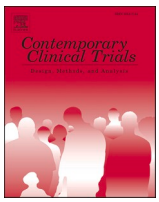
Contemporary Clinical Trials 136 (2024) 107401

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial



Imputation methods for informative censoring in survival analysis with time dependent covariates

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ARTICLE INFO

Keywords:
Time dependent covariates
Informative censoring
Tipping point
Jump to reference
Copy reference
Multiple imputation

ABSTRACT

Cox proportional hazards model has been an established model for survival analysis. The flexibility of incorporating time dependent covariates has made the analysis more suitable in many clinical trials when the time dependent covariates may be predictive factors for the events. Subjects are censored for various reasons, but they are usually nonnormatively censored in the analysis. Methods for informative censoring are not well studied for settings with time dependent covariates.

In this paper, we propose a few methods for informative censoring in survival analysis by Cox model with time dependent covariates, including tipping point method and Reference Based Imputation (Jump to Reference and Copy Reference). The implementation of these methods by multiple imputation is described and illustrated with two data examples.

1. Introduction

In clinical trials with time to event data, subjects are followed until the occurrence of the events of interest or censored. Censoring for time to event outcome may occur for a variety of reasons, such as reaching the end of follow-up period, loss to follow-up, or discontinuing study participation without subsequential data collected.

Like the missing data mechanism, there are similar censoring schemes for survival analysis: censored at random (CAR) and censored not at random (CNAR) [13,15]. CAR is also referred to as noninformative censoring, assuming that, the hazard of having an event at a time point after censoring is independent of the censoring conditional on the observed covariates. Censoring at the end of follow-up period is usually due to administrative constraints and can be considered unrelated to the study treatment or the disease progression, so CAR is a reasonable assumption for this type of administrative censoring. The Cox proportional hazards model is a popular method assuming CAR or noninformative censoring [5].

However, the CAR assumption cannot be verified based on observed data and may not be plausible for many practical cases. CNAR or informative censoring is a more reasonable assumption if censoring is dependent on the hazard of having an event even after accounting for all available covariates. Censored subjects may have a very different hazard of having an event compared to those in the study with the same covariates [13,15]. For example, if subjects discontinue from the study participation prematurely because of their own or their physician's preference, the discontinuation may be related to the study treatment and/or the status of disease condition. Ignoring the censoring scheme in the analysis may lead to similar issues arising from nonignorable missing data in clinical studies with continuous or categorical endpoints [3,12]. CNAR is a reasonable assumption for this type of nonignorable censoring. As a result, methods under CNAR are often helpful to provide sensitivity analyses to assess the robustness of results from the CAR censoring assumption.

The issue of missing data and statistical methods have been studied extensively in the literature, including methods under missing at random (MAR) and missing not at random (MNAR) [17,23,27]. Delta-adjusted method and tipping point analysis are methods for analysis of missing data under MNAR which explores the plausibility of MAR assumption [25]. Delta-adjusted method was further introduced for survival analysis with fixed covariates [15]. Tipping point analysis was proposed for survival analysis with fixed covariates [13]. Reference Based Imputation (RBI) methods are commonly used for missing data under MNAR in recent years in longitudinal clinical trials for continuous and binary endpoints [3,12,14,16,18], including Jump to Reference (J2R), Copy Reference (CR) and Copy Increments in Reference (CIR).

Cox proportional hazards model is widely used in the analysis of survival data to explain the effect of explanatory variables on hazard

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https://doi.org/10.1016/j.cct.2023.107401
Received 19 July 2023; Received in revised form 16 October 2023; Accepted 18 November 2023
Available online 22 November 2023

rates [5]. In many studies, covariate data are collected longitudinally during the trial and may be predictive for the events of interest. For example, hypertension status, relative weight, and lab data may be collected at selected periodic postbaseline time points. Cox proportional hazards model has been generalized to include time dependent covariates in the analysis [8]. One established way to fit Cox model with time dependent covariates is to use the counting process style of input [1]. Once the dataset has been transformed, time dependent covariates are treated just like fixed covariates in each interval.

A few methods under CAR and CNAR have been recently developed in the literature for analysis with fixed covariates [13]. When covariates are measured periodically after baseline, some of them may be predictive factors for future events, and including them in the imputation model is reasonable. CAR and CNAR imputation methods for survival analysis with time dependent covariates are not well studied in the literature. In this paper, we focus on informative censoring in survival analysis with time dependent covariates by Cox model, under CAR and CNAR censoring schemes. Specifically, tipping point method, and RBI methods including J2R and CR are proposed in Cox model with time dependent covariates. These proposed methods are novel for survival analysis with time dependent covariates. CIR is equivalent to CAR in time to event analysis [13], so it is not considered in this manuscript.

The remainder of the manuscript is organized as follows. In Section 2, we provide a brief overview for survival analysis by Cox proportional hazards model with time dependent covariates and describe different censoring schemes in the setting with time dependent covariates; in Section 3, we propose a few methods for informative censoring under CNAR, including delta-adjusted method, tipping point method, and RBI methods; in Section 4, we propose multiple imputation (MI) to implement the proposed methods; in Section 5, the proposed methods are illustrated by two real data examples; in Section 6, the paper is concluded with some discussions.

2. Survival analysis with time dependent covariates

2.1. Cox model with time dependent covariates

Consider a trial with eligible subjects randomized to two groups, treatment or reference group (for example, placebo or stand-of-care) with time to event outcomes. Let $Z_i = 1$ denote the treatment group and $Z_i = 0$ the reference/control group for subject $i = 1, \ldots, N$. Denote T_i^* the latent event time, C_i the time to censoring or discontinuation, and T_i^f the follow-up time. Usually C_i is$\leq T_i^f$ meaning the subject will be censored before or at the end of the follow-up period. The observed time is $T_i = min\left(T_i^*, C_i\right)$. In survival analysis, we need to have the event/censoring indicator $\Delta_i = I\left(T_i^* \leq C_i\right)$, where $\Delta_i = 1$ indicates an event and 0 indicates a censor.

In statistical analysis, we need to adjust for some covariates in the model, such as baseline characteristics. However, in real practice, some of the covariates are measured periodically and changing over time after baseline, which are referred to as time dependent covariates. For example, in a long term clinical trial, the hypertension status (with 0 and 1 as a binary time dependent covariate) and some laboratory values (as a continuous time dependent covariate) can change over time. We can denote a general covariate vector $\boldsymbol{X}_i(t)$, including fixed baseline covariates and time dependent covariates.

Cox proportional hazards model [5,6] is widely used in the analysis of time to event data to estimate the effect of explanatory variables on hazard rates through partial likelihood. The Cox proportional hazards model was generalized to allow time dependent covariates [1,22]:

$$\lambda(t|Z_i, \boldsymbol{X}_i(t)) = \lambda_0(t)e^{\beta Z_i + \alpha \boldsymbol{X}_i(t)}, \tag{1}$$

where β is the log-hazard ratio (Log HR) for the treatment versus reference group and $\lambda_0(t)$ is the baseline hazard function, and α is the effect associated with the time dependent covariate vector $X_i(t)$. The hazard function for subjects in reference group at time t (is)

$$\lambda_{ref}(t|Z_i, \boldsymbol{X}_i(t)) = \lambda(t|Z_i = 0, \boldsymbol{X}_i(t)) = \lambda_0(t)e^{\alpha \boldsymbol{X}_i(t)}.$$

2.2. Censoring scheme with time dependent covariates: CAR and CNAR

For clinical trials with time to event data, subjects are often censored if they don't have observed events at the end of the scheduled follow-up time. In real clinical trials, some subjects may prematurely discontinue before they experience any event and have no collected times and events.

These subjects can be censored as well in the analysis. Censoring schemes CAR and CNAR have been studied for fixed covariates [13,15,20]. The censoring schemes can be extended to the setting with time dependent covariates. If a subject i is censored at C_i, we need to consider the prior- and post-censoring parts for the underlying hazard function:

$$\lambda(t|Zi, Xi(t)) = \begin{cases} \lambda_{prior}(t|Z_i, \boldsymbol{X}_i(t)) = \lambda_0(t)e^{\beta Z_i + \alpha \boldsymbol{X}_i(t)}, t \leq C_i \\ \lambda_{post}(t|Z_i, \boldsymbol{X}_i(t)), t > C_i \end{cases}. \tag{2}$$

The cumulative hazard at time t is expressed as follows

$$\Lambda(t|Z_i, \boldsymbol{X}_i(t)) = \int_o^t \lambda(s|Z_i, \boldsymbol{X}_i(s))ds = -log(S(t|Z_i, \boldsymbol{X}_i(t))),$$

and the survival function is

$$S(t|Z_i, X_i(t)) = e^{-\Lambda(t|Zi, Xi(t))} = 1 - F(t|Z_i, \boldsymbol{X}_i(t)) = P\left(T_i^* > t\right). \tag{3}$$

If a subject is censored, the survival function after censoring is

$$S(t|t > C_i, Z_i, X_i(t)) = \frac{S_t(Z_i, X_i(t))}{S(C_i|Z_i, X_i(C_i))} = e^{-\int_{C_i}^t \lambda_{post}(s|Z_i, \boldsymbol{X}_i(s))ds}. \tag{4}$$

Noninformative censoring or CAR is a censoring scheme assuming the hazard of having an event at a time point after censoring is independent of the censoring conditional on the observed covariates. In other words, the hazard of having an event at a time point after censoring for censored subjects is the same as that for subjects before censoring [13,20].

Therefore, the hazard function after censoring under noninformative censoring or CAR is

$$\lambda post(t|Z_i, X_i(t)) = \lambda_0(t)e^{\beta Z_i + \alpha \boldsymbol{X}_i(t)}, t > C_i. \tag{5}$$

Since discontinued subjects are often censored due to the lack of observed events/times, noninformative censoring can be used as a censoring scheme to censor these subjects in the analysis. Although the CAR assumption is practically unverifiable, sensitivity analyses are often requested based on more realistic assumption that the censoring is informative and can provide treatment-related information about the hazard of having an event.

For survival analysis with time to event data, informative censoring or CNAR means subjects are censored selectively because they may have a very different hazard of having an event compared to those in the study with the same covariates [13]. In other words, CNAR means censoring is dependent on the hazard of having an event even after accounting for all available covariates [15]. Ignoring the censoring scheme in the analysis may lead to biased conclusion for treatment efficacy. Under the assumption of informative censoring or CNAR, the hazard of having an event at a time point after censoring or discontinuation is different from that for subjects before censoring or discontinuation:

$$\lambda post(t|Z_i, \boldsymbol{X}_i(t)) \neq \lambda_0(t)e^{\beta Z_i + \alpha \boldsymbol{X}_i(t)}, t > Ci. \quad (6)$$

3. Informative censoring with time dependent covariates

A few methods for informative censoring have been studied and proposed in survival analysis with fixed covariates under CNAR based on various assumptions for the hazard function after censoring [13], including tipping point method, Jump to Reference, and Copy Reference.

In this section, we will focus on methods for informative censoring in survival analysis with time dependent covariates.

3.1. Delta-adjusted method

A delta-adjusted method was proposed for Cox model with fixed covariates under the specific CNAR assumption that the hazard of having an event for treated subjects after censoring is multiplicatively increased compared to that for those who complete in the experimental treatment group by the end of the scheduled follow-up period. The delta-adjusted method was reformulated in an alternative way by specifying that the actual treatment effect can be discounted compared to that under noninformative censoring in Cox model with fixed covariates [13,20]. In the setting with time dependent covariates, we propose a delta-adjusted method and formulate it as:

$$\lambda post(t|Z_i, \boldsymbol{X}_i(t)) = \lambda_\phi(t|Z_i, \boldsymbol{X}_i(t)) = \lambda_0(t)e^{(1-\phi)\beta Z_i + \alpha \boldsymbol{X}_i(t)}, t > C_i. \quad (7)$$

ϕ ^{3} 0 is the sensitivity parameter interpreted as a discounted proportion of the log-hazard ratio β under CNAR. (7) implies the discounted effect $-\phi\beta$ on the log-hazard scale for discontinued subjects. The special case $\phi = 0$ corresponds to noninformative censoring under CAR.

The hazard in the reference group can be estimated from subjects in the reference group by noninformative censoring or CAR, assuming that censored subjects in the reference group would have similar hazard after censoring compared to that before censoring. This is also implied by (7) when $Z_i = 0$.

3.2. Tipping point analysis

The tipping point analysis is a method for analysis of missing data under MNAR to explore the deviation of MAR assumption by finding the tipping point as the minimum shift needed to make the result non-significant [25]. For survival analysis with fixed covariates, the tipping point analysis was proposed to explore the deviation of the CAR assumption to convert the treatment efficacy to become non-significant [13]. The tipping point method can be extended to the setting with time dependent covariates. Here the tipping point can be found by utilizing the delta-adjusted method through a series ϕ in (7) to identify the minimum shift $-\phi\beta$ on the Log HR β needed to make the result non-significant.

3.3. Jump to reference

Jump to Reference (J2R) assumes that the effect profile of the subjects who discontinue in the active treatment group will immediately jump to that of the subjects in the reference group after discontinuation [3,12,18]. In survival analysis with fixed covariates, J2R assumes that a subject in the treatment group will have the hazard after censoring or discontinuation equal to that of the subjects in the reference group after censoring [13]. Here we propose a J2R method for survival analysis with time dependent covariates, and assume the hazard function after censoring under J2R assumption is:

$$\lambda post(t|Z_i, \boldsymbol{X}_i(t)) = \lambda_{J2R}(t|Z_i, \boldsymbol{X}_i(t)) = \lambda_{ref}(t|\boldsymbol{X}_i(t)) = \lambda_0(t)e^{\alpha \boldsymbol{X}_i(t)}, t > C_i. \quad (8)$$

The hazard in the reference group can be estimated from the reference group by noninformative censoring or CAR. J2R can be formulated by utilizing the delta-adjusted method through formula (7) with $\phi = 1$:

$$\lambda_{J2R}(t|Z_i, \boldsymbol{X}_i(t)) = \lambda_0(t)e^{\alpha \boldsymbol{X}i(t)} = \lambda_{\phi=1}(t|Zi, \boldsymbol{X}i(t)), t > Ci.$$

3.4. Copy reference

Copy Reference (CR) is an established method for continuous and binary endpoints, which assumes subjects follow the behavior of the reference arm for the entire duration of the trial as if they were randomized to the reference group, and uses only observations from the reference group for imputing the missing values [4,7,10,12]. This method is conservative, but not as conservative as J2R since it still allows the carried-over treatment effect by using the prior observed values in the active treatment group as predictors and the mean effect profile of the subjects in the active treatment group will gradually transition to that of the subjects in the reference group [12,18,19].

A CR method was proposed for survival analysis with fixed covariates, assuming that if a subject is censored in the treatment group, the hazard of having an event for this subject is equal to that of the reference group regardless of the censoring time, as if this subject was randomized to the reference group [13]. Here we propose a CR method for survival analysis with time dependent covariates, assuming the hazard function under CR assumption is:

$$\lambda_{CR}(t|Z_i = 1, \boldsymbol{X}_i(t)) = \lambda(t|Z_i = 0, \boldsymbol{X}_i(t)) = \lambda_0(t)e^{\alpha \boldsymbol{X}_i(t)}, for\ all\ t. \quad (9)$$

The hazard in the reference group is estimated from the reference group by noninformative censoring or CAR. When a subject in the treatment group is censored, the CR method imputes a new event time based on the hazard function (9) using observations only from the reference group.

4. Multiple imputation for censored time with time dependent covariates

One established way to fit Cox model with time dependent covariates is the counting process style of input [1]. We need to transform the dataset to a dataset with counting process style of input by separating the history of covariates of a subject into multiple non-overlapping records in a few time intervals with start and stop times. The transformed dataset contains multiple time intervals $(T_1, T_2]$ starting at T_1 and ending at T_2, during which the values of the explanatory variables remain unchanged. Each record also contains the censoring status by T_2. Examples of data transforming can be found in the SAS/STAT 15.1 User's Guide The PHREG Procedure and [24].

Let's use a general data format with time dependent binary and continuous covariates to describe the transformed dataset with counting process style of input. A dataset with time dependent covariates was transformed to a dataset in the format of counting process style of input as in Table 1. Each subject has treatment group and a baseline covariate, time dependent covariates (binary"W1" and continuous"W2"), time to event/censoring"Etime" and time to the end of follow up time"FUtime", and multiple time intervals $(T1, T2]$; within each time interval $(T1, T2]$, the covariate vector (W_1, W_2) is different from that in the next interval and there is an event/censoring"Status" by T_2. For the last interval of a subject, the end T_2 is assigned to the time to event if an event occurs, time to censoring if the censoring occurs before the end of follow-up period, or time to the end of the follow-up period.

Once the dataset has been transformed, time dependent covariates

Table 1
Data format with counting process style of input.

ID	Treatment	Baseline	W1	W2	T1	T2	Etime	FUtime	Status
1	x	x	x	x	x	x	x	x	x
1	x	x	x	x	x	x	x	x	x
...									
2	x	x	x	x	x	x	x	x	x
2	x	x	x	x	x	x	x	x	x

are treated just like fixed covariates in each interval. In the model fitting by Cox model, we use the same model options as we do in the fixed covariate model. The only difference is that the model is based on the intervals $(T_1, T_2]$ instead of event time Etime. The analysis of Cox model with time dependent covariates can be handled by SAS PHREG procedure.

In the model fitting, we consider the piecewise constant baseline hazard function in the Cox model [5],

$$\lambda_0(t) = \lambda_j\left(a_{j-1} < t \le a_j\right), j = 1, 2, \ldots, J, \tag{10}$$

where $a_0 = 0 < a_1 < \ldots < a_{J-1} < a_J = \infty$ is a partition of the time for baseline function estimation. a_J is greater than the largest observed time and can be selected as the maximum time + 1 in practice. The intervals are chosen to have an approximately equal number of events and at least one observed event in each to ensure model convergence.

We can obtain the maximum likelihood estimates (MLEs) $\widehat{\lambda}_1, \ldots, \widehat{\lambda}_J$, $\widehat{\alpha}, \widehat{\beta}$ from the SAS PHREG procedure. Posterior draws of $\lambda_1, \ldots, \lambda_J, \alpha, \beta$ using the MLEs and estimated variance can be drawn directly from the SAS PHREG procedure using the Bayes statement with the piecewise model option.

For a subject i who is censored before the end of follow-up period, if the time dependent covariates are considered as predictive factors for future events, including them in the imputation model is reasonable. We can use the observed covariate $X_i\ (C_i)$ to impute the censored event time $T^* > C_i$, because $\boldsymbol{X}_i(C_i)$ is the last observed covariate vector before censoring and most relevant for the future events. We need to generate a uniform random variable w_i in the interval from $p_i \triangleq \widehat{F}(C_i|Z_i, X_i(C_i), \widehat{\alpha}, \widehat{\beta})$ to 1, where $p_i = \widehat{F}(C_i|Z_i, X_i(C_i), \widehat{\alpha}, \widehat{\beta}) = 1 - \widehat{S}(C_i|Z_i, X_i(C_i), \widehat{\alpha}, \widehat{\beta}) = 1 - e^{-\int_o^{C_i} \hat{\lambda}(t|Z_i, X_i(C_i), \hat{\alpha}, \hat{\beta}) ds}$.

Then we need to project w_i to impute time T^* by solving $w_i = \widehat{F}(t|Z_i, X_i(C_i), \widehat{\alpha}, \widehat{\beta}) = 1 - \widehat{S}(t|Z_i, X_i(C_i), \widehat{\alpha}, \widehat{\beta})$.This will ensure that the imputed event time is greater than the censoring time C_i because $w_i \ge p_i$. This is equivalent to solve (11) with a random variable u_i generated from uniform distribution in (0,1):

$$u_i = \widehat{S}(t|t > C_i, Z_i, X_i(C_i), \widehat{\alpha}, \widehat{\beta}). \tag{11}$$

The imputation can be facilitated by the delta-adjusted method with parameter ϕ. Specifically, the estimated survival function conditional on the observed covariates for a censored subject is

$$\widehat{S}(t|t > C_i, Z_i, \boldsymbol{X}_i(C_i), \widehat{\alpha}, \widehat{\beta}, \phi) = e^{-e^{(1-\phi)\hat{\beta}Z_i + \hat{\boldsymbol{\alpha}}\boldsymbol{X}_i(C_i)}\left(\hat{\Lambda}_0(t) - \hat{\Lambda}_0(C_i)\right)}.$$

Let $\left(a_{j_1-1}, a_{j_1}\right]$ be the interval that contains the discontinuation time C_i, and $\left(a_{j_2-1}, a_{j_2}\right]$ be the interval that contains the future imputed event time t, then

$$\widehat{\Lambda}_0(t) - \widehat{\Lambda}_0(C_i) = \begin{cases} \widehat{\lambda}_{j_1}(t - C_i), j_2 = j_1 \\ \widehat{\lambda}_{j_1}\left(a_{j_1} - C_i\right) + \sum_{j=j_1+1}^{j_2-1} \widehat{\lambda}_j\left(a_j - a_{j-1}\right) + \widehat{\lambda}_{j_2}\left(t - a_{j_2-1}\right), j_2 \ne j_1 \end{cases}. \tag{12}$$

The impute time T^* is the solution of

$$u_i = \widehat{S}(t|t > C_i, Z_i, \boldsymbol{X}_i(C_i), \widehat{\alpha}, \widehat{\beta}, \phi) = e^{-e^{(1-\phi)\hat{\beta}Z_i + \hat{\boldsymbol{\alpha}}\boldsymbol{X}_i(C_i)}\left(\hat{\Lambda}_0(t) - \hat{\Lambda}_0(C_i)\right)}. \tag{13}$$

The imputation can be done on multiple datasets and then the results from each imputed dataset can be combined by Rubin's rules [27]. Rubin's rule is proper when the analysis model is congenial to the imputation model [21]. However, because the MI is performed through.

Bayes imputation, the imputation model and analysis model may not be congenial. In such case, a Bootstrap-MI method can be proposed for the estimates and estimated variances [2]. In particular, we can first draw r (for example, $r = 200$) bootstrap samples with replacement of the original data, and then perform the MI steps described in Section 4 on each of the bootstrap samples to obtain r MI estimates/variances. The bootstrap estimate and variance are obtained from the sample estimate and variance of the $r(= 200)$ MI estimators.

4.1. Multiple imputation for delta-adjusted method

The Bayes MI method can be utilized for the imputation of censored event times which uses the Bayesian model to draw the model parameters from their posterior distributions for each imputed dataset. The specific imputation follows the steps for the delta-adjusted method with parameter ϕ (is)

- S1: If the dataset is in the format of one record for each subject, we need to transform it in a dataset with counting process style of input as in Table 1, described in the beginning of Section 4.
- S2: We obtain the MLEs and posterior Gibbs sampling draws (10,000 of iterations after the burn-in) directly from the SAS PHREG procedure on the dataset in the counting process style of input Table 1 using the Bayes statement with the piecewise model option.
- S3: A thinning of 200 for the Markov chain after a burn-in of 2000 iterations is used to achieve nearly independent posterior draws, resulting in 50 imputations.
- S4: For a subject i who is censored before the end of follow-up period, to impute the censored event time $T^* > C_i$, we need to generate a uniform random variable $u_i \sim (0, 1)$, and then project u_i to impute time $T^*$by solving (13) with a specific ϕ.
- S5: For the censored subject i, change the end time T_2 in the last interval to the minimum of the imputed time T^* and time to the end of follow-up period.

4.2. Multiple imputation for CAR

As proposed in Section 3, the MI for CAR can be performed in the above step S4 with $\phi = 0$.

4.3. Multiple imputation for tipping point method

As proposed in Section 3, the MI for tipping point method can be performed through a series ϕ in the above Step S4 to identify the minimum shift $-\phi\beta$ needed to make the result non-significant.

4.4. Multiple imputation for J2R

As proposed in Section 3, the MI for J2R can be performed in the above step S4 with $\phi = 1$.

4.5. Multiple imputation for CR

MI was proposed to implement CR for survival analysis with fixed covariates [13]. Here we propose MI for survival analysis with time dependent covariates. Specifically, it can be implemented by the following steps:

- S0: Adjust the treatment group for censored subjects to "reference" group.
- Follow S1, S2, S3, S4 and S5 in the MI steps specified in Section 4.1 to impute the censored event times T^* by setting CAR $\phi = 0$.

Then the censored event times are imputed by the CR method.

5. Illustration using a data example

We apply our methods on two data examples in this section. The methods illustrated here include CAR methods (Cox and Cox-MI), RBI methods under CNAR (J2R and CR), and tipping point analysis.

5.1. Example 1

Here we illustrate our proposed methods on the AIDS clinical trials 175: ACTG175. This dataset is available in the R package "speff2trial" on https://cran.r-project.org. ACTG 175 was a randomized trial evaluating antiretroviral therapy regimens among HIV-1 infected participants [11]. Trial arms consisted of zidovudine-only, zidovudine-didanosine, zidovudine-zalcitabine, and didanosine-only. Here, we restricted to two of the trial arms: zidovudine plus didanosine (Z = 1) with 522 subjects or zidovudine (Z = 0) with 532 subjects.

The time to event was defined as time from randomization to development of the acquired immunodeficiency syndrome (AIDS), death, or disease progression. CD4 counts were measured at baseline and postbaseline visits, which is considered a time dependent covariate for prediction of future events. We need to transform the dataset to a dataset with counting process style of input as in Table 1 described in Section 4.

The analysis under CAR is performed using Cox model without imputation and Cox model with multiple imputation (Cox-MI) with the time dependent covariate CD4 counts. 50 imputed datasets were obtained. The log-hazard ratio (Log HR β) and its SE, and hazard ratio and its SE are reported in Table 2. Bayes MI with Rubin's rules and bootstrap-MI methods are conducted to obtain the estimates and variances. The results from both CAR methods (Cox and CAR-MI) are similar.

The J2R and CR with multiple imputation under CNAR are also conducted. The CNAR methods are more conservative than the CAR methods which is consistent with the findings for continuous and binary endpoints. As seen from Table 2, the J2R gives a more conservative treatment effect than CR in terms of log-hazard ratio and hazard ratio. The SEs from bootstrap-MI method is slightly smaller than those from MI with Rubin's rules, which indicates that the congeniality between analysis model and imputation model may not hold for J2R and CR and bootstrap-MI is recommended. This is expected since J2R and CR methods are more conservative than CAR methods, because they assume the hazard after censoring in the treatment group is similar to that of the subjects in the reference group. In addition, J2R is more conservative than CR which is explained in Section 3.3 and 3.4.

To explore the deviation from CAR, we conduct tipping point analysis shown in Table 3. The tipping point is between 1.46 and 1.47, which means the study conclusion under CAR is reversed when the shift parameter for Log HR β is between 1.46 and 1.47. This gives us some confidence that the CAR assumption is plausible since we need a larger shift parameter to convert the conclusion.

Table 2
Results from CAR, J2R and CR Methods.

Method	Log HR β (SE)	HR (SE)		
CAR(Cox)	−0.813 (0.125)	0.444 (0.055)		
	Rubin's Rules		Bootstrap-MI	
	Log HR β (SE)	HR (SE)	Log HR β (SE)	HR (SE)
CAR(MI)	−0.807(0.121)	0.446 (0.054)	−0.807 (0.120)	0.446 (0.053)
CR(MI)	−0.587(0.117)	0.556(0.065)	−0.587 (0.113)	0.556 (0.062)
J2R(MI)	−0.550 (0.114)	0.577 (0.066)	−0.550 (0.110)	0.577 (0.063)

Table 3
Tipping point analysis.

Shift Parameter ϕ	Log-hazard Ratio β (SE)	p-value (1-sided)	Hazard Ratio (SE)	Tipping
1.43	−0.268 (0.127)	≤ 0.025	0.765 (0.097)	
1.44	−0.263 (0.128)	≤ 0.025	0.769 (0.098)	
1.45	−0.257 (0.128)	≤ 0.025	0.773 (0.099)	
1.46	−0.253 (0.128)	≤ 0.025	0.776 (0.099)	
1.47	−0.248 (0.127)	> 0.025	0.780 (0.099)	Yes

5.2. Example 2

Here we illustrate our methods with another data example. The "ScoreInd" dataset in the R package "InformativeCensoring" is available on https://cran.r-project.org. There are 400 subjects equally assigned to two treatment arms in the dataset, along with baseline covariate, time to event or censoring, event/censoring indicator and subject follow up time. The Cox model includes treatment groups and baseline values as covariates. "ScoreTimeDep" in the same R package is a dataset with time dependent covariates for the subjects in "ScoreInd" within time intervals from "start" to "end". Two time dependent covariates are included: W1, a binary time dependent covariate and W2, a continuous time dependent covariate. After merging them by subjects, we can get a dataset with counting process of input as in Table 1.

We conduct analysis assuming CAR using Cox model without imputation and Cox model with multiple imputation (Cox-MI) with time dependent covariates. The log-hazard ratio (Log HR β) and its SE, and hazard ratio and its SE are reported. Bayes MI with Rubin's rules and bootstrap-MI methods are conducted to obtain the estimates and variances. The results from both CAR methods (Cox and CAR-MI) are similar, which can be seen from the results in Table 4.

Under CNAR, we conduct the RBI methods using J2R and CR with multiple imputation under CNAR. The CNAR methods are more conservative than the CAR methods which is also consistent with the simulation. As seen from Table 4, the J2R gives a more conservative treatment effect than CR in terms of log-hazard ratio and hazard ratio. The SEs from bootstrap-MI method is slightly smaller than those from MI with Rubin's rules, which indicates that the congeniality between analysis model and imputation model may not hold for J2R and CR and bootstrap-MI is recommended.

To explore the deviation from CAR, we conduct tipping point

Table 4
Results from CAR, J2R and CR Methods.

Method	Log HR β (SE)	HR (SE)		
CAR(Cox)	−0.321 (0.148)	0.725 (0.107)		
	Rubin's Rules		Bootstrap-MI	
	Log HR β (SE)	HR (SE)	Log HR β (SE)	HR (SE)
CAR(MI)	−0.333(0.152)	0.718 (0.109)	−0.333 (0.152)	0.718 (0.109)
CR(MI)	−0.276(0.137)	0.759(0.104)	−0.276 (0.133)	0.759 (0.101)
J2R(MI)	−0.196 (0.139)	0.823 (0.114)	−0.196 (0.135)	0.822 (0.111)

Table 5
Tipping point analysis.

Shift Parameter ϕ	Log-hazard Ratio β (SE)	p-value (1-sided)	Hazard Ratio (SE)	Tipping
0.07	−0.304 (0.150)	≤0.025	0.738 (0.111)	
0.08	−0.300 (0.150)	≤ 0.025	0.741 (0.111)	
0.09	−0.293 (0.150)	≤ 0.025	0.746 (0.112)	
0.10	−0.281 (0.150)	> 0.025	0.755 (0.112)	Yes
0.11	−0.289 (0.150)	> 0.025	0.749 (0.112)	

analysis by evaluating a series of shift parameters. As shown in Table 5, the tipping point is between 0.08 and 0.09, which means the study conclusion under CAR is reversed when the shift parameter is between 0.09 and 0.1. This may indicate that the CAR assumption is not very plausible because a small shift parameter can convert our conclusion.

6. Discussion

In clinical trials with time to event data, subjects are censored for a variety of reasons. Noninformative methods under CAR are often used in practice such as the Cox proportional hazards model. The CAR assumption cannot be verified in practice and CNAR may be requested to evaluate the robustness of the CAR assumption.

The Cox proportional hazards with time dependent covariates is commonly used with the fixed covariates. Methods under CAR and CNAR have been recently developed in the literature for analysis with fixed covariates. Informative methods under CNAR for survival analysis with time dependent covariates are not well studied in the literature and the methods proposed in this paper fill the gap. We consider imputing censored times for Cox proportional hazards model with time dependent covariates in this paper under CAR and CNAR assumptions. A general case of both binary and continuous time dependent covariates can be incorporated in the methods proposed in this paper. Delta-adjusted method, tipping point method, and RBI methods are proposed in the analysis of Cox model with time dependent covariates.

In addition, multiple imputation is proposed to implement these methods and the results from each imputed dataset can be combined by Rubin's rules [27]. When the imputation model and analysis model may not be congenial, a Bootstrap-MI method can be recommended for the estimates and estimated variances.

The proposed imputation methods are illustrated by two real data examples.

ϕ and the imputation can depend on different censoring mechanisms since censored event time is imputed by patterns. The proposed model can be generalized to left censoring or interval censoring since the main idea is to use the hazard from the control group to impute the censored time, so the idea is still applicable in left censoring or interval censoring setting.

In reality, non-proportional hazards occur when the relationship between the event time and treatment changes over time. Methods for accommodating non-proportional hazards have been commonly used, such as piecewise exponential model, weighted log-rank tests, and including treatment-by-covariate interaction with time varying covariate [9]. The methods proposed in this paper can be extended to these methods to accommodating non-proportional hazards since the methods already incorporate time dependent covariates. What is needed is to impute the censored time based on the assumption of the hazards in the specific time period.

The Inverse probability Censoring weighting (IPCW) is an approach for time to event data. IPCW estimates the censoring model and compensates for censored subjects by giving extra weight to subjects who are not censored with an inverse of the conditional probability of having remained uncensored [26]. Typically, these weights are chosen in such a way that individuals who best match the censored subjects will receive more weight. The RBI method is a different method to deal with censored subjects based on the assumption that the effect profile after censoring will be similar to that of the reference group. The RBI methods with time dependent covariates provide alternative tools to analyze time to event data with informative censoring.

Disclosure

This publication was neither originated nor managed by AbbVie, and it does not communicate results of AbbVie-sponsored Scientific Research. It's considered a Out-of-scope publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The dataset for the ACTG175 trial in Example 1 is included in the R package “speff2trial” available on https://cran.r-project.org. The dataset for Example 2 is included in the R package “Informative-Censoring” available on https://cran.r-project.org.

Appendix A. SAS Code for Data Example 1

First, the transformed dataset has the following variables:

Table 6
Data format with counting process style of input.

PIDNUM	time	Treated	event	bsvalue	cd4	visit	tstart	tstop	Status	futime
10,124	156	0	0	504	353	20	0	20	0	200
10,124	156	0	0	504	66	96	20	156	0	200
10,140	169	1	0	235	339	20	0	20	0	200
10,140	169	1	0	235	26	96	20	169	0	200

The SAS code for the key step S4 in Section 4.1 to impute the censored event time with ϕ is as follows.

```
data raw3;
set raw2 end=eof;
array a{&nint};
array lambda{&nint};
do phi=0 to 1 by 0.2;
*the time-dep covariate should use the last observed, before censoring;
nu = -log(u)/exp(treated*(1-phi)*beta + bsvalue*gamma +
cd4_last*wcoff1);
* no imputation needed for subjects with events or for completers;
if event=1 or (event=0 and time=followup) then do;
time3 = time;
status3 = status;
end;
else do;
* locate the time interval that contains the censoring time;
j1 = 1;
do while (time >= a[j1]);
j1 = j1 + 1;
end;
* locate the time interval containing the censored event time;
* cumulative hazard in the first interval;
v = lambda[j1]*(a[j1] - time);
j2 = j1;
do while (nu > v and j2 < &nint);
j2 = j2 + 1; * cumulative hazard in current interval;
v = v + lambda[j2]*(a[j2] - a[j2-1]);
end;
* obtain the event time;
if j2 = j1 then
u3 = nu/lambda[j1] + time; * event in interval j1;
else
u3 = a[j2] - (v - nu)/lambda[j2]; * event in interval j2;
time3 = min(u3, followup);
time3=round(time3);
status3 = (u3 <= followup);
end;
output;
end;
drop lambda1-lambda&nint beta gamma;
run;
proc sort data=raw3; by phi imputation subj tstart; run;

proc sql;
create table newtime as
   select phi as phi, imputation as imputation,
          subj as subj, min(time3) as time4
          from raw3 group by phi, imputation, subj;
quit;
proc sort data=newtime;
by phi imputation subj;
run;
```

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