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The Comparison of Time Functions in the Extended Cox Regression Model

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Highlights

- This paper focuses on the comparison of time functions in the extended Cox regression model.
- It has been conducted the simulation study under different scenarios to compare the time functions.
- All computations are carried out by using R.

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Extended Cox model, Time function, Non-proportional hazards, Time dependent covariate, Proportional hazards

Abstract

Extended Cox regression model by using any form of time function is one of the alternative methods to the Cox regression model in non-proportional hazards case or time-dependent covariate problem. It is a key concern which time function should be used in which case for an extended Cox regression model. In this study, a comparison of the most commonly used time functions for the extended Cox regression model to obtain the effects of variables not satisfying the proportional hazard assumption is carried out. This simulation study assesses the ability of the time functions for the extended Cox regression model in modeling non-proportional hazards according to sample sizes, censoring rate, and prevalence ratio of the binary covariate. The results indicate that the linear time function (t) is more biased than the logarithmic time function (log(t)), which is a frequently used time function in modeling the hazard ratio. Also, it is shown that the use of time function 1/t has better results in most situations.

1. INTRODUCTION

Cox regression model (CRM) is the most commonly used model to analyze survival data or time to event data [1]. The advantages of the model are that there is no assumption about the shape of the underlying hazard function and relative effects can be directly estimated. But with these advantages of the model, CRM has a fundamental assumption of proportional hazard (PH) which requires a constant hazard ratio over time with different covariate levels. CRM cannot be used if the covariate does not satisfy the PH assumption [2, 3]. The violation of the PH assumption causes biased parameter estimations [4]. One of the alternative methods that carry out the non-proportionality problem is extended CRM. The model can be used to check the PH assumption as well as for obtaining a hazard ratio formula that considers the effects of variables not satisfying the PH assumption [5]. Extended CRM extends to a model that contains non-proportional covariates and the multiplication of these covariates with time or a function of time. That is, if the i^{th} non-proportional covariate is denoted as X_i, then we can define the i^{th} product term as $X_i g_i(t)$ where $g_i(t)$ is a function of time for the i^{th} variable. One difficulty with this approach is which time function g(t) to use is more suitable. A lot of form of g(t) was used in the literature to analyze such data. That is the main reason for the choice of topic in this article, to try to find some better guidelines for the researchers. One of the most common choices for the g(t) is to get the multiplication of the covariate or covariates with time, g(t) = t [5, 6]. This implies that for each X_i in the model as a main effect, there is a corresponding time-dependent variable in the model of the form $X_i \times t$. Another most used choice for the g(t) is the log of t [5, 6]. Also, numerous forms of time functions can be used. Sauerbrei et al. [7] and Persson and Khamis [8] used some other function of time to assess PH assumption with extended CRM in their study. We take into consideration t, log(t), square root of t, t square, exp(t), and 1/t as the form of time function in this study.

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There are several studies that involve time-dependent covariates in survival analysis. Some of them can be listed as follows:

Chai and Sun [9] study over Kernel-weighted local linear estimation approach to achieve a more flexible model for time-dependent covariates. The performance of their approach is tested through simulation studies and real data applications and the results show that more accurate and reliable time-varying effects are achieved.

Platt et al. [10] study CRM with time-dependent covariate and time varying effects of fetal and infant death via a real data example and a simulation study. It is shown that the effects of certain risk factors may not remain constant over time especially in the prenatal and postnatal periods. The proposed method explains the effects of factors on fetal and infant deaths over time more accurately.

Wang [11] studies CRM with unknown link function and time-dependent covariate. This approach helps to model situations where the coefficients and the link function can depend on both observed variables and time. The semi-parametric and the profile likelihood approach is used to estimate the coefficients. The results point out that wrong determination of the link function can create biases in the estimations.

Sparling et al. [12] study parametric survival model for interval censored data with time-dependent covariate. It is emphasized that complex survival structures involving time-dependent variables and interval censoring together increases modeling accuracy.

Zhang and Huang [13] study nonparametric survival analysis on time-dependent covariate effects in case-cohort sampling design. They state that the suggested method based on non-parametric approach capture the effects of covariates vary over time flexibly.

Kremers [14] studies concordance for survival time data with fixed and time-dependent covariates. They examine the definition and calculation of concordance index that is an important criterion used to evaluate the prediction accuracy of the model for the time-dependent covariates in a data with tied survival times.

Heinze and Dunkler [15] study how to avoid infinite estimates of time-dependent effects in small-sample survival studies. They recommend alternative statistical methods such as penalized regression techniques to avoid the problem of overestimation of coefficients and unstable model in case of small number of events.

Bower et al. [16] examines time-dependent effects in flexible parametric survival models. The study reveals that flexible parametric models depend on spline-based methods outperform classical methods in accurately capturing time-dependent effects. Also, their findings suggest that there is a reduction in biases of survival function.

Therneau et al. [17] study the time dependent covariates and coefficients in CRM in R. They examine how time-dependent covariates and time-dependent coefficients can be modelled within the CRM by using the counting process and start-stop data structures.

Husain et al. [18] model the factors that affect the survival time and rate of cure of breast cancer patients with the time function t. They showed that the degree of malignancy of the tumor has a significant effect on the survival time of patients.

Wu and Li [19] offer a flexible and effective joint analysis of multivariate interval-censored survival data and time-dependent covariates. Model parameters were obtained by the EM algorithm and the inferences for finite-dimensional parameters were made using the bootstrap method. Simulation studies have shown that model fit and inference approaches perform well under different sample sizes.

Suresh et al. [20] study a copula-based approach for dynamic prediction of survival with a binary time-dependent covariate. Their method allows specifying flexible models for marginal distributions and evaluating the fit of these models. The prediction performance of the proposed approach is compared with

joint modeling and landmarking methods through simulations and a real prostate cancer data set. The results demonstrate the flexibility and effectiveness of the copula-based method.

Austin et al. [21] examine the effects of time-varying covariates in Cox regression using fractional polynomials and restricted cubic splines. They used these methods to allow a regression coefficient to vary as a flexible function of time as an alternative to Cox regression model with time-dependent covariates.

Geraili et al. [22] evaluate the time-varying biomarkers in mortality outcome of 1641 COVID-19 patients in Iranian with extended CRM using t and log(t) time functions. The study also emphasizes that monitoring biomarkers that change over time has an importance in interpreting disease severity and risk of death. Their findings suggest that the extended CRM framework provides more accurate and reliable results in the presence of non-proportional hazards, aligning with our study's objective of comparing different time functions.

Maharela et al. [23] compare the performance of the stratified and extended CRMs under varying censoring rates, sample sizes, and survival distributions. They found that the extended CRM outperformed other models under every combination of censoring, sample size and survival distribution. However, they did not specify the time function used in their extended model, which further motivates our study to systematically evaluate the effects of different time functions in extended Cox regression.

The choice of time function is important in such studies and this situation supports the purpose of our study since time-dependent covariate is currently studied. Previous studies have examined time-dependent covariates, but not all have explicitly considered the choice of time functions. The choice of time function is crucial in survival studies involving time-dependent covariates, as previous literature has often overlooked or not clearly addressed the impact of selecting different time functions. This gap directly supports the purpose of our study, which focuses on the comparison of time functions in extended Cox regression models. In addition, researchers often prefer the extended CRM with the log(t) or t time function, and the Extended CRM with the 1/t time function is a form that researchers are not accustomed to. Most of the studies in the literature include applications for only one data set. In addition, to our knowledge, there is no study including how the time function should be selected according to sample size or censoring rate. In general, there are studies that suggest usage of alternative regression type model. By integrating insights from existing literature and applying them to our research context, we contribute to a more comprehensive understanding of how time functions influence the reliability of survival estimates. Since survival analysis is widely used by practitioners in different fields, our study was conducted to help them to choose of the correct time function.

The objective of this paper was to examine which time function is preferred to get a less biased estimator when fitting an extended CRM. A simulation study was run to evaluate the behavior of time functions in different sample sizes, censoring rates, and prevalence ratio of binary covariates. The rest of the paper is organized as follows. In section 2, we define the methods and notations. In section 3, we evaluate the used models' performances through simulation studies. In section 4, we make comparisons by analyzing three different real datasets. In section 5, we summarize our findings.

2. COX REGRESSION MODEL

One of the most applicable and used models in survival analysis to evaluate the effects of covariates is CRM also sometimes abbreviated to the Cox model or proportional hazards model. According to the CRM, the hazard function is given as follows:

$$h(t, \mathbf{X}) = h_0(t)\exp\left(\sum_{k=1}^{p} \beta_k X_k\right)$$

where $h_0(t)$ is the baseline hazard function at that time, X represents the covariates vector and β is a $1 \times p$ vector of regression parameters. Coefficient vectors of the covariates are estimated using a maximum

likelihood (ML) procedure [1, 24]. ML estimates are obtained by maximizing the partial likelihood function, which is expressed as follows:

$$L_i(\boldsymbol{\beta}) = \prod_{i=1}^{n} \left(\frac{\exp\left(\sum_{k=1}^{p} \beta_k X_k\right)}{\sum_{j \in R(T_i)} \exp\left(\sum_{k=1}^{p} \beta_k X_k\right)} \right)^{\delta_i}$$

where $R(T_i)$ is the risk set (all individuals still at risk at time Ti), and δ_i is the event indicator for individual i. PH assumption is a key assumption of CRM. The meaning of the PH assumption is that the ratio of the hazard function of one covariate level over another covariate level is constant, and not affected by time. If the PH assumption is not met, the CRM is not appropriate. In some cases, covariates may not meet the assumption of proportional hazards, and some alternative models are suggested. Extended CRM is one of these alternatives.

2.1. Extended Cox Regression Model

CRM extends to a model which contains non-proportional covariates and the multiplication of these covariates with a function of time. The extended CRM is defined as follows,

$$h\big(t, X(t)\big) = h_0(t) \exp\left(\sum_{k=1}^{p} \beta_k X_k + \sum_{k=1}^{p} \gamma_k X_k g_k(t)\right)$$

where $g_k(t)$ is a specified function of time for covariate X_k. This general form allows each covariate to have both a time-invariant effect β_k and a time-varying component $\gamma_k g_k(t)$. To reflect the PH assumption for some covariates, the model can be restructured by partitioning the covariates into two groups:

$$h\big(t, X(t)\big) = h_0(t) \exp\left(\sum_{\ell=1}^{p_1} \beta_\ell X_\ell + \sum_{k=p_1+1}^{p_2} \beta_k X_k + \sum_{k=p_1+1}^{p_2} \gamma_k X_k g_k(t)\right)$$

where p_1 denotes the number of covariates which meet the PH assumption and $p_2=p-p_1$ denotes the number of covariates which does not meet the PH assumption [5, 6].

This is sometimes referred to as the time-varying coefficient model. Likelihood function of extended CRM is expressed as follows:

$$L_i(\boldsymbol{\beta}) = \prod_{i=1}^{n} \left(\frac{\exp\left(\sum_{\ell=1}^{p_1} \beta_\ell X_\ell + \sum_{k=p_1+1}^{p_2} \beta_k X_k + \sum_{k=p_1+1}^{p_2} \gamma_k X_k g_k(t)\right)}{\sum_{j \in R(T_i)} \exp\left(\sum_{\ell=1}^{p_1} \beta_\ell X_\ell + \sum_{k=p_1+1}^{p_2} \beta_k X_k + \sum_{k=p_1+1}^{p_2} \gamma_k X_k g_k(t)\right)} \right)^{\delta_i}$$

where $R(T_i)$ is the risk set, and δ_i is the event indicator for individual i. As with the simpler CRM, an ML procedure is used to estimate the regression coefficients in the extended CRM. ML estimates are obtained by maximizing the partial likelihood function. The likelihood function of the extended CRM is maximized using the Newton-Raphson algorithm. This method iteratively updates parameter estimates by computing the gradient and Hessian of the likelihood function until convergence. For this method, the critical decision is to determine the form of the time function. t and log(t) are usually used for the time function g(t) and also the square root of t ($\sqrt{t}$), t square (t^2), and exp(t) are some other functions used for the same purpose. Also, we used 1/t as a time function in the simulation study, motivated by its inclusion in fractional polynomial approaches for modeling time-varying effects in Cox regression [21].

3. SIMULATION STUDIES

We used the simulation procedure of Schemper [25] and Ata and Demirhan [26] to generate non-proportional survival data. x_1 and x_2 are two 0/1 coded covariates and generated from Bernoulli(p) for four different prevalence of the binary covariates (p= 20, 40, 60 and 80 percent). We specified that two covariates have equal prevalence ratios. Survival times were generated from Weibull (α; γ) distribution and the setting of α and γ is chosen to define non-proportional hazards for x_1 and proportional hazards for x_2.

The shape parameters γ were taken as 1 for x_1=0 and as 3 for x_1=1, defining non-proportional hazards for x_1. The shape parameters α were taken as 0.8 for x_1=0 and x_2=0, as 1.5 for x_1=1 and x_2=0, as 2.2 for x_1=0 and x_2=1, and as 4.125 for x_1=1 and x_2=1. This configuration ensures that x_1 affects the time-dependence of the hazard (via changes in γ), while x_2 influences the baseline scale without altering the time-dependence, thereby preserving proportional hazards for x_2. Population regression parameters were taken as 0.7 for x_1 and 1.4 for x_2. The study of Persson and Khamis [27] was used to generate censoring times and determine the censored observations. Censoring times were drawn from the uniform distribution U(0, T) where T was determined to achieve the desired censoring rate. It was checked while the simulation code was carried out that observed censoring rates were in the range of ± 0.05 of the desired censoring rates. All computations were carried out by using the coxph() function in the R package survival [17].

We would like to study the effect of the censoring rates, sample sizes, and prevalence of the binary covariate on the beta estimates obtained from the models. Understanding how censoring rates, sample sizes, and the prevalence of the binary covariate affect beta estimates is crucial for ensuring the reliability of survival models. In real-world applications, survival data often include a high proportion of censored observations, which can impact the accuracy and stability of parameter estimates. Our study provides insights into how different levels of censoring influence model performance, helping researchers anticipate potential biases in their analyses. Additionally, sample size plays a key role in statistical inference, and our findings highlight how variations in sample size affect the precision of beta estimates. This is particularly relevant for studies with limited data, such as clinical trials with small patient cohorts or rare disease studies, where selecting an appropriate time function is critical to obtaining valid results. The prevalence of the binary covariate is another important factor, as imbalanced distributions can lead to issues such as estimation instability or reduced statistical power. Our study explores these effects, offering guidance on how researchers should interpret results when dealing with unevenly distributed covariates. By systematically evaluating these factors in a controlled simulation setting, our findings provide practical recommendations for researchers conducting survival analysis. This helps improve model selection and enhances the robustness of statistical conclusions in applied research. The comparison was carried out under three different censorship levels (that is, c=10, 30, and 60 percent), using four different sample sizes (n=30, 50, 100, and 1000) and for four different prevalence of the binary covariates (p= 20, 40, 60 and 80 percent). It was generated 1000 samples for each scenario. We compared the results of extended CRM with the time functions t, log(t), $\sqrt{t}$, t^2, and exp(t). In addition to the most used time functions in literature, the use of time function 1/t was also examined. The mean square error (MSE) and the mean absolute bias (MAE) values were obtained to compare the performance of the time functions examined in the simulation study. The MSE was calculated as the average of the squared differences between actual and predicted values of parameters and the MAE was defined as the average of the absolute difference between actual and predicted values of parameters, across all simulation scenarios. The MSE and the MAE results were reported in Table 1 and 2, respectively. Additionally, the log-likelihood values for extended CRMs with six different time functions were calculated for each scenario. These log-likelihood values were then ranked, and the proportions of each model providing the maximum log-likelihood value across 1000 repetitions were reported in Table 3. This approach allows for the identification of the model with the best fit, based on the time function that provides the maximum log-likelihood value, as a higher log-likelihood indicates a better fit to the data.

Table 1 shows the MSE results across simulation scenarios. For the sample size 30 with 10% and 30% censoring rate, minimum MSE is obtained in 40%, 60%, and 80% prevalence ratio by using the time function 1/t for the non-proportional covariate. The same result is also obtained for sample size 30 with 60% and 80% prevalence ratio of 60% censoring rates in extended CRM with the time function 1/t for non-proportional covariate. Minimum MSE is calculated with time function log(t) for all remaining cases of sample size 30. The function 1/t shows a good performance for the sample size 50, except for 30% and 60% censoring rates with 20% prevalence ratios and 60% censoring rate with 40% prevalence ratio. The estimations with time function log(t) have better results in the exceptional cases of sample size 50 for non-proportional covariate. The time function 1/t is not a usual function for the extended CRM but it performs well than the all functions used in all other cases, except for the sample size 100 at 60% censoring rate with 20% prevalence ratio, for non-proportional covariate in large sample sizes. In the exceptional case of a

sample size of 100 with a 60% censoring rate and a 20% prevalence ratio, the extended CRM with the time function log(t) yields the lowest MSE for the non-proportional covariate.

Table 2 presents the MAE results of the scenarios. Similar results with MSE are obtained in terms of MAE with exception of a few differences for the non-proportional covariate. The estimations with time function log(t) for the non-proportional covariate have better results in the all censoring rates of sample size 30 for the smallest prevalence ratio. Also log(t) performs well at the high censoring and smallest prevalence ratio in terms of MAE for sample size 50. In all remaining scenarios, the extended CRM with the time function 1/t have the smallest MAE value for non-proportional covariate.

In all scenarios, $g(t)=\sqrt{t}$ has the largest bias than the other methods in terms of MSE and MAE for non-proportional covariate but approximate results for proportional covariate within the other models. It is also obtained a decreasing bias with increasing sample size for $g(t)=t^2$ within the non-proportional covariate but not the minimum MSE or MAE across models. In all scenarios, more bias is obtained from the extended CRM with time function t when we compare to log(t) and 1/t when estimating the effect of the non-proportional covariate.

On the other hand, all methods have approximate results for proportional covariate (β_2) in all scenarios in terms of both MSE and MAE.

Table 3 shows the percentages of fitting using log-likelihood across simulations. It is seen that the proportion of the extended CRM with 1/t time function is the highest for all censoring and prevalence ratios and varies between 0.529 and 0.80 for the sample sizes 30, 50, and 100. Moreover, a pattern that higher censoring rates reduce the proportion of fit to the 1/t time function, especially under high prevalence conditions, is also evident in our findings. Increasing the sample size from 30 to 100 leads to a higher proportion of fitting for the extended CRM with the 1/t time function at 0.60 censoring rate. However, for a sample size of 1000, it is concluded that extended CRM with the 1/t time function provided the best model above 70% for prevalence ratios of 0.20 and 0.40 in all censoring rates. On the other hand, for prevalence ratio of 0.80, extended CRM with the log(t) time function provide the highest rate of fitting in all censoring rates and also the proportion of fitting decreased as the censoring increased. For the 0.60 prevalence ratio of 1000 sample size, while log(t) at 0.10 and 0.30 censor rates provide the highest rate of fitting, and at 0.60 censor rate extended CRM with 1/t provide a higher rate of fitting. Also, in very large sample size scenarios, the extended CRM with t, $\sqrt{t}$, t^2, and exp(t) provide the fit very few or never. Although the extended CRM with time function 1/t achieve the lowest MSE and MAE for the all scenarios of 1000 sample size across simulation replications, its fitting proportion remains relatively low for some exceptions. This suggests that while the model offers stable and consistently accurate estimates, it is not always the best performer for sample size 1000.

Table 1. *MSE Results for Extended CRM with Different Time Functions and Simulation Settings*

			β_1						β_2					
	c	**p**	**t**	**log(t)**	**1/t**	**√t**	**t^2**	**exp(t)**	**t**	**log(t)**	**1/t**	**√t**	**t^2**	**exp(t)**
n=30	10%	20%	15.69	2.64	6.67	46.79	6.88	11.92	8.00	8.00	7.97	8.01	7.96	7.93
		40%	9.85	4.39	2.00	24.59	5.19	5.51	10.45	10.67	10.97	10.57	10.24	10.08
		60%	10.98	5.32	1.61	24.10	6.47	6.19	13.10	12.88	12.58	13.03	13.04	12.76
		80%	17.72	10.13	3.81	38.65	10.49	9.96	18.97	19.76	21.42	19.40	18.31	17.47
	30%	20%	25.86	4.08	13.26	81.27	10.67	21.83	8.35	8.41	8.41	8.39	8.36	8.35
		40%	13.37	4.17	3.38	33.14	7.29	9.84	10.60	10.36	10.22	10.48	10.75	10.76
		60%	16.00	6.52	2.98	35.86	9.43	11.52	13.71	13.35	13.02	13.55	13.78	13.61
		80%	24.84	12.29	6.32	57.42	14.40	16.74	20.08	20.69	22.31	20.39	19.65	19.21
	60%	20%	40.74	4.61	23.95	134.76	15.36	58.71	7.05	6.84	6.76	6.93	7.36	7.25
		40%	24.10	5.37	8.34	64.79	12.19	25.70	10.12	9.85	9.82	9.97	10.35	10.30
		60%	27.74	7.65	7.10	66.30	15.97	26.69	13.94	13.25	12.88	13.58	14.42	14.25
		80%	46.67	14.57	11.02	110.68	27.11	41.34	23.82	23.44	23.64	23.70	24.03	23.48
n=50	10%	20%	9.36	2.15	2.14	25.00	4.57	6.03	7.76	7.75	7.68	7.77	7.70	7.64
		40%	7.03	2.92	0.65	16.18	3.98	3.64	9.47	9.40	9.28	9.45	9.43	9.36
		60%	8.60	4.23	0.72	18.55	5.08	4.28	11.98	11.83	11.60	11.93	11.93	11.71
		80%	14.79	7.91	1.78	31.64	8.49	7.27	17.03	17.17	16.76	17.20	16.50	15.90
	30%	20%	16.46	2.82	6.36	47.78	7.45	12.68	7.90	7.82	7.80	7.86	7.97	7.99
		40%	9.43	3.37	1.16	21.28	5.46	5.99	9.78	9.58	9.46	9.68	9.90	9.91
		60%	11.21	4.82	1.23	23.35	6.88	6.95	12.26	11.98	11.72	12.14	12.34	12.22
		80%	18.57	8.96	2.65	39.20	11.07	11.46	17.63	17.81	17.63	17.79	17.13	16.66
	60%	20%	39.59	4.10	21.25	127.22	15.66	44.57	8.05	7.87	7.82	7.95	8.27	8.25
		40%	21.51	4.88	5.29	54.22	11.54	21.22	9.96	9.75	9.73	9.84	10.19	10.12
		60%	20.66	6.12	3.88	46.86	12.23	18.61	11.86	11.53	11.32	11.70	12.07	12.07
		80%	31.33	10.07	7.24	71.62	18.53	27.93	17.72	17.63	17.78	17.68	17.64	17.46
n=100	10%	20%	6.42	1.92	0.66	16.30	3.26	3.21	7.62	7.61	7.50	7.64	7.50	7.40
		40%	5.98	2.60	0.29	13.82	3.34	2.73	9.03	9.05	8.95	9.07	8.90	8.76
		60%	7.66	3.75	0.38	16.84	4.38	3.30	11.35	11.29	11.10	11.35	11.24	10.98
		80%	11.66	6.12	0.70	24.99	6.58	4.80	15.12	15.05	14.75	15.14	14.86	14.38
	30%	20%	8.73	2.12	1.01	21.51	4.56	5.50	7.57	7.50	7.48	7.53	7.62	7.64
		40%	7.68	2.91	0.45	17.01	4.44	4.16	9.19	9.05	8.95	9.13	9.24	9.23
		60%	9.27	4.10	0.55	19.38	5.58	4.86	11.54	11.35	11.15	11.46	11.58	11.46
		80%	14.70	6.85	1.21	29.95	8.85	7.98	15.71	15.50	15.14	15.65	15.56	15.19
	60%	20%	16.84	2.70	4.19	43.66	8.71	16.14	7.73	7.56	7.53	7.62	7.94	7.96
		40%	13.24	3.51	1.35	28.55	7.96	10.75	8.99	8.74	8.64	8.85	9.23	9.26
		60%	15.58	4.90	1.65	31.67	9.80	12.79	11.12	10.82	10.64	10.96	11.33	11.34
		80%	23.10	7.79	2.60	46.61	14.63	19.33	15.06	14.75	14.45	14.92	15.16	15.07
n=1000	10%	20%	4.62	1.72	0.09	11.74	2.42	1.91	7.30	7.38	7.24	7.38	7.09	6.91
		40%	5.31	2.40	0.03	12.46	2.92	2.08	8.69	8.79	8.66	8.78	8.48	8.24
		60%	6.73	3.33	0.04	15.26	3.69	2.33	10.59	10.70	10.57	10.68	10.35	10.08
		80%	9.56	5.00	0.07	21.25	5.11	2.82	13.56	13.65	13.50	13.64	13.32	13.00
	30%	20%	5.79	1.88	0.06	14.03	3.08	2.55	7.43	7.36	7.31	7.40	7.44	7.42
		40%	6.56	2.66	0.09	14.49	3.77	2.98	8.94	8.85	8.75	8.90	8.94	8.87
		60%	8.30	3.68	0.17	17.56	4.86	3.66	10.92	10.81	10.67	10.88	10.89	10.76
		80%	11.74	5.39	0.29	24.25	6.83	4.88	13.83	13.71	13.51	13.79	13.77	13.54
	60%	20%	9.41	2.16	0.23	20.32	5.42	6.04	7.33	7.12	7.11	7.19	7.63	7.72
		40%	10.17	3.17	0.57	20.07	6.36	6.83	8.79	8.53	8.45	8.64	9.05	9.11
		60%	12.26	4.37	1.02	23.01	7.96	8.49	10.58	10.31	10.16	10.44	10.80	10.83
		80%	16.47	6.09	1.44	30.41	10.75	11.59	13.31	13.03	12.82	13.17	13.48	13.48

n: sample size, c: censoring rate, p: prevalence ratio, β_1: regression coefficient for the non-proportional covariate, β_2: regression coefficient for the proportional covariate

Table 2. *MAE Results for Extended CRM with Different Time Functions and Simulation Settings*

			β_1						β_2					
	c	**p**	**t**	**log(t)**	**1/t**	**√t**	**t^2**	**exp(t)**	**t**	**log(t)**	**1/t**	**√t**	**t^2**	**exp(t)**
n=30	10%	20%	3.42	1.44	1.62	5.59	2.38	2.90	2.73	2.74	2.73	2.74	2.72	2.72
		40%	2.81	1.76	0.97	4.26	2.11	2.11	3.11	3.11	3.10	3.11	3.10	3.09
		60%	3.04	2.15	0.92	4.41	2.36	2.22	3.53	3.51	3.47	3.53	3.52	3.49
		80%	3.78	2.92	1.46	5.47	2.89	2.67	4.24	4.30	4.35	4.28	4.16	4.08
	30%	20%	4.06	1.64	2.03	6.60	2.84	3.70	2.76	2.76	2.76	2.76	2.76	2.76
		40%	3.26	1.86	1.22	4.87	2.49	2.72	3.16	3.13	3.11	3.14	3.18	3.18
		60%	3.57	2.34	1.27	5.14	2.80	2.90	3.58	3.54	3.50	3.56	3.59	3.57
		80%	4.25	3.03	1.64	6.17	3.27	3.30	4.29	4.34	4.39	4.32	4.23	4.17
	60%	20%	4.57	1.56	2.49	7.51	3.15	5.16	2.53	2.50	2.49	2.51	2.56	2.55
		40%	4.04	2.02	1.75	6.02	3.10	3.96	3.03	2.99	2.98	3.01	3.06	3.05
		60%	4.38	2.49	1.76	6.26	3.50	4.16	3.50	3.44	3.41	3.47	3.54	3.53
		80%	5.25	3.25	2.32	7.58	4.16	4.83	4.29	4.30	4.31	4.30	4.29	4.26
n=50	10%	20%	2.85	1.37	0.99	4.52	2.03	2.22	2.73	2.73	2.71	2.73	2.71	2.70
		40%	2.56	1.65	0.61	3.85	1.93	1.83	3.04	3.03	3.01	3.04	3.03	3.01
		60%	2.82	1.99	0.68	4.12	2.17	1.96	3.42	3.40	3.37	3.41	3.41	3.38
		80%	3.61	2.66	1.03	5.23	2.73	2.42	4.06	4.07	4.02	4.07	4.00	3.93
	30%	20%	3.51	1.48	1.43	5.60	2.50	3.03	2.73	2.72	2.72	2.73	2.74	2.74
		40%	2.93	1.76	0.81	4.32	2.25	2.29	3.08	3.05	3.03	3.06	3.09	3.09
		60%	3.21	2.11	0.88	4.57	2.52	2.47	3.44	3.41	3.38	3.43	3.45	3.44
		80%	4.00	2.81	1.26	5.70	3.11	3.03	4.11	4.11	4.08	4.12	4.06	4.01
	60%	20%	4.67	1.60	2.26	7.54	3.29	4.77	2.72	2.70	2.69	2.71	2.75	2.75
		40%	4.04	1.95	1.48	5.99	3.12	3.85	3.04	3.01	2.99	3.03	3.08	3.07
		60%	4.11	2.32	1.41	5.82	3.28	3.80	3.36	3.32	3.29	3.34	3.38	3.38
		80%	4.92	2.93	1.86	6.97	3.92	4.50	4.04	4.02	4.00	4.03	4.03	4.01
n=100	10%	20%	2.46	1.35	0.61	3.88	1.77	1.72	2.74	2.74	2.72	2.74	2.72	2.70
		40%	2.41	1.59	0.43	3.65	1.81	1.63	2.99	2.99	2.98	3.00	2.97	2.94
		60%	2.72	1.91	0.48	4.03	2.06	1.78	3.35	3.34	3.32	3.35	3.33	3.29
		80%	3.32	2.41	0.65	4.85	2.49	2.08	3.86	3.85	3.81	3.86	3.83	3.77
	30%	20%	2.84	1.41	0.73	4.39	2.07	2.20	2.72	2.71	2.70	2.71	2.73	2.73
		40%	2.72	1.68	0.53	4.02	2.07	1.99	3.01	2.99	2.97	3.00	3.02	3.02
		60%	2.99	1.99	0.60	4.30	2.32	2.15	3.37	3.35	3.32	3.36	3.38	3.36
		80%	3.71	2.55	0.87	5.25	2.88	2.67	3.93	3.90	3.86	3.92	3.91	3.87
	60%	20%	3.71	1.49	1.27	5.65	2.77	3.49	2.72	2.69	2.69	2.70	2.76	2.76
		40%	3.51	1.81	0.90	5.05	2.75	3.09	2.96	2.92	2.91	2.94	3.00	3.01
		60%	3.80	2.15	1.05	5.31	3.05	3.37	3.30	3.25	3.23	3.28	3.33	3.33
		80%	4.59	2.69	1.32	6.36	3.69	4.11	3.82	3.78	3.75	3.80	3.83	3.82
n=1000	10%	20%	2.15	1.31	0.25	3.42	1.55	1.38	2.70	2.71	2.69	2.72	2.66	2.63
		40%	2.30	1.55	0.13	3.52	1.71	1.44	2.95	2.96	2.94	2.96	2.91	2.87
		60%	2.59	1.82	0.16	3.90	1.92	1.52	3.25	3.27	3.25	3.27	3.22	3.17
		80%	3.08	2.23	0.21	4.60	2.25	1.67	3.68	3.69	3.67	3.69	3.65	3.60
	30%	20%	2.40	1.37	0.20	3.73	1.75	1.59	2.72	2.71	2.70	2.72	2.73	2.72
		40%	2.56	1.63	0.25	3.80	1.94	1.72	2.99	2.97	2.96	2.98	2.99	2.98
		60%	2.88	1.92	0.37	4.18	2.20	1.91	3.30	3.29	3.26	3.30	3.30	3.28
		80%	3.42	2.32	0.47	4.91	2.61	2.20	3.72	3.70	3.67	3.71	3.71	3.68
	60%	20%	3.06	1.46	0.38	4.49	2.32	2.45	2.70	2.66	2.66	2.68	2.76	2.77
		40%	3.18	1.78	0.70	4.46	2.52	2.61	2.96	2.92	2.90	2.94	3.00	3.01
		60%	3.49	2.09	0.97	4.78	2.82	2.91	3.25	3.21	3.18	3.23	3.28	3.29
		80%	4.05	2.46	1.15	5.49	3.27	3.39	3.64	3.61	3.58	3.63	3.67	3.67

n: sample size, c: censoring rate, p: prevalence ratio, β_1: regression coefficient for the non-proportional covariate, β_2: regression coefficient for the proportional covariate

Table 3. *Percentages of Fitting Based on Time Functions Across Simulation Scenarios*

			Time functions									Time functions					
	c	p	t	log(t)	1/t	√t	t^2	exp(t)		c	p	t	log(t)	1/t	√t	t^2	exp(t)
n=30	10%	20%	0.018	0.060	0.725	0.041	0.014	0.142	n=100	10%	20%	0.018	0.060	0.725	0.041	0.014	0.142
		40%	0.013	0.091	0.762	0.051	0.009	0.074			40%	0.007	0.235	0.727	0.027	0	0.004
		60%	0.034	0.113	0.658	0.048	0.014	0.133			60%	0.011	0.298	0.619	0.058	0.005	0.009
		80%	0.027	0.100	0.647	0.046	0.042	0.138			80%	0.033	0.290	0.529	0.113	0.007	0.028
	30%	20%	0.007	0.041	0.749	0.029	0.043	0.131		30%	20%	0.02	0.131	0.761	0.057	0.003	0.028
		40%	0.016	0.063	0.743	0.044	0.018	0.116			40%	0.011	0.206	0.725	0.044	0	0.014
		60%	0.022	0.084	0.672	0.035	0.025	0.162			60%	0.024	0.238	0.633	0.072	0.004	0.029
		80%	0.02	0.061	0.644	0.033	0.051	0.191			80%	0.044	0.213	0.551	0.103	0.013	0.076
	60%	20%	0.004	0.022	0.795	0.016	0.103	0.06		60%	20%	0.012	0.061	0.798	0.033	0.017	0.079
		40%	0.011	0.042	0.711	0.024	0.085	0.127			40%	0.016	0.103	0.800	0.033	0.003	0.045
		60%	0.014	0.039	0.643	0.019	0.091	0.194			60%	0.025	0.114	0.687	0.069	0.011	0.094
		80%	0.014	0.037	0.555	0.022	0.126	0.246			80%	0.032	0.126	0.600	0.055	0.029	0.158
n=50	10%	20%	0.022	0.114	0.746	0.034	0.007	0.077	n=1000	10%	20%	0.022	0.114	0.746	0.034	0.007	0.077
		40%	0.015	0.150	0.746	0.042	0.003	0.044			40%	0.015	0.150	0.746	0.042	0.003	0.044
		60%	0.026	0.172	0.671	0.076	0.005	0.05			60%	0	0.704	0.296	0	0	0
		80%	0.044	0.16	0.618	0.064	0.023	0.091			80%	0	0.904	0.075	0.021	0	0
	30%	20%	0.022	0.077	0.762	0.035	0.013	0.091		30%	20%	0	0.165	0.835	0	0	0
		40%	0.021	0.097	0.756	0.055	0.005	0.066			40%	0	0.296	0.704	0	0	0
		60%	0.03	0.142	0.674	0.055	0.014	0.085			60%	0	0.592	0.408	0	0	0
		80%	0.035	0.107	0.637	0.063	0.025	0.133			80%	0	0.814	0.142	0.044	0	0
	60%	20%	0.009	0.037	0.777	0.04	0.05	0.087		60%	20%	0	0.247	0.749	0.004	0	0
		40%	0.009	0.056	0.746	0.039	0.042	0.108			40%	0	0.255	0.745	0	0	0
		60%	0.006	0.048	0.710	0.027	0.041	0.168			60%	0	0.358	0.637	0.005	0	0
		80%	0.023	0.045	0.588	0.035	0.073	0.236			80%	0.004	0.579	0.346	0.071	0	0

n: sample size, c: censoring rate, p: prevalence ratio

4. DATA APPLICATIONS

We used different data sets to see which time function is more suitable to analyze non-proportional hazards. The datasets used in this study were selected due to their relevance to the objectives of our research. Specifically, these datasets were chosen based on several factors: their sample sizes, censoring rates, and the inclusion of two binary explanatory variables. Models were run by using selected two binary covariates in which one is non-proportional and one is proportional in three of the data sets. This allows us to explore how the extended Cox regression model handles both types of covariates, providing valuable insights into the model's performance under different conditions. We used curve -log(-log) S(t) for all categories of the covariates and tested the Schoenfeld residuals to the examination of the PH assumptions. Data set 1 called as Anderson data was taken from Kleinbaum and Klein [5]. Survival times in weeks (in remission) of 42 leukemia patients, of which 30% are censored, in a clinical trial to compare treatment with placebo in Anderson data. The covariate sex (1=male, 0=female) was taken as a non-proportional covariate and the treatment indicator (1=placebo, 0=treatment) was taken as a proportional covariate. The prevalence ratio is 48% for the non-proportional covariate and 50% for the proportional covariate. Data set 2 called as melanoma data set was obtained from Andersen et al. [28]. Data set 2 consists of measurements made on patients with malignant melanoma. Each patient had their tumor removed by surgery at the Department of Plastic Surgery, University Hospital of Odense, Denmark during the period 1962 to 1977. The surgery consisted of the complete removal of the tumor together with about 2.5 cm of the surrounding skin. Survival time in days since the operation of 205 patients with malignant melanoma, of which 72% are censored. Patients, who are still alive or died from causes unrelated to their melanoma at the end of the follow-up period, are treated as censored observations. The covariate ulceration indicator (1=absent, 0=present) was taken as a non-proportional covariate, and sex (1=female, 0=male) was taken as a proportional covariate. Data set 3 was taken from Şafak and Tutkun [29]. Breastfeeding duration is taken into consideration in this study. Those who quit breastfeeding before 6 months were defined as failing, and those who continued to be breastfed for longer than 6 months were defined as censored. Failure time in months was the time elapsed between the time that babies started to be fed with breast milk and stopped feeding. 187 mothers who volunteered to participate were included in this study. 48% of the observations are censored. The covariate birth week (1=(≥37 weeks), 0=(<37 weeks)) was taken as a non-proportional covariate, and

alcohol/smoking (1=yes, 0=no) was taken as a proportional covariate. Table 4 shows a summary of the covariates. We ran the naive CRM and all extended CRM with time functions taken into consideration in simulations for the three data sets.

Table 4. *Summary of Data Sets*

Data	Covariate		n	%	Number of Event	Number of Censor	Censor Rate
Data Set 1	Sex (Non-proportional)	1=Male	20	0.48	14	6	30%
		0=Female	22	0.52	16	6	
	Treatment (Proportional)	1=Placebo	21	0.50	21	0	
		0=Treatment	21	0.50	9	12	
Data Set 2	Ulcer (Non-proportional)	1=Absent	115	0.56	16	99	72%
		0=Present	90	0.44	41	49	
	Sex (Proportional)	1=Female	126	0.61	28	98	
		0=Male	79	0.39	29	50	
Data Set 3	Birth week (Non-proportional)	1= >=37	130	0.70	66	64	48%
		0= <37	57	0.30	32	25	
	Alcohol/Smoking (Proportional)	1=yes	46	0.25	34	12	
		0=no	141	0.75	64	77	

Table 5 displays the results of the data sets described above. According to Akaike's Information Criterion (AIC), the model with the lowest AIC value is the best model that can explain the data. Based on Table 5, the AIC values for the extended CRM with time function 1/t are lower than the considered models for all three data sets. Similar to the simulation results, we also obtain approximate parameter estimations for the proportional covariate in all data sets. Thus, the extended models with time function 1/t are the best model based on the results of these data sets.

Table 5. *Results of Parameter Estimations for Real Data Sets with Different Time Functions*

Data	Model	b_1	b_2	g(t)*x_1	Log-Likelihood	LR	AIC
Data Set 1	Naive Cox	0.295 (0.424)	1.674*** (0.438)	-	-84.769	-	173.539
	g(t)= t	2.239** (0.827)	1.430** (0.444)	-0.234** (0.085)	-79.859	9.822	165.718
	g(t)= log(t)	5.126** (1.832)	1.366** (0.442)	-2.479** (0.861)	-77.919	13.701	161.839
	g(t)=1/t	-3.092* (1.22)	1.345** (0.441)	21.62** (8.246)	-76.908	15.725	159.815
	g(t)=√t	4.663** (1.589)	1.391** (0.443)	-1.586** (0.542)	-78.794	11.953	163.587
	g(t)=t^2	1.063* (0.532)	1.515*** (0.443)	-0.008* (0.003)	-81.751	6.037	169.503
	g(t)=exp(t)	0.389 (0.429)	1.644*** (0.440)	-4.401× 10-10 (4.167× 10-10)	-84.249	1.040	174.497
Data Set 2	Naive Cox	-1.418*** (0.297)	-0.517* (0.267)	-	-267.120	-	538.239
	g(t)= t	-2.340*** (0.661)	-0.502 (0.267)	0.246 (0.150)	-265.691	2.858	537.382
	g(t)= log(t)	-2.834*** (0.819)	-0.495 (0.267)	1.191* (0.586)	-264.474	5.292	534.948
	g(t)=1/t	-0.035 (0.712)	-0.493 (0.267)	-4.04 (2.196)	-263.630	6.980	533.260
	g(t)=√t	-3.564** (1.209)	-0.498 (0.267)	1.145 (0.603)	-265.085	4.070	536.170
	g(t)=t^2	-1.710*** (0.420)	-0.509 (0.267)	0.016 (0.016)	-266.578	1.085	539.155
	g(t)=exp(t)	-1.366*** (0.309)	-0.517 (0.267)	-0.0001 (0.0003)	-266.947	0.346	539.894
Data Set 3	Naive Cox	-0.209 (0.216)	-0.807*** (0.213)	-	-473.948	-	951.896
	g(t)= t	-1.044* (0.421)	-0.819*** (0.214)	0.288* (0.131)	-471.294	5.312	948.588
	g(t)= log(t)	-0.841* (0.333)	-0.810*** (0.214)	0.759* (0.307)	-470.537	6.827	947.073
	g(t)=1/t	0.461 (0.373)	-0.802*** (0.214)	-1.187* (0.544)	-470.363	7.174	946.726
	g(t)=√t	-1.820** (0.698)	-0.815*** (0.214)	0.998* (0.421)	-470.922	6.056	947.844
	g(t)=t^2	-0.646* (0.301)	-0.822*** (0.214)	0.038 (0.020)	-471.876	4.148	949.752
	g(t)=exp(t)	-0.405 (0.250)	-0.821*** (0.214)	0.002 (0.002)	-472.842	2.212	951.683

The numbers in parentheses are the standard error of the coefficient. *, ** and *** significant at 0.05, 0.01 and 0.001 significance level respectively. LR: Likelihood ratio test statistic for CRM and extended CRM with g(t), AIC: Akaike Information Criteria, b_1: coefficient for non-proportional covariate, b_2: coefficient for proportional covariate

5. CONCLUSION

Using CRM, the most used model in survival data can be resulted in suspicious parameter estimation in the case of violation of the PH assumption. The choice and interpretation of the time function in the extended Cox regression model may differ depending on the primary goal—whether the model is used to test the proportional hazards assumption or to improve prediction. Persson and Khamis [8] and Austin [30] studied statistical power to detect violation of the PH assumption by using some time functions. There is on-going debate regarding the most appropriate time function to use in extended CRM for modelling non-proportional hazards. For assumption testing, the time function serves to detect deviations from

proportionality, whereas for prediction, selecting an appropriate time function is crucial for capturing non-proportional covariate effects accurately and enhancing predictive performance. Mismodelling the functional form of a covariate may result in unreal non-proportional effects [6, 31]. The main aim is to the identification of functional forms of time which fit the data best. We used an extensive set of Monte Carlo simulations to compare the performance of the most used time functions in extended CRM in different sample sizes, censoring rates, and prevalence ratio of the binary covariate for prediction.

The simulation results show that,

- For the proportional covariate, all methods yield similar results across all scenarios in terms of both MSE and MAE. The choice of time function has minimal impact on the estimation of proportional covariate.
- In estimating the effect of the non-proportional covariate, commonly used time function g(t)=t, has more bias than the other most used time function log(t) in the extended CRM for obtaining a hazard ratio formula.
- The extended CRM with time function 1/t produced lower MAE and MSE in the estimation of non-proportional covariate effects across most simulation scenarios particularly under moderate to large sample sizes. The performance advantage of 1/t may diminish in very small sample sizes, where increased variability in estimation can occur due to the sharper curvature of the 1/t function at early time points.
- The extended CRM with time function log(t) demonstrated superior performance in terms of MAE and MSE for non-proportional hazards, particularly when data were subject to rare covariate exposure for small sample sizes.
- As the sample size increases, MSE and MAE values decrease for all functions, as expected, indicating improved estimation accuracy.
- High censoring rates negatively impact the accuracy of estimates.
- The prevalence of the binary covariate influences estimate reliability; imbalanced covariate distributions can amplify the effect of time function choice.
- Among the six time functions evaluated, the extended CRM with time function 1/t consistently yielded the highest proportion of best-fitting across nearly all settings. In contrast, extended CRM with time function log(t) emerged as a strong alternative under higher prevalence and censoring rates for very large sample size, occasionally outperforming the extended CRM with time function 1/t. The remaining time functions (t, $\sqrt{t}$, t^2, and exp(t)) showed negligible contribution, with very low or never best-fit proportions especially in very large samples.

In the extended CRM, time-dependent effects are introduced only for covariates that violate the PH assumption. Covariates that satisfy the PH assumption are modeled with constant coefficients, independent of time. Therefore, it is theoretically expected that the specification of the time function g(t) affects only the estimation of non-proportional covariates, while having no influence on the estimates of proportional covariates. This property ensures that the inclusion of time-varying terms does not introduce bias into the estimation of proportional covariate effects. As a result, similar parameter estimates obtained for the PH covariates across different extended models confirm the robustness of these estimates and support the theoretical foundations of the extended CRM.

The results support the need for attention in selection of time function based on study design characteristics to improve the robustness of survival analysis outcomes. The main aim is the identification of appropriate time functions that accurately capture time-varying effects in extended CRM. Based on our findings, the 1/t function demonstrated consistently lower bias and MSE across the most of the simulation scenarios. Theoretically, the 1/t transformation provides flexibility in modelling time-varying effects that are initially strong but weaken over time. This behaviour is especially relevant in clinical or survival settings, where the influence of certain covariates may decline with increasing time. These empirical results, combined with the theoretical appeal of 1/t in modelling diminishing covariate effects over time, suggest that its use by practitioners deserves greater consideration.

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CONFLICTS OF INTEREST

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