] + Q_{\tilde{h}} \Gamma_1^{-1} E[\Psi(Y, \Delta, X) \Psi(Y, \Delta, X)]' \Gamma_1^{-1} Q_{\tilde{h}}. 
\]
(A34)

**Condition 4 of Theorem 4 in [5].** As for condition 1, we write
\[
\sqrt{n} \left\{ (\hat{S}_n - S)(\Upsilon_n) - (\hat{S}_n - S)(\Upsilon_0) \right\} = \sqrt{n} \left\{ (S_n - S)(\Upsilon_n) - (S_n - S)(\Upsilon_0) \right\} + \sqrt{n} \left\{ (\hat{S}_n - S_n)(\Upsilon_n) - (\hat{S}_n - S_n)(\Upsilon_0) \right\}
\]
(A35)

For the second term in the right hand side of (A35), similarly to (A31)-(A32), we have
\[
(\hat{S}_n - S_n)(\Upsilon_n) - (\hat{S}_n - S_n)(\Upsilon_0) \\
= \frac{1}{n} \sum_{i=1}^{n} (1 - \Delta_i) \mathbb{I}_{\{Y_i \leq \tau_0\}} e^{\hat{\beta}_n Z_i} \left\{ \int_0^{Y_i} h_1(s) d\hat{\Lambda}_n(s) + \hat{\Lambda}_n(Y_i) h_2 Z_i \right\} \\
- \frac{1}{n} \sum_{i=1}^{n} (1 - \Delta_i) \mathbb{I}_{\{Y_i \leq \tau_0\}} e^{\hat{\beta}_n Z_i} \left\{ \int_0^{Y_i} h_1(s) d\Lambda_0(s) + \Lambda_0(Y_i) h_2 Z_i \right\} \\
= o_P(n^{-1/2})
\]

Using the boundedness in probability of $\hat{\beta}_n$ and $\hat{\Lambda}_n(\tau_0)$, the boundedness of the covariates, $\hat{\beta}_0$, $\Lambda_0(\tau)$, $\nabla \phi(\gamma, x)$ and the consistency results in Theorem 2, it follows that
\[
\left| \frac{1}{n} \sum_{i=1}^{n} (1 - \Delta_i) \mathbb{I}_{\{Y_i \leq \tau_0\}} e^{\hat{\beta}_n Z_i} \left( \int_0^{Y_i} h_1(s) d\hat{\Lambda}_n(s) + \hat{\Lambda}_n(Y_i) h_2 Z_i \right) \frac{\partial g_i}{\partial \phi}(Y_i, \hat{\beta}_n, \hat{\beta}_n, \gamma_0) \\
- e^{\beta_0 Z_i} \left( \int_0^{Y_i} h_1(s) d\Lambda_0(s) + \Lambda_0(Y_i) h_2 Z_i \right) \frac{\partial g_i}{\partial \phi}(Y_i, \beta_0, \beta_0, \gamma_0) \nabla \phi(\gamma_0, x) \right| = o_P(1)
\]

As a consequence, since $\hat{\gamma}_n - \gamma_0 = O_P(n^{-1/2})$, we obtain
\[
\sqrt{n} \left\{ (\hat{S}_n - S_n)(\Upsilon_n) - (\hat{S}_n - S_n)(\Upsilon_0) \right\} = o_P(1).
\]

It remains to deal with the first term on the right hand side of (A35). It suffices to show that, for any sequence $\epsilon_n \to 0$,
\[
\sup_{|\Lambda - \Lambda_0|_{\infty} \leq \epsilon_n, \|\beta - \beta_0\| \leq \epsilon_n} \frac{|(S_n - S)(\Upsilon) - (S_n - S)(\Upsilon_0)|}{n^{-1/2} \vee \|\beta - \beta_0\| \vee |\Lambda - \Lambda_0|_{\infty}} = o_P(1).
\]
Let
\[
a_1(y, \delta, z, x) = \delta e^{\beta z} \int_0^y h_1(s)d\Lambda(s) - \delta e^{\beta_0 z} \int_0^y h_1(s)d\Lambda_0(s),
\]
\[
a_2(y, \delta, z, x) = \delta e^{\beta z} \Lambda(y)h_2'z - \delta e^{\beta_0 z}\Lambda_0(y)h_2'z,
\]
and
\[
a_3(y, \delta, z, x) = (1 - \delta)I_{(y \leq \tau_0)}g(y, \Lambda, \beta, \gamma_0) \left\{ e^{\beta z} \int_0^y h_1(s)d\Lambda(s) + e^{\beta z} \Lambda(y)h_2'z \right\} \\
- (1 - \delta)I_{(y \leq \tau_0)}g(y, \Lambda_0, \beta_0, \gamma_0) \left\{ e^{\beta_0 z} \int_0^y h_1(s)d\Lambda_0(s) + e^{\beta_0 z}\Lambda_0(y)h_2'z \right\}
\]

Then, we have
\[
(S_n - S)(\Upsilon) - (S_n - S)(\Upsilon_0) = -\frac{1}{n} \sum_{i=1}^n \left\{ a_1(Y_i, \Delta_i, Z_i, X_i) - \mathbb{E} \left[ a_1(Y, \Delta, Z, X) \right] \right\} \\
-\frac{1}{n} \sum_{i=1}^n \left\{ a_2(Y_i, \Delta_i, Z_i, X_i) - \mathbb{E} \left[ a_2(Y, \Delta, Z, X) \right] \right\} \\
-\frac{1}{n} \sum_{i=1}^n \left\{ a_3(Y_i, \Delta_i, Z_i, X_i) - \mathbb{E} \left[ a_3(Y, \Delta, Z, X) \right] \right\}
\]

Next we consider the first term. The other two can be handled similarly. From a Taylor expansion we have
\[
\delta e^{\beta z} \int_0^y h_1(s)d\Lambda(s) - \delta e^{\beta_0 z} \int_0^y h_1(s)d\Lambda_0(s) \\
= (\beta - \beta_0)'z\delta e^{\beta_0 z} \int_0^y h_1(s)d\Lambda(s) + \delta e^{\beta_0 z} \int_0^y h_1(s)d(\Lambda - \Lambda_0)(s) + o(||\beta - \beta_0||).
\]

Hence
\[
\frac{1}{n} \sum_{i=1}^n \left\{ a_1(Y_i, \Delta_i, Z_i, X_i) - \mathbb{E} \left[ a_1(Y, \Delta, Z, X) \right] \right\} \\
\leq (\beta - \beta_0) \left\{ \frac{1}{n} \sum_{i=1}^n Z_i \Delta_i e^{\beta_0 Z_i} \int_0^{Y_i} h_1(s)d\Lambda(s) - \mathbb{E} \left[ Z\Delta e^{\beta_0 Z} \int_0^{Y} h_1(s)d\Lambda(s) \right] + o(1) \right\} \\
+ \frac{1}{n} \sum_{i=1}^n \left\{ \Delta_i e^{\beta_0 Z_i} \int_0^{Y_i} h_1(s)d(\Lambda - \Lambda_0)(s) - \mathbb{E} \left[ \Delta e^{\beta_0 Z} \int_0^{Y} h_1(s)d(\Lambda - \Lambda_0)(s) \right] \right\}.
\]

(A36)

By the law of large numbers
\[
\frac{1}{n} \sum_{i=1}^n \left\{ Z_i \Delta_i e^{\beta_0 Z_i} \int_0^{Y_i} h_1(s)d\Lambda(s) - \mathbb{E} \left[ Z\Delta e^{\beta_0 Z} \int_0^{Y} h_1(s)d\Lambda(s) \right] \right\} = o_P(1)
\]
and as a result, the first term in the right hand side of (A36) is \( o_p(\|\beta - \beta_0\|) \). The second term can be rewritten as

\[
\int_0^{\tau_0} D_n(s)h_1(s)d(\Lambda - \Lambda_0)(s)
\]

where

\[
D_n(s) = \frac{1}{n} \sum_{i=1}^n \{ \Delta_i \mathbf{1}_{\{Y_i \geq s\}} e^{\beta_0 s Z_i} - \mathbb{E} \left[ \Delta_i \mathbf{1}_{\{Y_i \geq s\}} e^{\beta_0 s Z_i} \right] \}.
\]

By integration by parts and the chain rule we have

\[
\int_0^{\tau_0} D_n(s)h_1(s)d(\Lambda - \Lambda_0)(s)
\]

\[
= D_n(\tau_0)h_1(\tau_0)(\Lambda - \Lambda_0)(\tau_0) - \int_0^{\tau_0} (\Lambda - \Lambda_0)(s)d[D_n(s)h_1(s)]
\]

\[
= D_n(\tau_0)h_1(\tau_0)(\Lambda - \Lambda_0)(\tau_0) - \int_0^{\tau_0} (\Lambda - \Lambda_0)(s)D_n(s)dh_1(s)
\]

\[
+ \frac{1}{n} \sum_{i=1}^n \left\{ \Delta_i(\Lambda - \Lambda_0)(Y_i)h_1(Y_i)e^{\beta_0 s Z_i} - \mathbb{E} \left[ (\Lambda - \Lambda_0)(Y_i)h_1(Y_i)\Delta e^{\beta_0 s Z_i} \right] \right\}
\]

Note that

\[
\mathbb{E} \left[ (\Lambda - \Lambda_0)(Y)h_1(Y)\Delta e^{\beta_0 s Z} \right] = \mathbb{E} \left[ e^{\beta_0 s Z} \int_0^{\tau_0} (\Lambda - \Lambda_0)(s)h_1(s)dH_1(s|X,Z) \big| X,Z \right]
\]

\[
= - \int_0^{\tau_0} (\Lambda - \Lambda_0)(s)h_1(s)d\mathbb{E} \left[ \Delta \mathbf{1}_{\{Y \geq s\}} e^{\beta_0 s Z} \right].
\]

It can be shown that \( \sqrt{n}D_n \) converges weakly to a tight, mean zero Gaussian process \( D \) in \( l^\infty([0,\tau_0]) \). Since \( h_1 \) is bounded, it follows

\[
\frac{|D_n(\tau_0)h_1(\tau_0)(\Lambda - \Lambda_0)(\tau_0)|}{\|\Lambda - \Lambda_0\|_\infty} = o_p(1)
\]

Moreover, since \( D_n \to 0 \) and \( h_1 \) is of bounded variation

\[
\frac{\int_0^{\tau_0} (\Lambda - \Lambda_0)(s)D_n(s)dh_1(s)}{\|\Lambda - \Lambda_0\|_\infty} \leq \sup_{t \in [0,\tau_0]} |D_n(s)| \int_0^{\tau_0} |dh(s)| \to 0.
\]

Finally, since \( \{ g_\Lambda(y,\delta,z) = \delta(\Lambda - \Lambda_0)(y)h_1(y)e^{\beta_0 s Z} : \|\Lambda - \Lambda_0\|_\infty \leq \epsilon_n \} \) is a Donsker class (product of bounded variation functions, uniformly bounded) and

\[
\mathbb{E} \left[ (\Lambda - \Lambda_0)(Y)^2 h_1(Y)^2 \Delta e^{2\beta_0 s Z} \right] = O(\epsilon_n^2) = o(1),
\]

we have that

\[
\sqrt{n} \frac{1}{n} \sum_{i=1}^n \left( \Delta_i(\Lambda - \Lambda_0)(Y_i)h_1(Y_i)e^{\beta_0 s Z_i} - \mathbb{E} \left[ (\Lambda - \Lambda_0)(Y_i)h_1(Y_i)\Delta e^{\beta_0 s Z_i} \right] \right)
\]
converges to zero in probability. So we obtain
\[
\frac{\int_0^n D_n(s)h_1(s)d(\Lambda - \Lambda_0)(s)}{n^{-1/2}\sqrt{\|\Lambda - \Lambda_0\|_\infty}} = o_P(1)
\]
The other two terms related to \(a_2\) and \(a_3\) can be treated similarly.

This concludes the verification of conditions of Theorem 4 in [5] (or Theorem 3.3.1 in [8]). Hence, the weak convergence of \(\sqrt{n}(\bar{Y}_n - Y_0)\) to the tight, mean zero Gaussian process \(G\) follows. Next we compute the covariance process of \(G\). From Theorem 3.3.1 in [8] we have
\[
\sqrt{n}\hat{S}(Y_0)(\bar{Y}_n - Y_0)(h) = \sqrt{n}(\hat{S}_n(Y_0) - S(Y_0))(h) + o_P(1).
\] (A37)

Moreover, in [5] it is computed that
\[
\hat{S}(Y_0)(\bar{Y}_n - Y_0)(h) = \int_0^\tau \sigma_1(h)(t)d(\hat{\Lambda}_n(t) - \Lambda_0(t)) + (\hat{\beta}_n - \beta_0)'\sigma_2(h)
\] (A38)
where \(\sigma = (\sigma_1, \sigma_2)\) is a continuous linear operator from \(H_\mu\) to \(H_\mu\) of the form
\[
\sigma_1(h)(t) = \mathbb{E}\left[\mathbb{I}_{\{Y \geq t\}}V(t, Y_0)(h)g(t, Y_0)e^{\beta_0^t Z}\right]
\]
\[
- \mathbb{E}\left[\int_t^\tau \mathbb{I}_{\{Y > s\}}V(t, Y_0)(h)g(s, Y_0)(1 - g(s, Y_0))e^{2\beta_0^s Z}d\Lambda_0(s)\right]
\]
and
\[
\sigma_2(h)(t) = \mathbb{E}\left[\int_0^\tau \mathbb{I}_{\{Y < t\}}W(t, Y_0)V(t, Y_0)(h)g(t, Y_0)e^{\beta_0^t Z}d\Lambda_0(t)\right]
\]
where
\[
V(t, Y_0)(h) = h_1(t) - (1 - g(t, Y_0))e^{\beta_0^t Z}\int_0^t h_1(s)d\Lambda_0(s) + h_2^t W(t, Y_0)
\]
and
\[
W(t, Y_0) = \left[1 - (1 - g(t, Y_0))e^{\beta_0^t Z}\Lambda_0(t)\right] Z
\]
In [5], it is also shown that \(\sigma\) is invertible with inverse \(\sigma^{-1} = (\sigma_1^{-1}, \sigma_2^{-1})\). Hence, for all \(g \in H_\mu\), let \(h = \sigma^{-1}(g)\). If in (A38) we replace \(h\) by \(\sigma^{-1}(g)\) and use (A37), we obtain
\[
\int_0^T g(t)d\sqrt{n}(\hat{\Lambda}_n(t) - \Lambda_0(t)) + \sqrt{n}(\hat{\beta}_n - \beta_0)'g_2
\]
\[
= -\sqrt{n}(\hat{S}_n(Y_0) - S(Y_0))(\sigma^{-1}(g)) + o_P(1) \overset{D}{\to} -G^*(\sigma^{-1}(g)).
\]
Since the previous result holds for all \(g \in H_\mu\), it follows that \((\sqrt{n}(\hat{\Lambda}_n - \Lambda_0), \sqrt{n}(\hat{\beta}_n - \beta_0))\) converges to a tight mean zero Gaussian process \(G\) with covariance
\[
Cov(G(g), G(\bar{g})) = Cov\left(G^*(\sigma^{-1}(g)), G^*(\sigma^{-1}(\bar{g}))\right)
\] (A39)
and the covariance of \(G^*\) is given in (A34).
Appendix B: Additional simulation results

In this section we report the simulation results for scenario 2 of the models 1-4, \( n = 200,400 \), that were omitted from the main paper and the results for sample size \( n = 1000 \) (all models and scenarios). In addition, Table A2 complements Tables 4 and 5 containing results for \( \hat{\beta} \).

References

[1] Ash, R. B. (1972) Real Analysis and Probability. Academic Press, New York.
[2] Burke, K. and Patilea, V. (2020) Supplementary Material for "A likelihood approach for cure regression models". TEST.
[3] Chen, X., Linton, O. and Van Keilegom, I. (2003) Estimation of semiparametric models when the criterion function is not smooth. Econometrica, 71 (5), 1591–1608.
[4] Murphy, S. A et. al. (1994) Consistency in a proportional hazards model incorporating a random effect. Ann. Stat., 22 (2), 712–731.
[5] Lu, W. (2008) Maximum likelihood estimation in the proportional hazards cure model. Ann. I. Stat. Math., 60 (3), 545–574.
[6] Patilea, V. and Van Keilegom, I. (2020) A general approach for cure models in survival analysis. To appear in: Ann. Stat.
[7] Scharfstein, D. O., Tsiatis, A. A. and Gilbert, P. B. (1998) Semiparametric efficient estimation in the generalized odds-rate class of regression models for right-censored time-to-event data. Lifetime Data Anal., 4 (4), 355–391.
[8] van der Vaart, A. W. and Wellner, J. A. (1996) Weak convergence and empirical processes. Springer Series in Statistics, Springer-Verlag, New York,With applications to statistics.
[9] Wellner, J. A. (1978) Limit theorems for the ratio of the empirical distribution function to the true distribution function. Z. Wahrsch. Verw. Gebiete, 45 (1), 73–88.
| Mod. | n | scen. | Par. | Cens. level 1 | Cens. level 2 | Cens. level 3 |
|-----|---|------|------|--------------|--------------|--------------|
|     |   |      |      | Bias Var. MSE | Bias Var. MSE | Bias Var. MSE |
| 1   | 200 | 2     | \(\gamma_1\) | 0.005 0.032 0.032 | -0.005 0.037 0.037 | -0.005 0.045 0.045 |
|     |    |       |      | 0.013 0.032 0.032 | 0.009 0.038 0.038 | 0.015 0.046 0.046 |
|     |    |       | \(\gamma_2\) | -0.024 0.093 0.094 | -0.035 0.116 0.118 | -0.018 0.137 0.137 |
|     |    |       |      | 0.017 0.096 0.096 | 0.016 0.123 0.123 | 0.046 0.144 0.146 |
|     |    |       | \(\beta\) | 0.019 0.033 0.033 | 0.025 0.035 0.036 | 0.011 0.041 0.041 |
|     |    |       |      | 0.018 0.033 0.031 | 0.023 0.036 0.036 | 0.007 0.042 0.042 |

| 400 | 2 | \(\gamma_1\) | 0.002 0.016 0.016 | 0.003 0.018 0.018 | 0.009 0.021 0.021 |
|     |   |      |      | 0.008 0.016 0.016 | 0.011 0.019 0.019 | 0.020 0.021 0.022 |
|     |   |       | \(\gamma_2\) | -0.017 0.046 0.047 | -0.016 0.054 0.054 | -0.013 0.070 0.070 |
|     |   |       |      | 0.012 0.046 0.047 | 0.018 0.055 0.055 | 0.025 0.068 0.068 |
|     |   |       | \(\beta\) | 0.001 0.014 0.014 | 0.019 0.019 0.019 | 0.001 0.020 0.020 |
|     |   |       |      | 0.000 0.014 0.014 | 0.017 0.019 0.019 | -0.001 0.020 0.020 |

| 2   | 200 | 2     | \(\gamma_1\) | -0.004 0.033 0.033 | -0.016 0.039 0.039 | -0.032 0.050 0.051 |
|     |    |       |      | 0.020 0.034 0.034 | 0.037 0.042 0.044 | 0.079 0.064 0.070 |
|     |    |       | \(\gamma_2\) | -0.016 0.041 0.041 | -0.037 0.044 0.045 | -0.054 0.057 0.060 |
|     |    |       |      | 0.029 0.044 0.045 | 0.031 0.052 0.053 | 0.064 0.075 0.079 |
|     |    |       | \(\beta\) | 0.004 0.016 0.016 | 0.008 0.017 0.017 | 0.008 0.018 0.018 |
|     |    |       |      | 0.002 0.016 0.016 | 0.003 0.018 0.018 | -0.005 0.019 0.019 |

| 400 | 2 | \(\gamma_1\) | 0.000 0.018 0.018 | -0.002 0.022 0.022 | -0.015 0.028 0.028 |
|     |   |      |      | 0.012 0.018 0.018 | 0.027 0.022 0.023 | 0.043 0.030 0.032 |
|     |   |       | \(\gamma_2\) | -0.019 0.021 0.021 | -0.022 0.025 0.026 | -0.045 0.031 0.033 |
|     |   |       |      | 0.007 0.022 0.022 | 0.018 0.027 0.027 | 0.023 0.033 0.033 |
|     |   |       | \(\beta\) | 0.005 0.007 0.007 | 0.010 0.008 0.008 | 0.009 0.010 0.010 |
|     |   |       |      | 0.004 0.007 0.007 | 0.007 0.008 0.008 | 0.001 0.011 0.011 |
Table A2
Bias, variance and MSE of $\hat{\beta}$ for secure (second rows) and our approach (first rows) in Model 3 and 4.

| Mod. | n  | scen. | Par. | Cens. level 1 | Cens. level 2 | Cens. level 3 |
|------|----|-------|------|---------------|---------------|---------------|
|      |    |       |      | Bias | Var. | MSE | Bias | Var. | MSE | Bias | Var. | MSE |
| 3    | 200| 1     | $\beta_1$ | -0.013 | 0.007 | 0.007 | -0.007 | 0.006 | 0.006 | -0.009 | 0.008 | 0.008 |
|      |    |       |       | -0.014 | 0.007 | 0.007 | -0.009 | 0.006 | 0.007 | -0.014 | 0.008 | 0.008 |
|      |    |       | $\beta_2$ | 0.007 | 0.003 | 0.003 | 0.006 | 0.003 | 0.003 | 0.005 | 0.004 | 0.004 |
|      |    |       |       | 0.007 | 0.003 | 0.003 | 0.008 | 0.003 | 0.003 | 0.007 | 0.004 | 0.004 |
|      |    |       | $\beta_3$ | 0.016 | 0.043 | 0.043 | 0.004 | 0.043 | 0.043 | 0.007 | 0.053 | 0.053 |
|      |    |       |       | 0.017 | 0.043 | 0.043 | 0.006 | 0.043 | 0.043 | 0.015 | 0.053 | 0.054 |
|      |    |       | $\beta_4$ | 0.018 | 0.066 | 0.066 | -0.002 | 0.081 | 0.081 | 0.021 | 0.099 | 0.100 |
|      |    |       |       | 0.018 | 0.066 | 0.066 | 0.001 | 0.083 | 0.083 | 0.033 | 0.104 | 0.105 |
| 4    | 200| 1     | $\beta_1$ | -0.012 | 0.005 | 0.005 | -0.010 | 0.005 | 0.005 | -0.006 | 0.005 | 0.005 |
|      |    |       |       | -0.013 | 0.005 | 0.005 | -0.013 | 0.005 | 0.005 | -0.013 | 0.005 | 0.005 |
|      |    |       | $\beta_2$ | 0.003 | 0.003 | 0.003 | 0.002 | 0.003 | 0.003 | 0.001 | 0.003 | 0.003 |
|      |    |       |       | 0.003 | 0.003 | 0.003 | 0.002 | 0.003 | 0.003 | 0.001 | 0.003 | 0.003 |
|      |    |       | $\beta_3$ | 0.002 | 0.032 | 0.032 | 0.000 | 0.036 | 0.036 | 0.000 | 0.040 | 0.040 |
|      |    |       |       | 0.002 | 0.032 | 0.032 | 0.000 | 0.037 | 0.037 | 0.000 | 0.041 | 0.041 |
| 3    | 400| 1     | $\beta_1$ | -0.005 | 0.002 | 0.002 | -0.003 | 0.002 | 0.002 | -0.003 | 0.003 | 0.003 |
|      |    |       |       | -0.005 | 0.002 | 0.002 | -0.005 | 0.002 | 0.002 | -0.003 | 0.003 | 0.003 |
|      |    |       | $\beta_2$ | 0.000 | 0.001 | 0.001 | 0.000 | 0.001 | 0.001 | -0.001 | 0.001 | 0.001 |
|      |    |       |       | 0.000 | 0.001 | 0.001 | 0.000 | 0.001 | 0.001 | -0.001 | 0.001 | 0.001 |
|      |    |       | $\beta_3$ | 0.002 | 0.015 | 0.015 | 0.000 | 0.017 | 0.017 | -0.002 | 0.018 | 0.018 |
|      |    |       |       | 0.002 | 0.015 | 0.015 | 0.000 | 0.017 | 0.017 | -0.001 | 0.018 | 0.018 |
| 3    | 400| 1     | $\beta_1$ | -0.004 | 0.002 | 0.002 | -0.004 | 0.003 | 0.003 | -0.004 | 0.003 | 0.003 |
|      |    |       |       | -0.005 | 0.002 | 0.002 | -0.005 | 0.003 | 0.003 | -0.005 | 0.003 | 0.003 |
|      |    |       | $\beta_2$ | 0.001 | 0.028 | 0.028 | -0.004 | 0.033 | 0.033 | -0.013 | 0.046 | 0.046 |
|      |    |       |       | 0.001 | 0.028 | 0.028 | -0.001 | 0.034 | 0.034 | 0.000 | 0.048 | 0.048 |
### Table A3

Bias, variance and MSE of \( \hat{\gamma} \) and \( \hat{\beta} \) for `smcure` (second rows) and our approach (first rows) in Model 3 (Scenario 2).

| Mod | n  | scen. | Par. | Cens. level 1 | Cens. level 2 | Cens. level 3 |
|-----|----|-------|------|---------------|---------------|---------------|
|     |    |       |      | Bias | Var. | MSE | Bias | Var. | MSE | Bias | Var. | MSE |
| 3   | 200| 2     | \( \gamma_1 \) | -0.056 | 0.261 | 0.264 | -0.215 | 0.344 | 0.390 | -0.379 | 0.422 | 0.566 |
|     |    |       |      | 0.091 | 0.299 | 0.308 | 0.090 | 0.454 | 0.462 | 0.127 | 0.755 | 0.771 |
|     |    |       |      | -0.055 | 0.124 | 0.127 | -0.123 | 0.137 | 0.152 | -0.198 | 0.165 | 0.204 |
|     |    |       |      | 0.183 | 0.178 | 0.212 | 0.275 | 0.268 | 0.344 | 0.390 | 0.485 | 0.638 |
| \( \gamma_2 \) | 0.023 | 0.401 | 0.402 | 0.087 | 0.512 | 0.519 | 0.162 | 0.612 | 0.639 |
|     | 0.164 | 0.488 | 0.514 | 0.278 | 0.729 | 0.806 | 0.427 | 1.159 | 1.341 |
| \( \gamma_4 \) | -0.049 | 0.321 | 0.324 | -0.093 | 0.421 | 0.429 | -0.164 | 0.543 | 0.570 |
|     | 0.036 | 0.367 | 0.369 | 0.086 | 0.547 | 0.554 | 0.062 | 0.795 | 0.799 |
| \( \beta_1 \) | 0.017 | 0.008 | 0.009 | 0.017 | 0.009 | 0.009 | 0.013 | 0.010 | 0.010 |
|     | 0.016 | 0.008 | 0.009 | 0.018 | 0.009 | 0.009 | 0.015 | 0.010 | 0.011 |
| \( \beta_2 \) | 0.004 | 0.004 | 0.004 | 0.007 | 0.004 | 0.004 | 0.005 | 0.005 | 0.005 |
|     | 0.004 | 0.004 | 0.004 | 0.009 | 0.004 | 0.004 | 0.008 | 0.005 | 0.005 |
| \( \beta_3 \) | 0.022 | 0.059 | 0.059 | 0.008 | 0.059 | 0.060 | -0.003 | 0.074 | 0.074 |
|     | 0.024 | 0.059 | 0.060 | 0.015 | 0.060 | 0.060 | 0.013 | 0.074 | 0.075 |

| 400 | 2  | \( \gamma_1 \) | -0.037 | 0.120 | 0.121 | -0.145 | 0.174 | 0.195 | -0.255 | 0.249 | 0.305 |
|     |    |      | 0.047 | 0.122 | 0.124 | 0.029 | 0.179 | 0.179 | 0.042 | 0.205 | 0.267 |
| \( \gamma_2 \) | -0.059 | 0.056 | 0.060 | -0.123 | 0.075 | 0.090 | -0.177 | 0.077 | 0.0108 |
|     | 0.090 | 0.068 | 0.076 | 0.110 | 0.098 | 0.110 | 0.173 | 0.125 | 0.155 |
| \( \gamma_4 \) | -0.020 | 0.181 | 0.182 | 0.026 | 0.245 | 0.246 | 0.080 | 0.337 | 0.344 |
|     | 0.066 | 0.194 | 0.198 | 0.124 | 0.261 | 0.276 | 0.212 | 0.380 | 0.425 |
| \( \beta_1 \) | -0.021 | 0.151 | 0.152 | -0.069 | 0.220 | 0.225 | -0.122 | 0.315 | 0.329 |
|     | 0.023 | 0.156 | 0.157 | 0.022 | 0.218 | 0.218 | 0.033 | 0.309 | 0.310 |
| \( \beta_2 \) | 0.011 | 0.004 | 0.004 | 0.008 | 0.004 | 0.004 | 0.013 | 0.005 | 0.005 |
|     | 0.011 | 0.004 | 0.004 | 0.007 | 0.004 | 0.004 | 0.013 | 0.005 | 0.005 |
| \( \beta_3 \) | 0.003 | 0.002 | 0.002 | 0.003 | 0.002 | 0.002 | 0.001 | 0.002 | 0.002 |
|     | 0.003 | 0.002 | 0.002 | 0.004 | 0.002 | 0.002 | 0.003 | 0.002 | 0.002 |
| \( \beta_4 \) | 0.019 | 0.028 | 0.029 | 0.002 | 0.029 | 0.029 | -0.001 | 0.033 | 0.033 |
|     | 0.020 | 0.028 | 0.029 | 0.006 | 0.029 | 0.029 | 0.009 | 0.034 | 0.034 |
Table A4
Bias, variance and MSE of \( \hat{\gamma} \) and \( \hat{\beta} \) for \texttt{smure} (second rows) and our approach (first rows) in Model 4 (Scenario 2).

| Mod | n  | scen | Par | Cens. level 1 | Cens. level 2 | Cens. level 3 |
|-----|----|------|-----|-------------|-------------|-------------|
|     |    |      |     | Bias | Var. | MSE | Bias | Var. | MSE | Bias | Var. | MSE |
| 4   | 200| 2    | \( \gamma \) | \(-0.121\) | 0.117 | 0.131 | \(-0.240\) | 0.140 | 0.198 | \(-0.375\) | 0.179 | 0.320 |
|     |    |      | \( \gamma \) | 0.006  | 0.134 | 0.134 | 0.001  | 0.170 | 0.170 | 0.003  | 0.231 | 0.232 |
|     |    |      | \( \gamma \) | 0.053  | 0.014 | 0.017 | 0.017  | 0.026 | 0.026 | 0.122  | 0.018 | 0.033 |
|     |    |      | \( \gamma \) | 0.041  | 0.018 | 0.056 | 0.056  | 0.020 | 0.024 | 0.077  | 0.027 | 0.033 |
|     |    |      | \( \gamma \) | \(-0.195\) | 0.137 | 0.175 | \(-0.348\) | 0.156 | 0.277 | \(-0.511\) | 0.165 | 0.426 |
|     |    |      | \( \gamma \) | 0.119  | 0.169 | 0.181 | 0.122  | 0.216 | 0.231 | 0.139  | 0.273 | 0.293 |
|     |    |      | \( \gamma \) | 0.096  | 0.156 | 0.165 | 0.157  | 0.189 | 0.213 | 0.240  | 0.229 | 0.287 |
|     |    |      | \( \gamma \) | 0.072  | 0.182 | 0.187 | 0.096  | 0.216 | 0.226 | 0.137  | 0.288 | 0.307 |
|     |    |      | \( \gamma \) | \(-0.038\) | 0.161 | 0.163 | \(-0.078\) | 0.185 | 0.191 | \(-0.149\) | 0.218 | 0.240 |
|     |    |      | \( \gamma \) | 0.046  | 0.175 | 0.177 | 0.058  | 0.220 | 0.223 | 0.047  | 0.254 | 0.257 |
|     |    |      | \( \beta_1 \) | 0.014  | 0.007 | 0.007 | 0.009  | 0.008 | 0.008 | 0.001  | 0.008 | 0.008 |
|     |    |      | \( \beta_1 \) | 0.017  | 0.007 | 0.007 | 0.016  | 0.008 | 0.008 | 0.014  | 0.008 | 0.008 |
|     |    |      | \( \beta_2 \) | 0.005  | 0.004 | 0.004 | 0.003  | 0.004 | 0.004 | 0.002  | 0.004 | 0.005 |
|     |    |      | \( \beta_2 \) | 0.005  | 0.004 | 0.004 | 0.005  | 0.004 | 0.004 | 0.005  | 0.004 | 0.005 |
|     |    |      | \( \beta_3 \) | 0.010  | 0.056 | 0.056 | \(-0.003\) | 0.063 | 0.063 | \(-0.022\) | 0.071 | 0.072 |
|     |    |      | \( \beta_3 \) | 0.015  | 0.057 | 0.057 | 0.011  | 0.064 | 0.064 | 0.006  | 0.072 | 0.072 |

| 400 | 2  |      | \( \gamma \) | \(-0.068\) | 0.057 | 0.062 | \(-0.169\) | 0.073 | 0.102 | \(-0.279\) | 0.089 | 0.167 |
|     |    |      | \( \gamma \) | 0.015  | 0.061 | 0.061 | 0.001  | 0.078 | 0.078 | \(-0.022\) | 0.097 | 0.098 |
|     |    |      | \( \gamma \) | 0.033  | 0.007 | 0.008 | 0.068  | 0.008 | 0.013 | 0.099  | 0.010 | 0.019 |
|     |    |      | \( \gamma \) | 0.019  | 0.008 | 0.008 | 0.030  | 0.010 | 0.011 | 0.044  | 0.012 | 0.014 |
|     |    |      | \( \gamma \) | \(-0.180\) | 0.073 | 0.105 | \(-0.311\) | 0.084 | 0.181 | \(-0.450\) | 0.093 | 0.296 |
|     |    |      | \( \gamma \) | 0.043  | 0.079 | 0.081 | 0.038  | 0.096 | 0.097 | 0.030  | 0.119 | 0.120 |
|     |    |      | \( \gamma \) | 0.050  | 0.078 | 0.080 | 0.119  | 0.096 | 0.110 | 0.177  | 0.118 | 0.149 |
|     |    |      | \( \gamma \) | 0.028  | 0.082 | 0.083 | 0.049  | 0.101 | 0.104 | 0.066  | 0.124 | 0.129 |
|     |    |      | \( \gamma \) | \(-0.060\) | 0.077 | 0.081 | \(-0.106\) | 0.096 | 0.107 | \(-0.150\) | 0.101 | 0.124 |
|     |    |      | \( \beta_1 \) | 0.003  | 0.082 | 0.082 | 0.001  | 0.099 | 0.099 | 0.003  | 0.116 | 0.116 |
|     |    |      | \( \beta_1 \) | 0.006  | 0.003 | 0.003 | 0.002  | 0.004 | 0.004 | \(-0.004\) | 0.004 | 0.004 |
|     |    |      | \( \beta_2 \) | 0.008  | 0.003 | 0.003 | 0.008  | 0.004 | 0.004 | 0.007  | 0.004 | 0.004 |
|     |    |      | \( \beta_2 \) | 0.002  | 0.002 | 0.002 | 0.002  | 0.002 | 0.002 | 0.002  | 0.002 | 0.002 |
|     |    |      | \( \beta_3 \) | 0.003  | 0.026 | 0.026 | \(-0.010\) | 0.030 | 0.030 | \(-0.023\) | 0.034 | 0.034 |
|     |    |      | \( \beta_3 \) | 0.007  | 0.026 | 0.026 | 0.002  | 0.031 | 0.031 | \(-0.001\) | 0.034 | 0.034 |
**Table A5**

Bias, variance and MSE of $\hat{γ}$ and $\hat{β}$ for secure (second rows) and our approach (first rows) in Model 1 and 2 ($n = 1000$).

| Mod. | n   | scen. | Par. | Cens. level 1 |         | Cens. level 2 |         | Cens. level 3 |         |
|------|-----|-------|------|---------------|---------|---------------|---------|---------------|---------|
|      |     |       |      | Bias | Var. | MSE | Bias | Var. | MSE | Bias | Var. | MSE |
| 1    | 1000| 1     | $γ_1$| 0.007| 0.011| 0.011| 0.008| 0.013| 0.013| 0.010| 0.015| 0.015|
|      |     |       |      | 0.016| 0.013| 0.012| 0.019| 0.013| 0.013| 0.022| 0.015| 0.016|
|      |     |       | $γ_2$| 0.006| 0.032| 0.032| -0.006| 0.037| 0.037| -0.006| 0.041| 0.041|
|      |     |       |      | 0.023| 0.033| 0.034| 0.027| 0.038| 0.039| 0.028| 0.043| 0.044|
|      |     |       | $β$  | 0.001| 0.005| 0.005| 0.002| 0.006| 0.006| 0.002| 0.006| 0.006|
|      |     |       |      | 0.000| 0.005| 0.005| 0.001| 0.006| 0.006| 0.000| 0.006| 0.006|
| 2    | 1000| 1     | $γ_1$| 0.005| 0.007| 0.007| 0.006| 0.008| 0.008| 0.007| 0.010| 0.010|
|      |     |       |      | 0.008| 0.007| 0.007| 0.011| 0.008| 0.008| 0.014| 0.010| 0.010|
|      |     |       | $γ_2$| 0.008| 0.019| 0.019| -0.006| 0.022| 0.022| -0.007| 0.026| 0.026|
|      |     |       |      | 0.012| 0.019| 0.020| 0.016| 0.023| 0.023| 0.018| 0.027| 0.027|
|      |     |       | $β$  | 0.000| 0.006| 0.006| -0.001| 0.007| 0.007| 0.000| 0.008| 0.008|
|      |     |       |      | -0.001| 0.006| 0.006| -0.002| 0.007| 0.007| -0.002| 0.008| 0.008|
| 3    | 1000| 1     | $γ_1$| 0.004| 0.011| 0.011| -0.008| 0.012| 0.012| -0.003| 0.018| 0.018|
|      |     |       |      | 0.004| 0.011| 0.011| -0.002| 0.013| 0.013| 0.009| 0.019| 0.019|
|      |     |       | $γ_2$| 0.004| 0.003| 0.007| -0.076| 0.123| 0.129| -0.107| 0.163| 0.175|
|      |     |       |      | 0.046| 0.099| 0.102| 0.058| 0.130| 0.134| 0.072| 0.167| 0.173|
|      |     |       | $β$  | 0.011| 0.018| 0.018| 0.005| 0.022| 0.022| 0.004| 0.026| 0.026|
|      |     |       |      | 0.009| 0.018| 0.018| 0.001| 0.022| 0.022| -0.005| 0.026| 0.026|
| 2    | 1000| 1     | $γ_1$| 0.006| 0.008| 0.008| 0.000| 0.009| 0.009| 0.007| 0.012| 0.012|
|      |     |       |      | 0.009| 0.008| 0.008| 0.007| 0.009| 0.009| 0.022| 0.013| 0.013|
|      |     |       | $γ_2$| 0.010| 0.007| 0.007| -0.011| 0.009| 0.009| -0.018| 0.011| 0.011|
|      |     |       |      | -0.002| 0.007| 0.007| -0.002| 0.009| 0.009| -0.005| 0.012| 0.012|
|      |     |       | $β$  | -0.001| 0.002| 0.002| 0.000| 0.003| 0.003| 0.001| 0.003| 0.003|
|      |     |       |      | -0.001| 0.002| 0.002| -0.001| 0.003| 0.003| -0.001| 0.003| 0.003|
| 3    | 1000| 1     | $γ_1$| -0.004| 0.006| 0.006| -0.010| 0.007| 0.007| -0.004| 0.010| 0.010|
|      |     |       |      | 0.002| 0.006| 0.006| 0.003| 0.008| 0.008| 0.022| 0.010| 0.011|
|      |     |       | $γ_2$| -0.012| 0.007| 0.008| -0.023| 0.009| 0.010| -0.031| 0.012| 0.012|
|      |     |       |      | 0.004| 0.008| 0.008| 0.000| 0.009| 0.009| 0.002| 0.012| 0.012|
|      |     |       | $β$  | 0.005| 0.003| 0.003| 0.006| 0.003| 0.003| 0.005| 0.004| 0.004|
|      |     |       |      | 0.004| 0.003| 0.003| 0.005| 0.003| 0.003| 0.004| 0.004| 0.004|
| 3    | 1000| 1     | $γ_1$| -0.011| 0.014| 0.014| -0.029| 0.014| 0.015| -0.054| 0.019| 0.022|
|      |     |       |      | 0.002| 0.016| 0.016| 0.015| 0.018| 0.018| 0.028| 0.029| 0.029|
|      |     |       | $γ_2$| -0.314| 0.144| 0.242| -0.583| 0.189| 0.729| -0.841| 0.237| 0.945|
|      |     |       |      | 0.045| 0.148| 0.151| 0.068| 0.175| 0.180| 0.137| 0.223| 0.242|
|      |     |       | $β$  | 0.004| 0.006| 0.006| 0.004| 0.008| 0.008| 0.006| 0.010| 0.010|
|      |     |       |      | 0.002| 0.006| 0.006| 0.001| 0.008| 0.008| 0.003| 0.010| 0.010|
| n   | scen. | Par. | Cens. level 1 | Cens. level 2 | Cens. level 3 |
|-----|-------|------|---------------|---------------|---------------|
|     |       |      | Bias          | Var.          | MSE           | Bias          | Var.  | MSE  | Bias          | Var.  | MSE  |
| 1000| 1     | γ₁   | 0.000         | 0.026         | 0.026         | 0.010         | 0.035         | 0.035 | 0.013         | 0.050 | 0.050 |
|     |       | γ₂   | −0.009        | 0.008         | 0.008         | −0.021        | 0.001         | 0.011 | −0.051        | 0.014 | 0.017 |
|     |       | γ₃   | 0.019         | 0.071         | 0.072         | 0.022         | 0.094         | 0.094 | 0.022         | 0.128 | 0.128 |
|     |       | γ₄   | 0.041         | 0.069         | 0.070         | 0.060         | 0.078         | 0.082 | 0.062         | 0.105 | 0.109 |
|     |       | β₁   | 0.004         | 0.001         | 0.001         | −0.030        | 0.087         | 0.088 | −0.095        | 0.124 | 0.133 |
|     |       | β₂   | 0.020         | 0.058         | 0.058         | −0.002        | 0.077         | 0.078 | 0.033         | 0.098 | 0.099 |
|     |       | β₃   | 0.001         | 0.007         | 0.007         | −0.006        | 0.008         | 0.008 | −0.003        | 0.009 | 0.009 |

| 2   | γ₁   | −0.025         | 0.046         | 0.047         | −0.071        | 0.077         | 0.082         | −0.142       | 0.117 | 0.137 |
|     | γ₂   | −0.057         | 0.022         | 0.025         | −0.097        | 0.030         | 0.040         | −0.108       | 0.038 | 0.050 |
|     | γ₃   | −0.041         | 0.068         | 0.070         | −0.024        | 0.125         | 0.126         | 0.015        | 0.169 | 0.170 |
|     | γ₄   | 0.009         | 0.006         | 0.006         | 0.044         | 0.104         | 0.106         | 0.059        | 0.132 | 0.136 |
|     | β₁   | 0.005         | 0.058         | 0.058         | 0.020         | 0.081         | 0.081         | 0.039        | 0.101 | 0.102 |
|     | β₂   | 0.003         | 0.001         | 0.001         | 0.002         | 0.002         | 0.002         | 0.002        | 0.002 | 0.002 |
|     | β₃   | 0.001         | 0.001         | 0.001         | 0.002         | 0.001         | 0.001         | −0.002       | 0.001 | 0.001 |

| 3   | γ₁   | 0.004         | 0.030         | 0.031         | −0.088        | 0.050         | 0.050         | −0.065       | 0.093 | 0.096 |
|     | γ₂   | −0.014         | 0.009         | 0.009         | −0.011        | 0.014         | 0.014         | 0.031        | 0.022 | 0.023 |
|     | γ₃   | 0.015         | 0.009         | 0.009         | 0.018         | 0.012         | 0.012         | 0.045        | 0.018 | 0.020 |
|     | γ₄   | 0.017         | 0.043         | 0.043         | 0.016         | 0.058         | 0.058         | 0.043        | 0.089 | 0.091 |
|     | β₁   | 0.007         | 0.002         | 0.002         | 0.008         | 0.003         | 0.003         | 0.005        | 0.003 | 0.003 |
|     | β₂   | 0.006         | 0.002         | 0.002         | 0.007         | 0.003         | 0.003         | 0.006        | 0.003 | 0.003 |
|     | β₃   | 0.000         | 0.001         | 0.001         | −0.002        | 0.001         | 0.001         | −0.004       | 0.017 | 0.017 |
|     | γ₁   | 0.000         | 0.001         | 0.001         | 0.014         | 0.013         | 0.013         | −0.004       | 0.016 | 0.016 |
Table A7
Bias, variance and MSE of $\hat{\gamma}$ and $\hat{\beta}$ for secure and our approach in Model 4 ($n = 1000$).

| n  | scen. | Par. | Cens. level 1 Bias | Var. | MSE | Cens. level 2 Bias | Var. | MSE | Cens. level 3 Bias | Var. | MSE |
|----|-------|------|---------------------|------|-----|---------------------|------|-----|---------------------|------|-----|
|    |       |      | $\gamma_1$         |      |     | $\gamma_2$         |      |     | $\gamma_3$         |      |     |
| 1000 | 1     | $\gamma_1$ | 0.022 | 0.027 | 0.030 | 0.033 | 0.033 | 0.010 | 0.038 | 0.058 |
|     |       | $\gamma_2$ | 0.044 | 0.027 | 0.008 | 0.032 | 0.032 | 0.012 | 0.038 | 0.038 |
|     |       | $\gamma_3$ | 0.013 | 0.007 | 0.007 | 0.007 | 0.007 | 0.012 | 0.038 | 0.038 |
|     |       | $\gamma_4$ | 0.015 | 0.007 | 0.007 | 0.008 | 0.008 | 0.008 | 0.012 | 0.038 | 0.038 |
| 2   |       | $\gamma_1$ | 0.049 | 0.024 | 0.027 | 0.116 | 0.031 | 0.044 | 0.207 | 0.040 | 0.083 |
|     |       | $\gamma_2$ | 0.066 | 0.024 | 0.024 | 0.004 | 0.031 | 0.031 | 0.020 | 0.039 | 0.039 |
|     |       | $\gamma_3$ | 0.019 | 0.003 | 0.003 | 0.049 | 0.003 | 0.003 | 0.079 | 0.004 | 0.011 |
|     |       | $\gamma_4$ | 0.066 | 0.003 | 0.003 | 0.011 | 0.004 | 0.004 | 0.018 | 0.005 | 0.005 |
| 3   |       | $\gamma_1$ | 0.022 | 0.015 | 0.015 | 0.002 | 0.019 | 0.019 | 0.029 | 0.026 | 0.027 |
|     |       | $\gamma_2$ | 0.004 | 0.015 | 0.015 | 0.001 | 0.018 | 0.018 | 0.001 | 0.023 | 0.023 |
|     |       | $\gamma_3$ | 0.005 | 0.001 | 0.001 | 0.001 | 0.002 | 0.002 | 0.006 | 0.002 | 0.002 |
|     |       | $\gamma_4$ | 0.051 | 0.016 | 0.019 | 0.034 | 0.015 | 0.017 | 0.041 | 0.021 | 0.022 |

Musta, Patilea, Van Keilegom/A presmoothing approach for mixture cure models 39