mathematics

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Modified Cox Models: A Simulation Study on Different Survival Distributions, Censoring Rates, and Sample Sizes

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Abstract: The classical Cox model is the most popular procedure for studying right-censored data in survival analysis. However, it is based on the fundamental assumption of proportional hazards (PH). Modified Cox models, stratified and extended, have been widely employed as solutions when the PH assumption is violated. Nevertheless, prior comparisons of the modified Cox models did not employ comprehensive Monte-Carlo simulations to carry out a comparative analysis between the two models. In this paper, we conducted extensive Monte-Carlo simulation to compare the performance of the stratified and extended Cox models under varying censoring rates, sample sizes, and survival distributions. Our results suggest that the models' performance at varying censoring rates and sample sizes is robust to the distribution of survival times. Thus, their performance under Weibull survival times was comparable to that of exponential survival times. Furthermore, we found that the extended Cox model outperformed other models under every combination of censoring, sample size and survival distribution.

Keywords: stratified; extended Cox; time-varying covariate; Weibull and exponential survival distribution; Monte-Carlo simulations

MSC: 62N03; 62N01

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Citation: Maharela, I.A.; Fletcher, L.; Chen, D.-G. Modified Cox Models: A Simulation Study on Different Survival Distributions, Censoring Rates, and Sample Sizes. *Mathematics* **2024**, *12*, 2903. https://doi.org/10.3390/math12182903

Academic Editor: Manuel Alberto M. Ferreira

Received: 18 August 2024
Revised: 11 September 2024
Accepted: 17 September 2024
Published: 18 September 2024

1. Introduction

The classical Cox model is the most commonly used approach for analysing right-censored data [1,2]. It is used across multiple fields of study, such as engineering, education, medicine, etc. [3,4]. Research and development to strengthen Cox model has been continued even since Zheng et al. [5]. However, it is based on the assumption of proportional hazards (PH), which limits its use [6]. As a result, modified versions of the Cox model need to be adapted to circumvent the violation of the PH assumption. Consequently, the stratified and the extended Cox models are two of the most popular extensions of the Cox procedure [7].

The stratified regression model modifies the PH approach by stratifying the explanatory variables, while the extended Cox technique incorporates one or more covariates that vary over time into the Cox model [8]. Numerous studies have employed both approaches as a solution for non-proportional risks. For example, Ata and Sozer [9] applied both models to study lung cancer. Subsequently, Maryma [10] used the two approaches to overcome the violation of proportional hazards when analysing the breastfeeding span in Lampung province. More recently, Purnami et al. [11] investigated factors contributing to improved mental health using the time-dependent Cox model and the stratified procedure, while Seo and Yuk [12] used both extensions of the Cox model to assess fracture risk and osteoporosis in patients undergoing hysterectomy. Moreover, research by Phonskaningtyas [13] used the adjusted Cox approaches to evaluate the impact of spiritual intervention on chronic kidney failure patients. However, the literature suggests that prior studies merely applied the stratified and extended Cox regression approach, they did not assess the adequacy of the models in handling PH violation through simulations [14].

Monte-Carlo simulation studies are a valuable tool in investigating the performance of statistical models [15]. For instance, Mehrotra et al. [16] employed simulations to illustrate the advantages of the two-step unstratified Cox model against the stratified Cox approach. Subsequently, Olaniran and Abdullah [17] also used Monte-Carlo simulations to investigate the efficiency of the newly developed Bayesian extended Cox model to handle non-proportional data against the standard PH model and the extended Cox model. Meanwhile, Adeleke et al. [7] studied only the extended Cox model at varying levels of sample sizes and censoring rates. On the other hand, Ratnaningsih et al. [18] assessed the performance of both modifications against that of the Cox model and the stratified-extended Cox model through Monte-Carlo simulations. Nonetheless, most of the studies did not evaluate the statistical properties of the stratified against the extended Cox procedures under different survival distributions.

Using a singular survival distribution is problematic as several statisticians have pointed out that more flexibility is required when selecting the distribution of survival times such that the simulated data can reflect real data [15,19,20]. Furthermore, Bender et al. [21] claimed that most Cox related simulation studies used the exponential or Weibull distribution for survival time. Hence, in this paper, in addition to assessing the effect of different combinations and censoring and sample sizes on the models, simulations are used to investigate the performance of the extended Cox model against the stratified approach when survival times follow the Weibull distribution versus the exponential distribution.

2. Methods and Simulations Results

2.1. Methodology

The Cox proportional hazards model (in short, the Cox model) quantifies the relationship between several covariates and the hazard rate of an event of interest [22]. Suppose T is a non-negative random variable denoting survival time; then, the Cox model is expressed by

$$h(t|\boldsymbol{X}) = h_0(t)\, exp(\boldsymbol{\beta}^{\boldsymbol{t}}\boldsymbol{X}), \tag{1}$$

where $\boldsymbol{X} = (x_1, x_2, \ldots, x_p)$ is a vector of time-independent covariates, $h(t|\boldsymbol{X})$ is the hazard function, $h_0(t)$ is the baseline hazard function, and $\boldsymbol{\beta} = (\beta_1, \beta_2, \ldots, \beta_p)^t$ denotes a vector of regression coefficients [23]. Suppose that for a sample size of n, data consists of (T_i, X_i, d_i), $i = 1, 2, \ldots, n$, where T_i is the survival time of the i-*th* subject, X_i a vector of explanatory variables, and d_i the censoring indicator defined by

$$d_i = \begin{cases} 1 & \text{if } T_i \leq C_i \quad \text{not censored} \\ 0 & \text{if } T_i > C_i \quad \text{censored,} \end{cases}$$

while C_i are censoring times [24]. The sum of probabilities of the event of interest time t_i over all subjects at risk is indexed by l. Subsequently, $R(t_i)$ denotes a set of subjects who are at risk at time t_i. Therefore, unknown parameters in the Cox model are estimated by maximizing the log partial likelihood function, defined by

$$LL(\boldsymbol{\beta}) = log\left[\prod_{i=1}^{n} \frac{h_0(t_i)exp(\boldsymbol{\beta}^{\boldsymbol{t}}\boldsymbol{X}_i)}{\sum_{l\epsilon R(t_i)} h_0(t_i)\, exp(\boldsymbol{\beta}^{\boldsymbol{t}}\boldsymbol{X}_l)}\right]^{d_i}, \tag{2}$$

where $d_i = I(T_i \leq C_i)$ [25].

2.2. Stratified Cox Model

Stratification entails controlling for predictors that do not meet the PH assumption by dividing the data into strata with different baseline hazard functions [26]. Suppose the covariate that does not satisfy the assumption PH has G levels. Thus, G is the total number of strata, $g = 1, 2, \ldots, G$, while $i = 1, 2, \ldots, n_g$ represents the number of subjects in the g-th stratum [25]. The stratified Cox model is defined by

$$h_g(t|\boldsymbol{X}) = h_{0g}(t)\, exp(\boldsymbol{\beta^t X}), \tag{3}$$

where $h_g(t|\boldsymbol{X})$ is the risk function for a subject from the g-*th* stratum and $h_{0g}(t)$ is the baseline hazard function for each stratum. Similarly to the Cox model, the partial likelihood function enables inference for the stratified approach in which $L_g(\beta)$ is the partial likelihood function from stratum g, defined by

$$L_g(\beta) = \prod_{i=1}^{n_g} \left[\frac{exp(\boldsymbol{\beta^t X}_{ig})}{\sum_{l \epsilon R(t_{ig})} exp(\boldsymbol{\beta^t X}_{(l)})} \right]^{d_{ig}} \tag{4}$$

where t_{gi} denotes observed time for the i-*th* subject in stratum g, $R(t_{gi})$ represents subjects in the g-*th* stratum at risk at time t_{gi}, and $\boldsymbol{X}_{gi}$ is a vector of explanatory variables [26].

2.3. Extended Cox Model

A Cox regression model that includes covariates that vary over time is called an extended Cox model [27]. The model is given by

$$h(t|\boldsymbol{X(t)}) = h_0(t)\, exp(\boldsymbol{\beta^t X} + \boldsymbol{\beta(t) X(t)}), \tag{5}$$

where $\boldsymbol{\beta}$ is a vector of time fixed regression coefficients, $\boldsymbol{\beta(t)}$ a vector of time-varying coefficients and, unlike the Cox regression model, the exponential component in the extended model contains both the time constant $\boldsymbol{X} = (x_1, x_2, \ldots., x_{p_1})$ and time-dependent covariates $\boldsymbol{X(t)} = (x_1(t), x_2(t), \ldots, x_{p_2}(t))$ [8]. Inference for unknown regression coefficients in the extended model is made in the same way as for the Cox model in (1), maximizing the partial likelihood, or better still the log partial likelihood function, to obtain estimates [25]. The formula of the likelihood function is the same as for the PH model, except that the value for time-dependent covariates is assessed for each risk set.

2.4. Simulation Studies

We conducted Monte-Carlo simulations to investigate the simultaneous effect of censoring, sample size, and distribution of survival time on the performance of the Cox, as well as stratified and extended models when the proportional hazards assumption is not satisfied. We adapted the algorithms of [28] to generate right-censored non-proportional data from an extended Cox model that includes one time-dependent predictor. Data were simulated by the time-varying model:

$$h(t|\boldsymbol{X(t)}) = h_0(t)\, exp(\boldsymbol{\beta^t X} + \boldsymbol{\beta(t) z(t)}). \tag{6}$$

Steps to generate the non-proportional data are as follows:

1. **Covariates:** two time-independent covariates, $x_1 \sim N(0, 1)$ and $x_2 \sim Binom(0.5)$, and a single dichotomous time-dependent variable, which is defined as

$$z(t) = \begin{cases} 0, & t < t_s \quad \text{(unexposed/ untreated)} \\ 1, & t \geq t_s \quad \text{(exposed/treated)}, \end{cases}$$

where t_s is the time at which $z(t)$ changes from untreated to treated.

2. **Potential switching times:** the probable exposure time for each subject in a study such that all subjects are likely to switch from unexposed to exposed is generated by

$$t_s = -\frac{log(\mu)}{\lambda\, exp(a_0 + a_1 x_1 + a_2 x_2)} \tag{7}$$

where $\lambda = 1$ is the hazard function for an exponential distribution, and $(a_0, a_1, a_2) = (1, 1, 1)$ are regression coefficients [29,30].

3. **Weibull survival times:** Weibull survival times are generated by

$$T = \begin{cases} \left(\frac{-log(u)}{\lambda exp(\boldsymbol{\beta}^t \mathbf{X})}\right)^{1/\alpha} & \text{if} \quad -log(u) < \lambda exp(\boldsymbol{\beta}^t \mathbf{X}) t_s^{\alpha} \\ \left(\frac{-log(u) - \lambda exp(\boldsymbol{\beta}^t \mathbf{X}) t_s + \lambda exp(\boldsymbol{\beta}^t \mathbf{X} + \beta(t)) t_s}{\lambda exp(\boldsymbol{\beta}^t \mathbf{X})}\right)^{1/\alpha} & \text{if} \quad -log(u) \geq \lambda exp(\boldsymbol{\beta}^t \mathbf{X}) t_s^{\alpha}, \end{cases} \quad (8)$$

where the shape parameter equals $\alpha = 0.5$ for a decreasing hazard rate over time.

4. **Exponential survival times:** exponential event times are then generated by

$$T = \begin{cases} \frac{-log(u)}{\lambda exp(\boldsymbol{\beta}^t \mathbf{X})} & \text{if} \quad -log(u) < \lambda exp(\boldsymbol{\beta}^t \mathbf{X}) t_s \\ \frac{-log(u) - \lambda exp(\boldsymbol{\beta}^t \mathbf{X}) t_s + \lambda exp(\boldsymbol{\beta}^t \mathbf{X} + \beta(t)) t_s}{\lambda exp(\boldsymbol{\beta}^t \mathbf{X} + \boldsymbol{\beta}(\boldsymbol{t}))} & \text{if} \quad -log(u) \geq \lambda exp(\boldsymbol{\beta}^t \mathbf{X}) t_s \end{cases} \quad (9)$$

where $\lambda = 1$, $\boldsymbol{\beta}^t \mathbf{X} = \beta_1 x_1 + \beta_2 x_2$, where $\beta_1 = \beta_2 = 1$, and $\beta(t) = -0.5$.

5. **Censoring times:** censoring times are generated from the uniform distribution $(0, \theta)$, where θ is selected to yield the desired censoring rate: 10%, 30%, and 45%.

6. **Data frame:** Steps 1 to 4 produces right-censored survival data that constitutes of the observed time $Z_i = min(T_i, C_i)$ for the ith subject, censoring indicator $d_i = I(T_i \leq C_i)$, invariant covariates X_i, and the time-variant variable $z(t)$, the time where the time-varying covariate $z(t)$ switches from 0 to 1 $t_0 = min(Z_i, ts)$. The final dataset consists of $(T_i^*, d_i, X_i, z(t))$.

For both distributions, we simulated 10,000 datasets ($m =$ 10,000) for each combination of factors. Each dataset is analysed using the following statistical models: Cox PH, stratified and extended Cox model. We report the bias, model-based standard errors (Est SE), empirical standard errors (Emp SE), coverage probabilities (Cov 95%), and mean squared errors (MSE) for each model.

The extended Cox model is the true model, since it was used to generate the data. We first examine the simulation results where the event times were generated from the Weibull distribution and then those for the exponential distribution.

2.4.1. Weibull Survival Times

Table 1 offers results at 10% censoring. As expected, the extended Cox model outperformed the other models by having minimal biases, coverage probabilities around 95% and the lowest MSEs for all parameters. In contrast, the misspecified Cox model performed the worst, with significantly higher biases, poor coverage, and the largest MSE values in each sample. The three survival models produced comparable standard error estimates. With regard to the effect of sample size, the biases, standard errors and MSEs of all statistical models decreased with increasing sample size. However, coverage probabilities from the Cox PH and Stratified decreased significantly when the sample size increased. This phenomenon is expected when the decline in coverage results from bias [19]. Thus, the confidence interval narrows in on an incorrect value as the sample size increases.

Table 2 summarizes the results of the three survival regression models when censoring is at 30%. Similarly to the results observed at low censoring (Table 1), the Cox model yielded the highest biases and mean squared errors at each sample size, while the extended Cox model produced minimum bias and MSEs. In addition, the extended Cox model is the only approach that provided coverage close to the nominal value of 95%. The results presented in Table 2 showed a decrease in biases, standard errors, and MSEs for all models with increasing sample size.

Table 3 presents the mean estimates when censoring is 45%. From the table, it can be seen that the extended Cox model provided the best fit for the simulated data sets with the lowest biases, standard errors (Est and Emp) and MSEs compared to PH and the stratified model. Similarly, the model yielded consistent coverage probabilities approaching the nominal 95% for all covariates.

Table 1. Weibull survival times: simulation results comparing Cox PH, stratified and extended models under non-proportional hazards at 10% censoring, $\beta_1 = \beta_2 = 1$ and $\beta(t) = -0.5$.

Model	Parameter	Bias	Est SE	Emp SE	Cov 95%	MSE
				n = 50		
Cox PH	β_1	0.2826	0.2397	0.2564	0.8165	0.1456
	β_2	0.2806	0.3721	0.4033	0.8935	0.2413
	β_t	−1.1843	0.4145	0.4677	0.1781	1.6212
Stratified	β_1	0.2650	0.2496	0.2627	0.8587	0.1392
	β_2	0.2572	0.3822	0.4055	0.9122	0.2305
Extended	β_1	0.0573	0.2391	0.2503	0.9495	0.0659
	β_2	0.0530	0.3651	0.3880	0.9427	0.1533
	β_t	−0.0409	0.4171	0.4351	0.9442	0.1910
				n = 1000		
Cox PH	β_1	0.1963	0.0465	0.0485	0.0096	0.0409
	β_2	0.1978	0.0744	0.0775	0.2468	0.0451
	β_t	−1.0278	0.0811	0.0878	0.0000	1.0641
Stratified	β_1	0.1915	0.0468	0.0485	0.0131	0.0390
	β_2	0.1901	0.0742	0.0763	0.2741	0.0419
Extended	β_1	0.0024	0.0479	0.0481	0.9486	0.0023
	β_2	0.0018	0.0749	0.0746	0.9508	0.0056
	β_t	−0.0015	0.0864	0.0869	0.9498	0.0075

Est SE = model based standard error, Emp SE = empirical standard error, Cov 95% = coverage probability for 95% confidence intervals, MSE = Mean Squared Error.

Table 2. Weibull survival times: simulation results comparing Cox PH, stratified and extended models under non-proportional hazards at 30% censoring, $\beta_1 = \beta_2 = 1$ and $\beta(t) = -0.5$.

Model	Parameter	Bias	Est SE	Emp SE	Cov 95%	MSE
				n = 50		
Cox PH	β_1	0.3090	0.2676	0.2887	0.8326	0.1788
	β_2	0.3075	0.4181	0.4547	0.8962	0.3013
	β_t	−1.1695	0.4653	0.5134	0.2817	1.6312
Stratified	β_1	0.2885	0.2783	0.2970	0.8706	0.1714
	β_2	0.2788	0.4292	0.4568	0.9186	0.2864
Extended	β_1	0.0670	0.2646	0.2793	09474	0.0825
	β_2	0.0574	0.4081	0.4337	0.9464	0.1914
	β_t	−0.0466	0.4646	0.4852	0.9471	0.2376
				n = 1000		
Cox PH	β_1	0.2122	0.0513	0.0536	0.0131	0.0479
	β_2	0.2156	0.0829	0.0859	0.2657	0.0539
	β_t	−1.0158	0.0909	0.0960	0.0000	1.0409
Stratified	β_1	0.2059	0.0515	0.0536	0.0185	0.0453
	β_2	0.2037	0.0826	0.0845	0.3099	0.0486
Extended	β_1	0.0028	0.0527	0.0528	0.9511	0.0028
	β_2	0.0017	0.0833	0.0832	0.9493	0.0069
	β_t	−0.0015	0.0959	0.0966	0.9507	0.0093

Est SE = model based standard error, Emp SE = empirical standard error, Cov 95% = coverage probability for 95% confidence intervals, MSE = Mean Squared Error.

At a high censoring percentage (45%), Table 3 showed a downward trend in biases for all models with larger sample sizes. The biases of the Cox and stratified regression decreased slightly, while the biases of the extended time-varying approach decreased sharply.

In assessing the influence of censoring level when the assumption of proportionality does not hold and survival times follow the Weibull distribution, the results summarized in Tables 1–3 indicate that an increase in censoring led to an appreciation in bias, a loss in precision, and accuracy across all models. However, estimates from the extended exhibited robustness to the censoring rate by producing coverage probabilities very close to 95%. Meanwhile, the Cox and stratified approaches consistently brought about coverage probabilities well below 95% at every censoring level. Moreover, just as increasing the sample size led to confidence intervals that targeted the wrong "true" value in misspecified models, an increment in censoring had the same effect on 95% confidence intervals.

Table 3. Weibull survival times: simulation results comparing Cox PH, stratified and extended models under non-proportional hazards at 45% censoring, $\beta_1 = \beta_2 = 1$ and $\beta(t) = -0.5$.

Model	Parameter	Bias	Est SE	Emp SE	Cov 95%	MSE
				n = 50		
Cox PH	β_1	0.3388	0.3055	0.3334	0.8492	0.2259
	β_2	0.3358	0.4519	0.5277	0.9049	0.3911
	β_t	−1.1566	0.05335	0.5852	0.4101	1.6802
Stratified	β_1	0.3145	0.3170	0.3410	0.8872	0.2152
	β_2	0.3029	1.4418	0.5640	0.9274	0.4099
Extended	β_1	0.0808	0.2988	0.3186	0.9457	0.1080
	β_2	0.0663	0.4681	0.4993	0.9470	0.2536
	β_t	−0.0529	0.5282	0.5551	0.9471	0.3109
				n = 1000		
Cox PH	β_1	0.2258	0.0576	0.0601	0.0224	0.0546
	β_2	0.2325	0.0946	0.0979	0.3095	0.0637
	β_t	−0.9986	0.1036	0.1069	0.0000	1.0086
Stratified	β_1	0.2186	0.0578	0.0599	0.0315	0.0514
	β_2	0.2174	0.0942	0.0962	0.3646	0.0565
Extended	β_1	0.0030	0.0587	0.0584	0.9510	0.0034
	β_2	0.0026	0.0947	0.0946	0.9520	0.0089
	β_t	−0.0084	0.1083	0.1081	0.9511	0.0117

Est SE = model based standard error, Emp SE = empirical standard error, Cov 95% = coverage probability for 95% confidence intervals, MSE = Mean Squared Error.

2.4.2. Exponential Survival Times

Table 4 contains the results of all models when the censoring level is 10%, and the probability distribution of survival is exponential. Table 4 shows that estimators from the PH and stratified regression approaches had significantly higher biases and MSEs at different sizes of the generated sample than the extended model. The estimates of the time-dependent extended technique produced confidence intervals that resulted in coverage probabilities close to the nominal 95% level. In contrast, the other two models brought coverage probabilities of less than 90%.

Examining the effect of increasing sample size on the three survival models when censoring is low, we observed that the bias of the estimators tends to decrease; the standard errors decreased, leading to estimates with greater precision. Regarding the Cov 95%, the extended Cox regression model estimates induced steady coverage probability that did not sway from the desired nominal value of 95%.

Table 5 gives simulation results when the censoring rate is set at 30% under exponential survival times. Again, we observed that the extended model is exceedingly more efficient about bias, standard errors, Cov 95%, and MSE estimates. Together with the stratified model, the PH model gave rise to inadequate coverage probabilities that not only consistently derailed from the nominal level of 95%, but confidence intervals from the two models narrowed into the wrong value when the sample became larger. Hence, the coverage probabilities decreased by more than 50% when the sample size increased from 50 to 1000. Moreover, the coverage probabilities obtained from the extended model do not vary much (approximated to 95%) for all sample sizes.

Table 4. Exponential survival times: simulation results comparing Cox PH, stratified and extended models under non-proportional hazards at 10% censoring, $\beta_1 = \beta_2 = 1$ and $\beta(t) = -0.5$.

Model	Parameter	Bias	Est SE	Emp SE	Cov 95%	MSE
				n = 50		
Cox PH	β_1	0.2666	0.2348	0.2554	0.8279	0.1363
	β_2	0.2586	0.3684	0.4072	0.8917	0.2326
	β_t	−1.9392	1.1496	0.5756	0.0065	4.0916
Stratified	β_1	0.2364	0.2424	0.2615	0.8687	0.1243
	β_2	0.2244	0.3762	0.4066	0.9147	0.2157
Extended	β_1	0.0538	0.2338	0.2451	0.9444	0.0629
	β_2	0.0471	0.3602	0.3837	0.9423	0.1494
	β_t	−0.0378	0.4781	0.4946	0.9456	0.2459
				n = 1000		
Cox PH	β_1	0.1706	0.0452	0.0467	0.0335	0.0313
	β_2	0.1705	0.0733	0.0768	0.3653	0.0349
	β_t	−1.7911	0.0915	0.0988	0.0000	3.2179
Stratified	β_1	0.1519	0.0456	0.0471	0.0848	0.0253
	β_2	0.1499	0.0735	0.0757	0.4730	0.0282
Extended	β_1	0.0024	0.0472	0.0470	0.9502	0.0022
	β_2	0.0017	0.0744	0.0741	0.9532	0.0055
	β_t	−0.0011	0.1008	0.0997	0.9533	0.0099

Est SE = model based standard error, Emp SE = empirical standard error, Cov 95% = coverage probability for 95% confidence intervals, MSE = Mean Squared Error.

Table 5. Exponential survival times: simulation results comparing Cox PH, stratified and extended models under non-proportional hazards at 30% censoring, $\beta_1 = \beta_2 = 1$ and $\beta(t) = -0.5$.

Model	Parameter	Bias	Est SE	Emp SE	Cov 95%	MSE
				n = 50		
Cox PH	β_1	0.2807	0.2584	0.2795	0.8501	0.1569
	β_2	0.2718	0.4073	0.4465	0.9015	0.2732
	β_t	−2.0481	0.5085	0.5775	0.0067	4.5281
Stratified	β_1	0.2552	0.2672	0.2859	0.8871	0.1469
	β_2	0.2416	0.4174	0.4466	0.9189	0.2578
Extended	β_1	0.0622	0.2544	0.2658	0.9477	0.0745
	β_2	0.0527	0.3949	0.4153	0.9472	0.1752
	β_t	−0.0370	0.5051	0.5214	0.9503	0.2732
				n = 1000		
Cox PH	β_1	0.1828	0.0489	0.0509	0.0390	0.0360
	β_2	0.1827	0.0804	0.0843	0.3863	0.0405
	β_t	−1.8189	0.0958	0.1035	0.0000	3.3194
Stratified	β_1	0.1631	0.0494	0.0514	0.0875	0.0292
	β_2	0.1602	0.0807	0.0829	0.4918	0.0326
Extended	β_1	0.0028	0.0511	0.0509	0.9505	0.0026
	β_2	0.0015	0.0816	0.0815	0.9515	0.0066
	β_t	−0.0013	0.1061	0.1054	0.9540	0.0111

Est SE = model based standard error, Emp SE = empirical standard error, Cov 95% = coverage probability for 95% confidence intervals, MSE = Mean Squared Error.

Table 6 provides results from the respective models when censoring is at 45%. It is evident from the table that the estimates from the Cox model have the most considerable bias and MSE, while the estimates from the extended model exhibited the most negligible bias and mean squared error. In addition, the misspecified PH model incited the worst coverage, followed by the stratified model.

Table 6. Exponential survival times: simulation results comparing Cox PH, stratified and extended models under non-proportional hazards at 45% censoring, $\beta_1 = \beta_2 = 1$ and $\beta(t) = -0.5$.

Model	Parameter	Bias	Est SE	Emp SE	Cov 95%	MSE
			n = 50			
Cox PH	β_1	0.3153	0.2926	0.3263	0.8561	0.2058
	β_2	0.3025	0.4678	0.5222	0.9034	0.3642
	β_t	−2.1212	0.5574	0.6356	0.0123	4.9034
Stratified	β_1	0.2868	0.3031	0.3332	0.8936	0.1933
	β_2	0.2671	0.4806	0.5201	0.9286	0.3418
Extended	β_1	0.0750	0.2841	0.3034	0.9448	0.0977
	β_2	0.0581	0.4485	0.4741	0.9483	0.2281
	β_t	−0.0428	0.5487	0.5691	0.9498	0.3257
			n = 1000			
Cox PH	β_1	0.1943	0.0542	0.0566	0.0497	0.0409
	β_2	0.1960	0.0909	0.0960	0.4300	0.0476
	β_t	−1.8586	0.1029	0.1100	0.0000	3.4663
Stratified	β_1	0.1733	0.0547	0.0570	0.1113	0.0333
	β_2	0.1714	0.0912	0.0941	0.5381	0.0382
Extended	β_1	0.0028	0.0565	0.0562	0.9521	0.0032
	β_2	0.0022	0.0921	0.0923	0.9499	0.0085
	β_t	−0.0012	0.1144	0.1136	0.9555	0.0129

Est SE = model based standard error, Emp SE = empirical standard error, Cov 95% = coverage probability for 95% confidence intervals, MSE = Mean Squared Error.

Assessing the impact of different censoring levels on the estimates from the respective models when survival times follow the exponential distribution and the data were generated in violation of the Cox proportional hazard model assumption. Biases, standard errors, and MSEs increased with increasing censoring levels. Thus, the estimates of the three approaches showed a loss of precision and accuracy.

Generally, for all three models, the results from Tables 1–6 established whether duration follows the Weibull or exponential distribution; the respective models produced comparable results. Furthermore, the performance measures displayed similar trends regarding the censoring rate and sample size. All in all, when the assumption of proportional hazards is violated, the Cox, stratified, and extended regression models revealed some robustness to the distribution of survival time.

3. Discussion and Conclusions

Stratification and the inclusion of time-varying covariates are two of the most common modifications of the Cox regression model that aim to solve the problem of non-proportionality. However, a review of the literature has shown that while the two extensions have been widely compared using real data analyses, empirical comparison through comprehensive Monte-Carlo simulations using a wide range of sample sizes and censoring is still lacking. Therefore, we conducted extensive Monte-Carlo simulation studies to evaluate the performance of the two models when the PH assumption is violated.

For non-proportional simulations with survival times following the Weibull distribution, we observed superior performance of the extended Cox model for all combinations of different sample sizes and censoring rates. The finding agrees with the results of [31], where the author found that the extended Cox approach performs satisfactorily at various censoring levels and sample sizes when PH is violated. Meanwhile, the stratified approach fitted similarly to the violated Cox model at all censoring percentages and sample sizes.

Similarly to the performance under Weibull survival times, the Cox extended model showed the best performance with regard to biases, coverage probabilities, and mean squared errors when event times followed the exponential distribution. However, the model's efficiency is comparable to the misspecified Cox and stratified PH models. Thus, suggesting that the two modified models are inadequate in addressing the problem of non-proportionality [32]. Finally, the three models showed some robustness to the distribution of survival times when the PH assumption is not met. In other words, the models' estimates obtained when the duration follows the Weibull distribution are comparable to those obtained when the exponential distribution generates the duration. Such is to be expected for semi-parametric models [8].

However, just like the stratified Cox model, the time-varying extended Cox model has some limitations in dealing with non-proportionality. For instance, Dunkler et al. [33] claimed that the model is only beneficial when most variables in a study are time-independent. Subsequently, Olaniran and Abdullah [17] expressed concerns about using the partial likelihood function in estimating the model, as this may lead to a loss of efficiency. Finally, Ratnaningsih et al. [32] argued that using the stratified and extended Cox models separately is inefficient when considering non-proportional hazards. They suggested combining the two models; a stratified-extended Cox model is more appropriate for non-proportionality. A thorough evaluation of the combined model is of interest for future research. Nevertheless, this chapter provides a comprehensive examination of the advantages and disadvantages of the two most common extensions of the Cox model when proportionality is not met.

Author Contributions: Conceptualization, I.A.M. and D.-G.C.; methodology, I.A.M., L.F. and D.-G.C.; formal analysis, I.A.M. and L.F.; writing—original draft, I.A.M.; writing—review and editing, L.F. and D.-G.C.; supervision, L.F. and D.-G.C.; project administration, I.A.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work is partially supported by South Africa National Research Foundation (NRF) and South Africa Medical Research Council (SAMRC) (South Africa DST-NRF-SAMRC SARChI Research Chair in Biostatistics, Grant number 114613).

Data Availability Statement: No new data were created or analyzed in this study.

Acknowledgments: The authors would like to thank the reviewers for their constructive comments which significantly improved the quality of this paper.

Conflicts of Interest: The authors declare no conflicts of interest.

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