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Survival Model With Doubly Interval-Censored Data and Time-Dependent Covariates

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***Abstract*—In this paper a survival model with doubly interval censored (DIC) data and time dependent covariate is discussed. DIC data usually arise in follow-up studies where the lifetime, $T = W - V$ is the elapsed time between two related events, the first event, V and the second event, W where both events are interval censored (IC). The work starts by describing an algorithm that can be used to simulate doubly interval censored data. Following that the parameter estimates of the model are studied via a comprehensive simulation study. Finally the Wald and jackknife confidence interval estimation procedures are explored for the parameters of this model thorough coverage probability study.**

***Index Terms*—doubly censored, time dependent covariate, Wald, jackknife.**

I. Introduction

THe analysis of doubly interval censored data begins when De Gruttola and Lagakos [9] proposed a non-parametric estimation procedure based on the Turnbulls self-consistency algorithm. Following that, the analysis of DIC data has been studied extensively using nonparametric and semiparametric regression approaches. Reich et al. [13] proposed the likelihood contribution for a doubly interval censored lifetime. In this research we adapted Reich et al.s idea and proposed a parametric model by assuming both initial event time and lifetime follow exponential distribution.

It is rather common in any analysis to find time dependent covariates, for example, blood pressure, cholesterol level and age. These covariates that do not remain at a fixed value over time. A time dependent covariate, $x(t)$ may take values that follow a step function thus remaining constant within an interval but changes from one interval to another. Most literature on time varying covariates involve the extension of the semi parametric Cox proportional hazards model because it easily accommodates time varying covariates. This is due to the partial likelihood function, which is determined by the ordered survival times and not by the actual survival times. Authors who have made a contribution include Crowley and Hu [7],Wulfsohn and Tsiatis [20], Murphy and Sen [16], Marzec and Marzec [15], Cai and Sun [5], Zucker and Karr [21], Martinussen et al.[14], Goggins[8] and Hastie and Tibshirani [11].

Apart from the Cox model, there has also been work on time varying covariates with discrete-time using the logistic regression model by authors such as Brown [4], Hankey and Mantel [10] and Pons [18]. Other works involve the accelerated failure time model with time varying covariates which was discussed by Cox and Oakes [6], Nelson [17], Robins and Tsiatis [19] and Bagdonavicius and Nikulin [3]. Arasan and Lunn ([1],[2]) has discussed the bivariate exponential model with time varying covariate. Kiani and Arasan [12] discussed the Gompertz model with time dependent covariate for mixed case interval censored data.

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II. The Model

DIC data often arise in the follow-up studies where the survival time of interest is time between two events where both events are IC. For instance, infection by a virus as the first event and onset of the disease as the second event. DIC data include right censored(RC) and IC survival time data as special cases. In order to formulate the censoring scheme let V and W be two non-negative continuous random variables representing the times of two related consecutive events where both of them are IC and $V \leq W$. Then, the survival time of interest could be defined as, $T = W - V$. Also, T is a non-negative continuous random variable. Let survivor functions of V, T and W be $S(v)$, $S(t)$ and $S(w)$. Here it is assumed that V and T follow the exponential distribution.

Any value that V takes is IC when its exact value is unknown and only an interval $(V_L, V_R]$ is observed where $V \in (V_L, V_R]$ and $V_L \leq V_R$ with probability 1. Similarly, any value that W takes is IC when the exact value of W is unknown and only an interval $(W_L, W_R]$ is observed where $W \in (W_L, W_R]$ and $W_L \leq W_R$ with probability 1. Finally, an observation on T is DIC when the exact value of T is unknown and only one interval $(W_L - V_R, W_R - V_L]$ is observed where $T \in (W_L - V_R, W_R - V_L]$ and $W_L - V_R \leq W_R - V_L$ with probability 1. Let $f_V(v)$ and $f_T(t)$ be the probability density functions of V and T and $f_W(w)$ be the undefined probability density function of W. Following Reich et al. [13], if $f_T(t)$ is known and v is given and $t = w - v$ then the joint p.d.f. of V and W would be

$$f(v, w) = f_V(v) f_T(w - v).$$

So, the likelihood function for a DIC data is

$$\begin{aligned} L(\lambda, \gamma) &= \int_{v_L}^{v_R} \int_{w_L}^{w_R} f(v, w) dw dv \\ &= \int_{v_L}^{v_R} \int_{w_L}^{w_R} f_V(v) f_T(w - v) dw dv. \end{aligned}$$

Distributional assumptions on V and T will allow us to obtain the above likelihood function of the observations. Here it is assumed time to first event, V, and survival time, T, follow the exponential distribution.

III. Technique for Simulating Doubly Interval-Censored Data

This section looks at the simulation of DIC data when the survivor functions of the T and V are known and the attendance probability of the subjects for follow-ups can take any number between 0 to 1. To simulate n subjects, firstly the vectors $(t_i, v_i, w_i, v_{L_i}, v_{R_i}, w_{L_i}, w_{R_i})$ are produced. Here t_i, v_i and as a result w_i can be easily generated via simulation because $S(v)$ and $S(t)$ are known and also, $W = V + T$. However, the same is not the case with the simulation of $(v_{L_i}, v_{R_i}, w_{L_i}, w_{R_i})$.

In real life, $v_{L_i}, v_{R_i}, w_{L_i}$ and w_{R_i} may only be certain predetermined points on the time axis or discrete follow-up times, because it is impossible to observe subjects continuously.. In order to simulate these times, we consider a sequence of potential inspection times or $\boldsymbol{PO} = (po_1, po_2, ..., po_h)$ and assume that the subjects should be inspected or examined at these times. The subject's attendance probability at each of the po_j's is indicated by p where $0 \leq p \leq 1$ and $j = 1, 2, ..., h$. There are three possible cases for the subject's attendance probability.

1) $p = 1$, subjects attend all of the po_j's.
2) $p = 0$, subjects miss all of the po_j's.
3) $0 < p < 1$, subjects will attend to some of the po_j's and will miss others.

Depending on the value of p each subject will have a sequence of actual inspection times or $\boldsymbol{AC_i}$=$(ac_{i1}, ac_{i2}, ..., ac_{ik_i})$ where $0 \leq k_i \leq h$. The following assumptions are made before moving on to the simulation algorithm.

- There are h potential inspection times which are known by design.
- All subjects are observed in the first potential inspection time or po_1.
- Subjects will attend potential inspection times with probability p.
- Times for the first event are generated from a known $S(v)$.
- Survival times are generated from a known $S(t)$.
- For each i, v_i and w_i could not be in the same interval.
- V can be only IC or observed exactly (OE).
- W cannot be left censored (LC).

In order to generate DIC data for the first subject or $(v_{L_1}, v_{R_1}]$ and $(w_{L_1}, w_{R_1}]$ where attendance probability is p, the following algorithm is used:

1) Generate v_1 from $S(v)$ and t_1 from $S(t)$ and calculate $w_1 = v_1 + t_1$.
2) Generate $u_j \sim U(0, 1)$, where $j = 2, 3, ..., k$ and assume $u_1 = 0$.
3) Define an indicator variable for po_j's,
$$I_j = \begin{cases} 1 & \text{if subject attend } po_j \ (u_j \leq p); \\ 0 & \text{if subject miss } po_j \ (u_j > p). \end{cases}$$
4) Create the sequence of actual inspection times or $\boldsymbol{AC_1}$ where $k_1 = \sum_{j=1}^{h} I_j$.
5) Select the largest member of $\boldsymbol{AC_1}$ which is less than v_1 as a v_{L_1} and smallest member of $\boldsymbol{AC_1}$ which is more than or equal v_1 as a v_{R_1}. Define a time-window $[E_{11}, E_{21}]$ then if
$$v_1 \in [E_{11}, E_{21}] \Rightarrow V \text{ is OE}.$$
6) Select the largest member of $\boldsymbol{AC_1}$ which is less than w_1 as a w_{L_1} and smallest member of $\boldsymbol{AC_1}$ which is more than or equal w_1 as a w_{R_1}. Define a time-window $[E_{31}, E_{41}]$ then if
$$w_1 \in [E_{31}, E_{41}] \Rightarrow W \text{ is OE}.$$
Thus, if
$$w_1 > ac_{1k_1} \Rightarrow W \text{ is RC} \Rightarrow (w_{L_1}, w_{R_1}] = (ac_{1k_1}, +\infty).$$
7) If $v_{L_1} = w_{L_1}$ and $v_{R_1} = w_{R_1}$, then generate two new values for v_1 and t_1 and calculate w_1 then go to step (5).

IV. Exponential Model with Doubly Interval-Censored Data and Time-Dependent Covariates (EDICTD model)

In this section it is assumed that the time to first event, V, and survival time, T, both follow the exponential distribution with parameters λ and θ respectively. In addition, one vector of TD covariates are incorporated into the proposed model, $\boldsymbol{Y}$, where it affects T.

In the model with TD covariates we are dealing with covariates whose values change over time and not fixed throughout the study. Let $Y_1, Y_2, ..., Y_q$ represent q TD covariates. Suppose that for the i^{th} subject, the m^{th} covariate has updated at a sequence of update times $\tau_{im0}, \tau_{im1}, ..., \tau_{imk_{im}}$, where $m = 1, 2, ..., q$. τ_{im0} is the time origin, 0, and we consider it to be start of the study.

$\{\tau_{imj}\}$ represents the set of the update times, where $j = 0, 1, ..., k_{im}$. If $k_{im} = 0$, this simply means that the covariate was not updated during the subject's follow-up.

In order to accommodate covariate effects to the hazard function let$\boldsymbol{y_{im}}$=$(y_{im0}, y_{im1}, ..., y_{imk_{im}})$ represents the full history of the m^{th} covariate for the i^{th} subject which is updated at $\{\tau_{imj}\}$. It is clear that y_{im0} is the covariate's baseline value, y_{im1} is the covariate's value after first update and $y_{imk_{im}}$ is the covariate's value after k_{im}^{th} update.

We can easily detect whether a subject's covariate has updated during the follow-up because subject is monitored continuously. We could observe the occurrence of the update at time τ_{imj} and record y_{imj}.

We consider the case where covariate values follow a step function which means it stays constant at y_{imj} within the interval $\left[\tau_{imj}, \tau_{im(j+1)}\right)$, and changes to $y_{im(j+1)}$ in the following interval. An example of this kind of covariate could be a change in a patient's condition from one level to another level during the study period.

For the i^{th} subject let $\boldsymbol{Y_{i[(t_i)]}}$ denote the complete history of the covariate values up to time t_i. $\boldsymbol{Y_{i[(t_i)]}}$=$(\boldsymbol{y_{i1}}_{[(t_i)]}, \boldsymbol{y_{i2}}_{[(t_i)]}, ..., \boldsymbol{y_{iq}}_{[(t_i)]})$ where $\boldsymbol{y_{im}}_{[(t_i)]}$ is the vector of the m^{th} covariate values up to time t_i.

For the i^{th} subject let $\boldsymbol{Y_{i[t_i]}}$ denote vector of covariate values at time t_i.
$\boldsymbol{Y'_{i[t_i]}}$=$(y_{i1[t_i]}, y_{i2[t_i]}, ..., y_{iq[t_i]})$ where $y_{im[t_i]}$ is the m^{th} covariate's value at time t_i.

For the i^{th} subject the hazard function of the V is
$$h_\lambda(v_i) = e^\lambda,$$
the survivor function is
$$S_\lambda(v_i) = \exp(-v_i e^\lambda),$$

and the probability density function is

$$f_\lambda(v_i) = \exp(\lambda - v_i e^\lambda).$$

The hazard function for the i^{th} subject conditional on the given vector $\boldsymbol{Y_{i[t_i]}}$ can be expressed as

$$h_{\boldsymbol{\theta}}(t_i|\boldsymbol{Y_{i[t_i]}}) \quad = \quad \exp(\lambda_{i[t_i]}) = \exp(\beta_0 + \boldsymbol{\beta Y_{i[t_i]}}),$$

where $\boldsymbol{\beta}$=$(\beta_1, \beta_2, ..., \beta_q)$ and the vector of the parameters is $\boldsymbol{\theta}$=$(\beta_0, \boldsymbol{\beta})$.

Let us consider this model with a single TD covariate and at most one covariate update time τ_{i1}. For the i^{th} subject, the hazard function before and after update time is

$$\begin{aligned} h_{\boldsymbol{\theta}}(t_i|y_{i0}) = e^{\beta_0+\beta_1 y_{i0}} = h_0(t_i), \\ h_{\boldsymbol{\theta}}(t_i|y_{i1}) = e^{\beta_0+\beta_1 y_{i1}} = h_1(t_i). \end{aligned}$$

The likelihood function involving both censored and uncensored subjects is given by

$$\begin{aligned} L = \prod_{i=1}^{n} & \left[\int_{v_{L_i}}^{v_{R_i}} \int_{w_{L_i}-v}^{w_{R_i}-v} f_\lambda(v) f_{\boldsymbol{\theta}}(t|\boldsymbol{Y_{i[(t+v)]}}) dt dv \right]^{\delta_{DI_i}} \\ & \times \left[\int_{v_{L_i}}^{v_{R_i}} \int_{w_{L_i}-v}^{\infty} f_\lambda(v) f_{\boldsymbol{\theta}}(t|\boldsymbol{Y_{i[(t+v)]}}) dt dv \right]^{\delta_{IR_i}} \\ & \times \left[S_{\boldsymbol{\theta}} \left(t_{L_i}|\boldsymbol{Y_{i[(t_{L_i})]}} \right) - S_{\boldsymbol{\theta}} \left(t_{R_i}|\boldsymbol{Y_{i[(t_{R_i})]}} \right) \right]^{\delta_{SI_i}} \\ & \times \left[f_{\boldsymbol{\theta}} \left(t_i|\boldsymbol{Y_{i[(t_i)]}} \right) \right]^{\delta_{DE_i}} \left[S_{\boldsymbol{\theta}} \left(t_{E_i}|\boldsymbol{Y_{i[(t_{E_i})]}} \right) \right]^{\delta_{ER_i}}. \end{aligned}$$

The likelihood contributions for the i^{th} subject can be any of the following cases:

- T is DIC (both V and W are IC) and covariate is updated
- T is DIC (both V and W are IC) and covariate is not updated.
- V is IC, W is RC and covariate is updated.
- V is IC, W is RC and covariate is not updated.
- T is IC (either V or W is IC) and covariate is updated
- T is IC (either V or W is IC) and covariate is not updated.
- T is OE (both V and W are OE) and covariate is updated.
- T is OE (both V and W are OE) and covariate is not updated.
- T is RC (V is OE and W is RC) and covariate is updated.
- T is RC (V is OE and W is RC) and covariate is not updated.

A. Simulation Study

A simulation study using 1000 samples each with n=50, 100, 150, 200, 250, 300 and 350 was conducted for this model. The values of 2, 0.4 and 0.08 were chosen as the parameters of λ, β_0 and β_1.

The update time or τ_{i1} was generated from the exponential distribution with parameter ν. The value of ν can be adjusted to obtain larger or smaller values of τ_{i1}.

Random numbers from the uniform distribution on the interval (0,1), u_{1i}, were generated to produce v_i,

$$v_i = \frac{-\ln(u_{1i})}{e^\lambda}.$$

Random numbers from the uniform distribution on the interval (0,1), u_{2i}, were generated to produce t_i,

$$t_i = \begin{cases} \frac{-\ln(u_{2i}) + \tau_{i1}(e^{\gamma_{i1}} - e^{\gamma_{i0}})}{e^{\gamma_{i1}}}, & u_{2i} < \exp(-\tau_{i1} e^{\gamma_{i1}}); \\ \frac{-\ln(u_{2i})}{e^{\gamma_{i0}}}, & \text{otherwise}. \end{cases}$$

Two time-windows are defined in order to randomly select some subjects that are OE on V or W. The time-window for OE on V is
$[E_{1i}, E_{2i}] = [v_{L_i} + (v_{R_i} - v_{L_i})u_{3i} - \epsilon, v_{L_i} + (v_{R_i} - v_{L_i})u_{3i} + \epsilon]$,
and for OE on W is
$[E_{3i}, E_{4i}] = [w_{L_i} + (w_{R_i} - w_{L_i})u_{4i} - \epsilon, w_{L_i} + (w_{R_i} - w_{L_i})u_{4i} + \epsilon]$,
where $\epsilon = 0.004$ and u_{3i} and u_{4i} are random numbers generated from the uniform distribution, $U(0, 1)$.

B. Simulation Results

The simulation study was conducted to assess the bias, SE and RMSE of the estimates at different study periods, attendance probabilities and sample sizes. From Table I, we can see that the 30 months study period generates more DIC data compared to the 20 months study period. Twenty months study period generates more RC data on W.

From Tables II, II and IV we can clearly see that the bias, SE and RMSE values of the $\widehat{\lambda}$, $\widehat{\beta}_0$ and $\widehat{\beta}_1$ decrease with the increase in p, sample size and study period. RMSE's of the all three parameters are relatively small indicating that the estimation procedures works well for the model.

V. Wald and Jackknife Confidence Interval Estimates

In this section the performance of two CI estimates when applied to the parameters of the model are compared and analyzed. The first method is the asymptotic normality CI or Wald and the second is the alternative computer based technique known as the jackknife method. For discussions in the following sections we will use β_1 as our example and similar procedures would then apply for the rest of the parameters.

TABLE I
AVERAGE PERCENTAGES OF DIFFERENT DATA TYPES FOR EDICTD MODEL

p	1		0.8		0.6	
Updated covariates (%)	43		45		48	
Study periods	20	30	20	30	20	30
T is DIC (%)	76.60	82.36	78.41	84.51	80.12	86.79
V is IC and W is RC (%)	8.43	2.26	8.76	2.39	9.47	2.58
T is IC (%)	12.93	13.81	10.80	11.75	8.64	9.46
T is OE (%)	0.34	0.36	0.18	0.21	0.09	0.11
T is RC (%)	0.46	0.09	0.30	0.07	0.23	0.06

TABLE II
BIAS, SE AND RMSE OF $\widehat{\lambda}$ FOR THE EDICTD MODEL

Study periods		30			20		
p		1	0.8	0.6	1	0.8	0.6
50	Bias	-0.0087	-0.0209	-0.0397	-0.0204	-0.0312	-0.0506
	SE	0.1552	0.1573	0.1576	0.1567	0.1527	0.1549
	RMSE	0.1555	0.1587	0.1625	0.1580	0.1559	0.1630
100	Bias	-0.0049	-0.0186	-0.0404	-0.0196	-0.0307	-0.0509
	SE	0.1113	0.1148	0.1136	0.1095	0.1080	0.1096
	RMSE	0.1114	0.1163	0.1206	0.1112	0.1123	0.1208
150	Bias	-0.0097	-0.0235	-0.0461	-0.0231	-0.0347	-0.0546
	SE	0.0879	0.0896	0.0892	0.0870	0.0849	0.0866
	RMSE	0.0884	0.0926	0.1004	0.0900	0.0917	0.1024
200	Bias	-0.0145	-0.0283	-0.0501	-0.0258	-0.0372	-0.0546
	SE	0.0753	0.0762	0.0751	0.0753	0.0739	0.0866
	RMSE	0.0767	0.0813	0.0903	0.0796	0.0828	0.1024
250	Bias	-0.0138	-0.0286	-0.0506	-0.0255	-0.0368	-0.0584
	SE	0.0669	0.0665	0.0668	0.0676	0.0658	0.0671
	RMSE	0.0683	0.0724	0.0838	0.0723	0.0754	0.0890
300	Bias	-0.0137	-0.0285	-0.0512	-0.0262	-0.0370	-0.0587
	SE	0.0637	0.0642	0.0643	0.0630	0.0621	0.0626
	RMSE	0.0652	0.0702	0.0821	0.0682	0.0723	0.0858
350	Bias	-0.0152	-0.0292	-0.0514	-0.0266	-0.0378	-0.0590
	SE	0.0572	0.0578	0.0577	0.0576	0.0570	0.0567
	RMSE	0.0592	0.0648	0.0773	0.0635	0.0684	0.0818

TABLE III
BIAS, SE AND RMSE OF $\widehat{\beta}_0$ FOR THE EDICTD MODEL

Study periods		30			20		
p		1	0.8	0.6	1	0.8	0.6
50	Bias	0.0073	-0.0058	-0.0325	0.0022	-0.0270	0.0193
	SE	0.1381	0.1363	0.1330	0.1357	0.1312	0.1398
	RMSE	0.1383	0.1364	0.1369	0.1357	0.1339	0.1412
100	Bias	0.0066	-0.0060	-0.0326	0.0072	-0.0215	0.0231
	SE	0.0983	0.0972	0.0943	0.0971	0.0929	0.0987
	RMSE	0.0985	0.0973	0.0998	0.0973	0.0953	0.1014
150	Bias	0.0032	-0.0100	-0.0361	0.0050	-0.0237	0.0206
	SE	0.0767	0.0757	0.0736	0.0765	0.0745	0.0776
	RMSE	0.0768	0.0764	0.0820	0.0767	0.0781	0.0803
200	Bias	0.0001	-0.0127	-0.0391	0.0030	-0.0251	0.0180
	SE	0.0677	0.0670	0.0651	0.0680	0.0659	0.0694
	RMSE	0.0677	0.0682	0.0760	0.0680	0.0705	0.0717
250	Bias	-0.0002	-0.0132	-0.0397	0.0032	-0.0253	0.0183
	SE	0.0602	0.0594	0.0575	0.0611	0.0591	0.0619
	RMSE	0.0602	0.0608	0.0699	0.0612	0.0643	0.0646
300	Bias	-0.0001	-0.0131	-0.0395	0.0033	-0.0253	0.0184
	SE	0.0557	0.0552	0.0529	0.0562	0.0547	0.0573
	RMSE	0.0557	0.0568	0.0660	0.0563	0.0603	0.0602
350	Bias	-0.0010	-0.0137	-0.0403	0.0030	-0.0258	0.0182
	SE	0.0510	0.0504	0.0483	0.0512	0.0498	0.0523
	RMSE	0.0510	0.0523	0.0629	0.0513	0.0560	0.0553

TABLE IV
BIAS, SE AND RMSE OF $\widehat{\beta}_1$ FOR THE EDICTD MODEL

Study periods		30			20		
p		1	0.8	0.6	1	0.8	0.6
50	Bias	-0.0397	-0.0418	-0.0492	-0.0373	-0.0401	-0.0438
	SE	0.2000	0.2038	0.2103	0.2095	0.2063	0.2139
	RMSE	0.2039	0.2081	0.2160	0.2128	0.2102	0.2184
100	Bias	-0.0317	-0.0323	-0.0335	-0.0286	-0.0321	-0.0320
	SE	0.1343	0.1358	0.1409	0.1359	0.1396	0.1405
	RMSE	0.1380	0.1396	0.1449	0.1389	0.1432	0.1441
150	Bias	-0.0309	-0.0324	-0.0383	-0.0316	-0.0340	-0.0378
	SE	0.1129	0.1151	0.1181	0.1171	0.1204	0.1205
	RMSE	0.1171	0.1196	0.1241	0.1213	0.1251	0.1263
200	Bias	-0.0379	-0.0382	-0.0414	-0.0360	-0.0373	-0.0373
	SE	0.0957	0.0975	0.0989	0.0978	0.0985	0.1002
	RMSE	0.1029	0.1047	0.1072	0.1043	0.1053	0.1069
250	Bias	-0.0348	-0.0389	-0.0407	-0.0317	-0.0346	-0.0388
	SE	0.0850	0.0863	0.0852	0.0879	0.0888	0.0895
	RMSE	0.0919	0.0947	0.0944	0.0934	0.0953	0.0975
300	Bias	-0.0307	-0.0336	-0.0379	-0.0292	-0.0337	-0.0365
	SE	0.0795	0.0802	0.0795	0.0812	0.0811	0.0807
	RMSE	0.0852	0.0869	0.0880	0.0863	0.0879	0.0886
350	Bias	-0.0278	-0.0308	-0.0342	-0.0269	-0.0284	-0.0309
	SE	0.0723	0.0739	0.0729	0.0739	0.0747	0.0749
	RMSE	0.0774	0.0801	0.0806	0.0787	0.0800	0.0810

A. Wald Confidence Interval Estimates

Let $\widehat{\boldsymbol{\theta}}$ be the maximum likelihood estimator for the vector of parameters $\boldsymbol{\theta}$ and $l(\boldsymbol{\theta})$ the log-likelihood function of $\boldsymbol{\theta}$. Following Cox and Hinkley (1974), under mild regularity conditions, $\widehat{\boldsymbol{\theta}}$ is asymptotically normally distributed with mean $\boldsymbol{\theta}$ and covariance matrix $I^{-1}(\boldsymbol{\theta})$, where $\mathbf{I}(\boldsymbol{\theta})$ is the Fisher information matrix evaluated at the true value of the $\boldsymbol{\theta}$. The matrix $\mathbf{I}(\boldsymbol{\theta})$ can be estimated by the observed information matrix $\mathbf{I}(\widehat{\boldsymbol{\theta}})$. The $\widehat{\mathtt{var}}(\widehat{\beta}_1)$ is the $(2,2)^{th}$ element of matrix $I^{-1}(\widehat{\boldsymbol{\theta}})$. The $100(1-\alpha)\%$ CI for β_1 is

$$\widehat{\beta}_1 - z_{1-\frac{\alpha}{2}}\sqrt{\widehat{\mathtt{var}}(\widehat{\beta}_1)} < \beta_1 < \widehat{\beta}_1 + z_{1-\frac{\alpha}{2}}\sqrt{\widehat{\mathtt{var}}(\widehat{\beta}_1)}.$$

B. Jackknife Confidence Interval Estimates

For a data set with n observation, the i^{th} jackknife sample is defined to be $\boldsymbol{x}$ with the i^{th} observation removed. So, the i^{th} jackknife sample would consist of $(n-1)$ observations, all except the i^{th} subject.

$$\boldsymbol{x_{(i)}} = (x_1, x_2, ..., x_{i-1}, x_{i+1}, ..., x_n).$$

The jackknife estimate of bias and SEs are computed from the jackknife samples. Let $\widehat{\beta}_{1(i)}$ be the MLE of the parameter β_1 based on the jackknife sample $\boldsymbol{x_{(i)}}$. Then, the new estimate, $\widehat{\beta}_{1(jack)}$ is defined by

$$\widehat{\beta}_{1(jack)} = \widehat{\beta}_1 - (n-1)(\widehat{\beta}_{1(.)} - \widehat{\beta}_1),$$

where

$$\widehat{\beta}_{1(.)} = \sum_{i=1}^{n} \frac{\widehat{\beta}_{1(i)}}{n},$$

and $\widehat{\beta}_1$ is the MLE of the parameter β_1 obtained from the full sample $\boldsymbol{x}= (x_1, x_2, ..., x_n)$. The jackknife estimate of the SE is

$$\widehat{\mathtt{SE}}_{jack}(\widehat{\beta}_1) = \sqrt{\frac{n-1}{n}\sum_{i=1}^{n}(\widehat{\beta}_{1(i)} - \widehat{\beta}_{1(.)})^2}.$$

If $t_{(1-\frac{\alpha}{2}, n-1)}$ is the $(1-\frac{\alpha}{2})$ quantile of the student's t distribution at (n-1) degrees of freedom, the $100(1-\alpha)\%$ CI for β_1 is

$$\widehat{\beta}_{1(jack)} \pm t_{(1-\frac{\alpha}{2}, n-1)}\widehat{\mathtt{SE}}_{jack}(\widehat{\beta}_1).$$

C. Coverage Probability Study

The coverage probability of a CI is the probability that the interval contains the true parameter value and should preferably be equal or close to the nominal coverage probability, $1-\alpha$.

A coverage probability studies was conducted using $N = 1500$ samples of sizes $n = 50, 100, 150, 200, 250, 300$ and 350 to compare the performance of the CI estimates at $\alpha = 0.05$ and $\alpha = 0.1$ where α is the nominal error probability. Values of the parameters were chosen are the same as those chosen for the simulation study.

The study period was assumed 20 months with monthly follow-ups and $p = 1$, for all patients. Following that, we calculated the estimated total error probabilities by adding the number of times in which an interval did not contain the true parameter value divided by the total number of samples.

Following Doganaksoy and Schmee (1993), if the total error probability is greater than $\alpha + 2.58 \times \mathtt{SE}(\widehat{\alpha})$, then the method is termed anti-conservative; if the total error probability is less than $\alpha - 2.58 \times \mathtt{SE}(\widehat{\alpha})$, then the method is termed conservative and if the larger error probability is more than 1.5 times the smaller one, then the method is termed asymmetrical.

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Standard error of estimated error probability is approximately

$$\mathrm{SE}(\widehat{\alpha}) = \sqrt{\frac{\alpha(1-\alpha)}{N}}.$$

D. Coverage Probability Results and Discussion

Tables V and VI show number of conservative, anti-conservative and asymmetrical intervals for parameters λ and β_0 and β_1 at two levels of the nominal error probabilities, $\alpha = 0.05$ and 0.1 for both Wald and jackknife methods. Figure I illustrates the estimated left and right error probabilities for parameters λ and β_0 and β_1 at two levels of the nominal error probabilities for both methods. Finally, Table

Both the Wald and jackknife methods produce asymmetrical intervals for almost all sample sizes and all parameters at both $\alpha = 0.05$ or 0.1, see Tables V and VI. There were only 1 conservative interval and 2 anti-conservative intervals (when $\alpha = 0.1$) produced by the Wald method. However, there was no conservative interval produced by the jackknife method, but many anti-conservative intervals were produced for parameters λ and β_1.

From Figure I and Tables V and VI we can observe that both the Wald and jackknife methods perform only moderately for all parameters. However the low number of conservative and anti-conservative intervals and also the simplicity of the Wald method as compared to the jackknife, does provide a motivation for its use. Increasing the sample size does improve the performance slightly but caution should be exercised due to the high number of asymmetrical intervals produced.

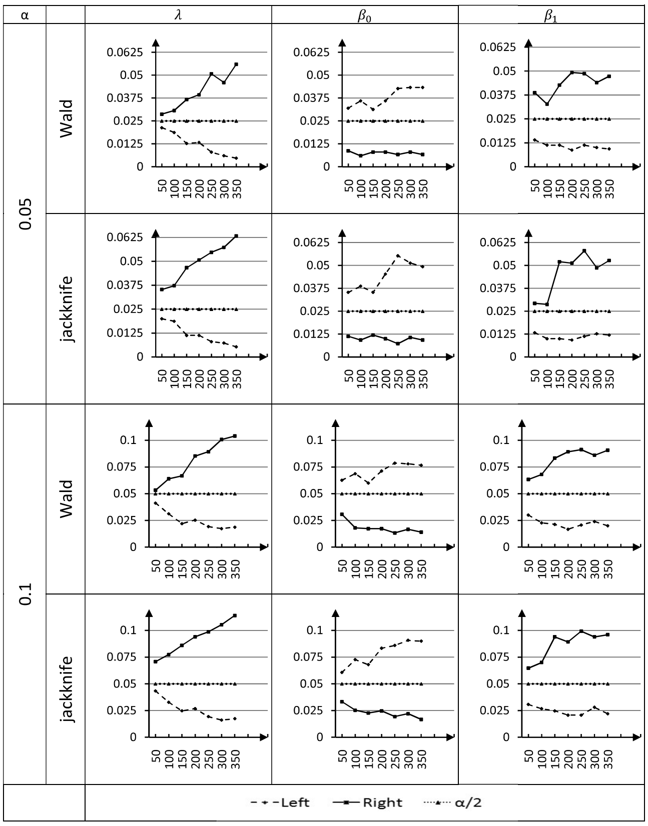

Fig. 1. Estimated Error Probabilities of Wald and Jackknife Methods for the EDICTD model

VI. Conclusion

In this research the MLE for the parameters of a survival model with doubly interval-censored data and time-dependent covariates was analyzed. It was shown that the bias, SE and RMSE values decrease when the study period, attendance probability and sample size increase. We also evaluated two CI estimation methods for the parameters of the models. Both the Wald and jackknife performed only moderately for the parameters of the EDICTD model.

The discussion in this research was restricted to two covariate levels. Thus, it would be possible to carry out further work to include more covariate levels. Other survival models could also be developed further to include TD covariates in the presence of DIC data. This research only focused on Wald and jackknife CI estimation methods while other CI estimation methods that depend on the asymptotic normality of the MLE method like LR and other alternative CI estimation methods such as the bootstrap could be studied in the future.

TABLE V
Performance of Wald method for the EDICTD model

	$\alpha = 0.05$									$\alpha = 0.1$								
	C			AC			Asy			C			AC			Asy		
n	λ	β_0	β_1	λ	β_0	β_1	λ	β_0	β_1	λ	β_0	β_1	λ	β_0	β_1	λ	β_0	β_1
50								*	*								*	*
100							*	*	*							*	*	*
150							*	*	*		*					*	*	*
200							*	*	*							*	*	*
250							*	*	*							*	*	*
300							*	*	*				*			*	*	*
350							*	*	*				*			*	*	*
subtotal	0	0	0	0	0	0	6	7	7	0	1	0	2	0	0	6	7	7
total		0			0			20			1			2			20	

C: Conservative, AC: Anti-conservative, Asy: Asymmetrical

TABLE VI
Performance of jackknife method for the EDICTD model

	$\alpha = 0.05$									$\alpha = 0.1$								
	C			AC			Asy			C			AC			Asy		
n	λ	β_0	β_1	λ	β_0	β_1	λ	β_0	β_1	λ	β_0	β_1	λ	β_0	β_1	λ	β_0	β_1
50							*	*	*							*	*	*
100							*	*	*							*	*	*
150							*	*	*						*	*	*	*
200							*	*	*				*			*	*	*
250				*	*	*	*	*	*				*		*	*	*	*
300				*			*	*	*				*		*	*	*	*
350				*		*	*	*	*				*		*	*	*	*
subtotal	0	0	0	3	1	2	7	7	7	0	0	0	4	0	4	7	7	7
total		0			6			21			0			8			21	

C: Conservative, AC: Anti-conservative, Asy: Asymmetrical

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