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Research Article

A new adjusted Bayesian method in Cox regression model with covariate subject to measurement error

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Abstract

An important bias can occur when estimating coefficients by maximizing the known partial likelihood function in the Cox regression model with the measurement error covariate. We focus here on Bayesian methods in order to adjust measurement error and aim to propose an adjusting Bayesian method. Constructing simulation studies using Markov Chain Monte Carlo simulation techniques to investigate the performance of models. We compare the proposed method with the existing method that used partial likelihood function, Bayesian Cox regression model ignoring measurement error, the adjusted Bayesian Cox regression model that exists in the literature by a simulation study which consists of different sample sizes, censoring rates, reliability levels, and regression coefficients. Simulation studies indicate that the proposed method outperformed others given some scenarios. A real data set is analyzed for an illustration of the findings.

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1. Introduction

Measurement error occurs when the actual values of explanatory variables can not be obtained due to laboratory error, calibration error in the measuring instruments, or sampling [17]. Biological measurements such as blood pressure and CD4 count, which are frequently used in survival analysis, are mostly variables with measurement error. When the values of explanatory variables that contain measurement error are used in classical analyses, they will cause misleading results [22]. Cox model, being the most commonly used model in survival analysis is easy to understand, apply and does not depend on any distribution. If the measurement error is not taken into consideration, the estimates of regression coefficients obtained by the partial likelihood method in the Cox model will cause bias [25].

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The simplest and most commonly assumed form of measurement error model is the additive error model also known as the classical error model. The error terms are assumed to have zero mean and, typically, constant variance. With the increasing advantage of flexible model structure and available software programs, adjusted Bayesian methods become popular for coping with the measurement error problem. Bayesian approaches provide a flexible framework for analysis by combining a prior distribution and expert knowledge, considering the measurement error of explanatory variables whose true values can not be observed [21].

Bayesian methods have also become much more useful in the analysis of survival data with recently developed software programs. The process for the Cox regression model generally follows these steps: determination of a prior distribution for the regression coefficients and baseline hazard function or baseline cumulative hazard function, creating the likelihood function, obtaining the posterior distribution, and making inferences [14].

The gamma process is commonly used prior to the baseline cumulative hazard in the Bayesian Cox regression model. Cumulative hazard increases are assumed to be independent during the gamma process. However, this may not be realistic in many applications. It also does not allow reflecting activity between adjacent intervals [20]. The use of the polygonal function defined by [4] for the baseline hazard function instead of the gamma process has been proposed as an alternative method to Bayesian approaches used in the correction of measurement error in the Cox regression model.

In this study, we propose a new adjusting Bayesian method for measurement error and compare the performances of the following four models; partial likelihood method for the Cox regression model, Bayesian Cox regression model ignoring measurement error, Bayesian Cox regression model adjusting measurement error using gamma process and the proposed method that adjusting measurement error using polygonal prior for baseline cumulative hazard function in the estimation of the beta regression coefficient. The additive error model is defined with replicate observations to adjust the covariate measurement error effect.

The remainder of the paper proceeds as follows: In Section 2, we describe the models and notations. Section 3 presents a comparison of approaches through simulation studies, while Section 4 makes comparisons using a real data set as known primary biliary cirrhosis (PBC) data from the Mayo Clinic study in R. Finally, conclusions of the results and extensions of the proposed method are given in Section 5.

2. Methods

2.1. Cox regression model

Cox regression model is given as

$$\lambda(t, \mathbf{X}) = \lambda_0(t) exp\left(\sum_{i=1}^{p} \beta_i x_i\right), \tag{2.1}$$

where $\lambda_0(t)$ is unspecified baseline hazard function, $\mathbf{X}$ is a vector of covariates and $\boldsymbol{\beta}$ is the vector of coefficient of the covariates $x_1, x_2, \ldots, x_p$.

$\boldsymbol{\beta}$ vector can be estimated by maximizing the partial likelihood function by using iterative methods like the Newton-Raphson method in the Cox regression model [7, 8].

The likelihood function $L(\boldsymbol{\beta})$ for the Cox regression model is given by

$$L(\boldsymbol{\beta}) = \prod_{j=1}^{k} \frac{exp\left(\boldsymbol{\beta}' \boldsymbol{X}_{(j)}\right)}{\sum_{l \in R_{t_{(j)}}} exp\left(\boldsymbol{\beta}' \boldsymbol{X}_l\right)},$$

in which $\boldsymbol{X}_{(j)}$ is the vector of covariates for the individual who fails at the jth ordered failed time, $t_{(j)}$, k is the number of failed times and $R_{t(j)}$ is the set of individuals who are not failed or uncensored at a time just before $t_{(j)}$ [7].

2.2. Additive measurement error model

Assume we have n observation with the data that are given as (Y, Z, X), with Y_i denoting the outcome variable, X_i unobservable true value of covariate with measurement error, $\boldsymbol{W_i}$ observed value of measurement error covariate, and $\boldsymbol{Z_i}$ fully observed covariates without measurement error.

The additive measurement error model is as follows:

$$W_{ij} = X_i + \varepsilon_{ij}, \quad j = 1, 2.$$

ε_{ij} are error terms with mean zero and constant variance σ_ε^2. There is no correlation between ε_{i1} and ε_{i2}. The error term is independent of X_i, $\boldsymbol{Z_i}$, and Y_i. We assume the existence of an internal replication sub-study to be able to calculate the measurement error variance [6, 17].

2.3. Bayesian approach

2.3.1. Bayesian Cox regression model. With the advancements in statistical software, Bayesian analysis started to be used increasingly to perform inferences in the Cox regression model like other statistical models. Bayesian inference is the process of adapting a probability model to a data set and summarizing the results of the model parameters with a probability distribution. The main feature of Bayesian methods is the use of probability to measure uncertainty in inferences based on statistical data analysis [11]. The prior knowledge along with a given set of observations is used in Bayesian analysis in order to make statistical inferences. Operational or observational data and previous experiments can be the prior information.In Bayesian analysis, the data and parameter vector $\boldsymbol{\theta}$ are considered random variables. In addition to the probabilistic model produced by the data, a prior distribution $p(\boldsymbol{\theta})$ expressing the prior knowledge is defined. The prior distribution is combined with the likelihood function $L(\boldsymbol{\theta}) = L(\boldsymbol{\theta}|D)$ where D shows the data collected. The posterior distribution of the parameters $p(\boldsymbol{\theta}|D)$, according to the Bayes rule, can be written as follows [19]:

$$p(\boldsymbol{\theta}|D) = \frac{L(\boldsymbol{\theta})p(\boldsymbol{\theta})}{\int\limits_{\Theta} L(\boldsymbol{\theta})p(\boldsymbol{\theta})d\boldsymbol{\theta}} \propto L(\boldsymbol{\theta})p(\boldsymbol{\theta}).$$

The process in the Bayesian Cox regression model generally consists of determining the prior distribution for regression coefficients and the baseline hazard function or the baseline cumulative hazard function, generating the likelihood function, obtaining the posterior distribution, and making inferences [14].

One of the most frequently used processes for the Cox regression model is the Gamma process. Let us denote the Gamma distribution with $G(\alpha, \beta)$, $\alpha > 0$ shape parameter, $\beta > 0$ scale parameter, and the cumulative baseline hazard function is given by $H_0(t) = \int\limits_0^t \lambda_0(t)dt$. The gamma process is denoted by $H_0(t) \sim GP(c_0 H^*(t), c_0)$. Let $H^*(t)$, $t \geq 0$, be an increasing left continuous function such that $H^*(0) = 0$. The Gamma Process is defined as having the following properties:

(i) $H_0(t) = 0$,
(ii) $\lambda_0(t) = H_0(t) - H_0(s) = G(c_0(H^*(t) - H^*(s), c_0), \quad t > s.$

The increments in the cumulative hazard are the hazard function. These increments are independent and Gamma distributed in the gamma process property. We note here that

$H^*(t)$ can be viewed as the mean of the process and c_0 indicates the weight or confidence parameter about the mean [14, 16].

Counting process that is one of the practical and alternative ways used in the analysis of complex survival models was used to analyze Bayesian models [18]. The counting process approach was first developed by [1] as a method that combines the components of stochastic integration, martingale theorem, and the counting process. Andersen and Gill [2] extended the counting process for analyzing survival data. Having n subjects in a study, for subject i, $i = 1, 2, \ldots, n$, $I_i(t)$ is the intensity process for a counting process given covariate vector $(X_1, X_2, \ldots, X_p)$ and $Y_i(t)$ is the at-risk indicator, i.e., the set of subjects still at risk at the time, T_i, of failure for subject i (i.e., alive and uncensored at a time point just before time t). Furthermore, the process $N_i(t)$ can be observed to count the number of failures that occurred in the interval [0,t]. Anderson and Gill [2] show that under model (2.1), the intensity process for $N_i(t)$ is

$$I_i(t)dt = Y_i(t)exp(\boldsymbol{\beta}'\boldsymbol{X}_i)d\Lambda_0(t),$$

where $d\Lambda_0(t)$ represents the instantaneous probability that the subject at risk at time t has an event in the next time interval [t,t+dt).

$D = N_i(t), Y_i(t), X_i; i = 1, 2, \ldots, n)$ denote the observed data, according the Cox regression model, joint distribution can be written as follows:

$$L(D|\boldsymbol{\beta}, \Lambda(t)) = \prod_{i=1}^{n} L_i(D|\boldsymbol{\beta}, \Lambda_i(t)),$$

where the factorizes of the likelihood of the data are

$$L_i(D|\boldsymbol{\beta}, \Lambda_i(t)) = exp\left(-\int\limits_{t\geq 0} I_i(t)dt\right)\prod_{t\geq 0}(I_i(t))^{dN_i(t)}, \qquad i = 1, 2, \ldots, n.$$

With the Bayesian approach, the joint posterior distribution can be written as [20]

$$P(\boldsymbol{\beta}, \Lambda_0(t)|D) \propto L(D|\boldsymbol{\beta}, \Lambda_0(t))P(\boldsymbol{\beta})P(\Lambda_0(t)).$$

Here, the primary interest is the regression parameters $\boldsymbol{\beta}$. For the regression parameters $\boldsymbol{\beta}$, a common default prior is normal prior with mean zero. The second interested parameter is the baseline cumulative hazard function $\Lambda_0(t)$. The Gamma process is used as the prior distribution for the baseline cumulative hazard function. $H_0(t) \sim GP(c_0H^*(t), c_0)$ has Gamma process and $H^*(t)$ is an increasing function where $H^*(0) = 0$ [14, 16].

2.3.2. Bayesian adjustment for Cox regression model with measurement error covariate. The joint posterior distribution of the model parameters $(Y_i, X_i, W_{i1}, W_{i2}|\boldsymbol{Z_i})$ for adjusting measurement error with the Bayesian approach in the Cox regression model can be written as follows:

$$P((Y_i, X_i, W_{i1}, W_{i2}|\boldsymbol{Z_i}) \propto P(Y_i|X_i, \boldsymbol{Z_i}, \boldsymbol{\beta}, \Lambda_0(t))P(\boldsymbol{W_i}|X_i, \sigma_\varepsilon^2)P(X_i|\boldsymbol{Z_i}, \gamma).$$

Y_i is the outcome with components of (T_i, δ_i) and the additional parameters, $\Lambda_0(t)$ denote the baseline cumulative hazard function. The first component of joint posterior distribution that is the term for regression model focuses on inference for regression parameters $\boldsymbol{\beta}$ and baseline cumulative hazard function $\Lambda_0(t)$, the second component is measurement error model with the assumption of the error measurements W_{ij} follow an additive error model, with independent normally distributed errors. The final specifies a model for the unobserved covariate X_i, conditional on $\boldsymbol{Z_i}$.

One of the approaches in the adjusted Bayesian Cox regression model, the Gamma process is used as a prior for $\Lambda_0(t)$ [3]. The idea of smoothing by determining a prior for the vector $\boldsymbol{\tau}$, was first proposed by [10], and then it was developed by [4]. The use of the polygonal function defined for the baseline hazard function instead of the gamma process

that assumes the independence of cumulative hazard increases, was used for measurement error problem in the Cox regression model [15].

We proposed an alternate approach that defines the polygonal function for the baseline hazard function instead of the gamma process for the Bayesian approach that is used in handling (by adjusting) the measurement error problem. By using the proposed new method, as a difference from the existing model using the gamma process, it is aimed to reflect dependency between time intervals and obtain less biased coefficient estimates for beta in the Cox regression model with measurement error covariate.

Polygonal prior to the baseline cumulative hazard. Beamonte and Bermúdez [4] used the non-negative polygonal function with the corner points at times $a_0 = 0 < a_1 < a_2 < \ldots < a_{Tmax} < a_{Tmax+1}$ for the baseline hazard function $\lambda_0(t)$, which is the non-parametric part of the model. Here it takes its polygonal values $\tau_0 = 0 < \tau_1 < \tau_2 < \ldots < \tau_{Tmax} < \tau_{Tmax+1}$, respectively and, when considered to be fixed after the time point a_{Tmax+1}, the baseline hazard function can be written as follows:

$$\lambda_0(t) = \begin{cases} \tau_j + \dfrac{(\tau_{j+1} - \tau_j)(t - a_j)}{a_{j+1} - a_j}, & if\ a_j \le t \le a_{j+1}, \quad j = 1, 2, \ldots, T_{max}. \\ \tau_{T_{max}+1}, & if\ t \ge T_{max} + 1. \end{cases}$$

Cumulative hazard increases, assumed to be independent during the gamma process, are unrealistic in many applications because of not reflect activity between adjacent intervals. Prior determination for the $\boldsymbol{\tau}$ vector to smoothing, where can be defined as the first-degree autocorrelation process, was proposed by [10] in a similar study. In [10]], the vector $\boldsymbol{\tau}$ is defined as

$$\tau_{j+1} = \tau_j exp(e_j), \quad j = 1, 2, \ldots, T_{max}$$

and

$$\tau_1 \sim Gamma(\tau_1 | a_\tau, b_\tau),$$

with a_τ, $b_\tau = 0.01$. It is assumed that the $(e_1, e_2, \ldots, e_{Tmax})$ in $\boldsymbol{\tau}$ vector has an independent log-normal distribution with zero mean and σ_e^2 variance. Here, the term variance shows the distribution

$$\sigma_e^2 \sim Gamma(\tau.e | a_e, b_e)$$

and $\tau.e$ is equal to $1/\sigma_e^2$.

It shows that getting the $a_e = b_e = 0.001$ implies that a prior mean 1 and variances 500 for the parameter τ_1 [20]. Parameter estimations can be obtained from the MCMC samples for this approach.

3. Simulation study

3.1. Study design

T_i, survival time, was generated according to [5] paper with the identified parameters determined in the Cox regression model under the proportional hazards assumption. The actual value of the explanatory variable containing the measurement error Xi and the explanatory variable without measurement error Z_i were generated from the multivariate normal distribution with the mean 0 and the variance 1, the covariance between them is 0.25. The sample sizes were 30, 50, and 100 in scenarios for three different cases. Scenarios were produced for the low, medium and high censored rates respectively 0.10, 0.30, 0.60 with regression parameters $\beta_X, \beta_Z = 0.5, 1.0, 1.5$.

20% of the measurements with having the same error variance were obtained as the second repetitive measurement of the erroneous variable. This error variance was chosen

such that unconditional reliability $\rho = \sigma_X^2/(\sigma_X^2 + \sigma_U^2)$ and results were obtained for 0.50, 0.70, and 0.90, respectively, to demonstrate low, medium, and high reliability.

In the Bayesian analysis of the Cox regression model, in addition to the determination of a prior distribution for the regression parameters and some sub-model parameters, it requires a prior distribution for the baseline cumulative hazard function $\Lambda_0(t)$. The identified prior distribution for $\Lambda_0(t)$ is assumed to be independent of other prior distributions, including β. Gamma prior described by [24] was used for $\Lambda_0(t)$ in the predefined Bayesian Cox regression model adjusted for the measurement error and the Bayesian Cox regression model ignoring measurement error. We proposed the polygonal function to determine prior to $\Lambda_0(t)$ as the adjusted Bayesian model for the measurement error in this article.

In the simulation, non-informative priors suggested by [12] were used for all model parameters. The independent normal prior suggested by [13] was adapted for β_X and β_Z. For all variance parameters, the inverse Gamma distribution IG (0.5.0.5) was used. Failure times were taken as the corner points of polygonal function. All models were run with five parallel chains for Bayesian models. Gelman-Rubin convergence test was used as the convergence criterion and it was assumed that the chains were sufficiently mixed for the value of 1.01 and smaller. In the case of the greater value, the number of initial iterations has been increased. For all scenarios, the number of iterations where convergence is provided was run.

We used Gibbs sampling, one of the Monte Carlo Markov Chain (MCMC) techniques that emerged as a class of sampling algorithms to overcome statistical modeling problems without analytical solutions in Bayesian models. For Bayesian inferences, 500 repetitions were taken for each scenario using Just Another Gibbs Sampler (JAGS) in the R package program.

3.2. Simulation results

In our simulation we used to following four methods to estimate $\boldsymbol{\beta}$, the proposed adjusted Bayesian method used polygonal prior with measurement error accounted for (ABP-CRM), adjusted Bayesian method used gamma prior with measurement error accounted for (ABG-CRM), Bayesian method used Gamma prior with Cox regression model ignoring measurement error (B-CRM) and Naive Cox's partial likelihood method ignoring measurement error (CRM). The features of the abbreviations of the models are briefly summarized in Table 1.

Table 1. Used four models to estimate $\boldsymbol{\beta}$.

Model	**Prior for $\boldsymbol{\Lambda_0(t)}$**	**Measurement Error**
ABP-CRM	Polygonal	Yes-Measurement Error
ABG-CRM	Gamma	Yes-Measurement Error
B-CRM	Gamma	No
CRM	-	No

The mean square error (MSE) and coverage probability (CP) are used to compare the performance of the models. Tables 2-4 show the results of the evaluated methods. Figure 1 shows the visual summary for the high reliability results of the simulations.

Comparing the four models in all scenarios, B-CRM and CRM have approximate results in terms of MSE and CP. MSE with the CP for the 95% nominal level is shown in Table 2 for the regression parameter 0.5. CP decreased with increasing sample size for B-CRM and CRM in all reliability levels. B-CRM and CRM have poorer CP results in low and medium reliability levels. In low reliability, except for 0.10 censored rate of 100 sample size, ABP-CRM has close or smaller MSE with good CP compared with B-CRM and CRM. But, ABG-CRM has a closer MSE with good CP compared with B-CRM and

CRM for 0.10 censored rate of 100 sample size. In the medium reliability, except for 0.30 censored rate of 100 sample size results were similar to low reliability scenarios. In the high-reliability B-CRM or CRM perform well with smaller MSE and acceptable level of CP against adjusted models, but also at least one of the adjusted models can be a good alternative with close MSE.

Table 2. MSE and CP of 95 percent credible/confidence interval results for $\beta = 0.5$ based on 500 replications per scenario.

n	beta	censoring	reliability	$MSE_{ABG-CRM}$	$CP_{ABG-CRM}$	$MSE_{ABP-CRM}$	$CP_{ABP-CRM}$	MSE_{B-CRM}	CP_{B-CRM}	MSE_{CRM}	CP_{CRM}
30	0.5	0.10	0.5	0.21152	0.976	**0.08345**	0.986	0.09988	0.646	0.10154	0.648
30	0.5	0.10	0.7	0.20869	0.964	**0.06895**	0.990	0.07176	0.856	0.07430	0.854
30	0.5	0.10	0.9	0.18572	0.946	**0.06030**	0.996	0.06296	0.950	0.06899	0.948
30	0.5	0.30	0.5	0.19528	0.992	**0.09228**	0.990	0.10439	0.676	0.10661	0.668
30	0.5	0.30	0.7	0.19388	0.978	**0.07532**	0.990	0.07564	0.896	0.07858	0.896
30	0.5	0.30	0.9	0.17812	0.970	0.06752	0.988	**0.06675**	0.956	0.07388	0.95
30	0.5	0.60	0.5	0.25186	0.970	0.16695	0.988	**0.14471**	0.778	0.15089	0.788
30	0.5	0.60	0.7	0.24814	0.960	0.15581	0.982	**0.13046**	0.900	0.14405	0.908
30	0.5	0.60	0.9	0.24009	0.964	0.14659	0.974	**0.13233**	0.938	0.16037	0.938
50	0.5	0.10	0.5	0.16228	0.976	**0.05104**	0.992	0.08291	0.430	0.08303	0.43
50	0.5	0.10	0.7	0.14346	0.948	**0.04320**	0.988	0.04657	0.812	0.04650	0.804
50	0.5	0.10	0.9	0.09786	0.924	0.03954	0.978	**0.03362**	0.926	0.03468	0.926
50	0.5	0.30	0.5	0.19361	0.974	**0.07111**	0.982	0.09110	0.512	0.09140	0.514
50	0.5	0.30	0.7	0.16969	0.960	0.06021	0.980	**0.05465**	0.816	0.05505	0.82
50	0.5	0.30	0.9	0.11245	0.938	0.05001	0.982	**0.04181**	0.946	0.04374	0.946
50	0.5	0.60	0.5	0.21029	0.960	0.11604	0.964	**0.10856**	0.672	0.10959	0.670
50	0.5	0.60	0.7	0.19221	0.956	0.10406	0.966	**0.07794**	0.878	0.08005	0.876
50	0.5	0.60	0.9	0.14790	0.946	0.09268	0.960	**0.07277**	0.940	0.07878	0.942
100	0.5	0.10	0.5	0.13403	0.964	0.17616	0.974	0.08177	0.130	**0.08160**	0.130
100	0.5	0.10	0.7	0.07528	0.960	**0.02944**	0.986	0.03627	0.600	0.03601	0.610
100	0.5	0.10	0.9	0.03060	0.940	0.12817	0.970	**0.01780**	0.920	0.01784	0.920
100	0.5	0.30	0.5	0.14535	0.960	0.10543	0.990	0.08156	0.208	**0.08145**	0.198
100	0.5	0.30	0.7	0.08670	0.950	0.09014	0.986	0.04036	0.656	**0.04005**	0.664
100	0.5	0.30	0.9	0.03491	0.956	0.07775	0.974	**0.02005**	0.922	0.02021	0.932
100	0.5	0.60	0.5	0.17351	0.960	**0.07939**	0.974	0.09127	0.388	0.09113	0.386
100	0.5	0.60	0.7	0.11334	0.950	0.06271	0.972	0.05175	0.768	**0.05144**	0.776
100	0.5	0.60	0.9	0.05609	0.946	0.04431	0.960	**0.03376**	0.938	0.03440	0.942

ABG-CRM: adjusted Bayesian method with gamma prior, ABP-CRM: adjusted Bayesian method with polygonal prior, B-CRM: Bayesian Cox regression model, CRM: Cox regression model, MSE: Mean square error, CP: Coverage probability of the 95% credible/confidence interval, n: sample size.

Table 3. MSE and CP of 95 percent credible/confidence interval results for $\beta = 1$ based on 500 replications per scenario.

n	beta	censoring	reliability	$MSE_{ABG-CRM}$	$CP_{ABG-CRM}$	$MSE_{ABP-CRM}$	$CP_{ABP-CRM}$	MSE_{B-CRM}	CP_{B-CRM}	MSE_{CRM}	CP_{CRM}
30	1	0.10	0.5	**0.13284**	0.986	0.26458	0.944	0.37577	0.198	0.37102	0.204
30	1	0.10	0.7	**0.13341**	0.996	0.15917	0.966	0.20163	0.590	0.19718	0.610
30	1	0.10	0.9	0.15789	0.978	**0.09792**	0.988	0.09988	0.900	0.11561	0.918
30	1	0.30	0.5	**0.14382**	0.994	0.28770	0.928	0.39388	0.224	0.38956	0.236
30	1	0.30	0.7	**0.13670**	0.994	0.17827	0.956	0.21270	0.616	0.20764	0.638
30	1	0.30	0.9	0.15763	0.994	0.10842	0.980	**0.09892**	0.926	0.11552	0.930
30	1	0.60	0.5	**0.23882**	0.984	0.40375	0.938	0.41435	0.420	0.41023	0.432
30	1	0.60	0.7	**0.20561**	0.986	0.30457	0.950	0.26102	0.734	0.26867	0.764
30	1	0.60	0.9	0.20247	0.986	0.23426	0.954	**0.16687**	0.942	0.23016	0.944
50	1	0.10	0.5	**0.10038**	0.996	0.16203	0.930	0.36995	0.024	0.36587	0.024
50	1	0.10	0.7	0.11125	0.990	**0.09099**	0.962	0.17515	0.380	0.16870	0.392
50	1	0.10	0.9	0.11314	0.966	**0.05416**	0.980	0.05632	0.890	0.05596	0.904
50	1	0.30	0.5	**0.11709**	0.986	0.17896	0.934	0.37169	0.052	0.36713	0.056
50	1	0.30	0.7	0.12198	0.982	**0.10703**	0.958	0.18040	0.430	0.17274	0.46
50	1	0.30	0.9	0.11932	0.968	0.07050	0.970	0.06584	0.902	**0.06538**	0.912
50	1	0.60	0.5	**0.15744**	0.984	0.24733	0.944	0.38022	0.194	0.37310	0.194
50	1	0.60	0.7	**0.14078**	0.978	0.16746	0.956	0.20374	0.608	0.19417	0.64
50	1	0.60	0.9	0.13055	0.968	0.12177	0.952	**0.09877**	0.922	0.10737	0.926
100	1	0.10	0.5	**0.10162**	0.982	0.11653	0.930	0.37770	0.000	0.37534	0.000
100	1	0.10	0.7	**0.08195**	0.978	0.19606	0.944	0.17792	0.070	0.17418	0.074
100	1	0.10	0.9	0.05213	0.944	0.04765	0.972	0.03992	0.788	**0.03746**	0.802
100	1	0.30	0.5	**0.11388**	0.980	0.21527	0.928	0.37981	0.000	0.37695	0.000
100	1	0.30	0.7	**0.09226**	0.972	0.13662	0.938	0.17861	0.128	0.17380	0.148
100	1	0.30	0.9	0.05419	0.958	0.11255	0.944	0.04706	0.812	**0.04432**	0.826
100	1	0.60	0.5	0.15078	0.978	**0.15043**	0.916	0.39246	0.028	0.38801	0.030
100	1	0.60	0.7	0.13310	0.968	**0.10971**	0.902	0.19872	0.298	0.19197	0.322
100	1	0.60	0.9	0.08653	0.946	0.08036	0.910	0.07274	0.828	**0.07032**	0.860

ABG-CRM: adjusted Bayesian method with gamma prior, ABP-CRM: adjusted Bayesian method with polygonal prior, B-CRM: Bayesian Cox regression model, CRM: Cox regression model, MSE: Mean square error, CP: Coverage probability of the 95% credible/confidence interval, n: sample size.

Table 4. MSE and CP of 95 percent credible/confidence interval results for $\beta = 1.5$ based on 500 replications per scenario.

n	beta	censoring	reliability	$MSE_{ABG-CRM}$	$CP_{ABG-CRM}$	$MSE_{ABP-CRM}$	$CP_{ABP-CRM}$	MSE_{B-CRM}	CP_{B-CRM}	MSE_{CRM}	CP_{CRM}
30	1.5	0.10	0.5	**0.25293**	0.974	0.79215	0.572	1.00356	0.024	0.96974	0.040
30	1.5	0.10	0.7	**0.13339**	0.986	0.50993	0.758	0.55324	0.236	0.50112	0.320
30	1.5	0.10	0.9	**0.09199**	0.996	0.29215	0.898	0.20309	0.756	0.19211	0.832
30	1.5	0.30	0.5	**0.25948**	0.972	0.80467	0.672	0.99641	0.040	0.95983	0.054
30	1.5	0.30	0.7	**0.14210**	0.998	0.53196	0.800	0.55439	0.298	0.49537	0.382
30	1.5	0.30	0.9	**0.09812**	0.992	0.31627	0.920	0.20681	0.840	0.19038	0.898
30	1.5	0.60	0.5	**0.41268**	0.968	0.98420	0.756	1.00062	0.152	1.09426	0.210
30	1.5	0.60	0.7	**0.25756**	0.980	0.73055	0.824	0.26374	0.446	0.55016	0.590
30	1.5	0.60	0.9	**0.17592**	0.988	0.51830	0.884	0.29123	0.852	0.37833	0.890
50	1.5	0.10	0.5	**0.14608**	0.984	0.56098	0.556	0.98885	0.000	0.97182	0.000
50	1.5	0.10	0.7	**0.08522**	0.988	0.32578	0.746	0.51263	0.056	0.47932	0.092
50	1.5	0.10	0.9	**0.06998**	0.998	0.15621	0.882	0.13834	0.684	0.11314	0.772
50	1.5	0.30	0.5	**0.16921**	0.970	0.58102	0.670	1.00969	0.004	0.98667	0.004
50	1.5	0.30	0.7	**0.10089**	0.992	0.35408	0.784	0.53608	0.094	0.49505	0.158
50	1.5	0.30	0.9	**0.08454**	0.992	0.18803	0.876	0.16414	0.724	0.13724	0.808
50	1.5	0.60	0.5	**0.25812**	0.970	0.70363	0.766	1.01566	0.020	0.98261	0.034
50	1.5	0.60	0.7	**0.16129**	0.984	0.48350	0.808	0.56902	0.238	0.51320	0.294
50	1.5	0.60	0.9	**0.11476**	0.986	0.31738	0.838	0.21641	0.794	0.19081	0.858
100	1.5	0.10	0.5	**0.11526**	0.956	0.81564	0.616	1.03230	0.000	1.02393	0.000
100	1.5	0.10	0.7	**0.07216**	0.980	0.51111	0.698	0.53771	0.000	0.51992	0.000
100	1.5	0.10	0.9	**0.03998**	0.994	0.31449	0.862	0.12958	0.392	0.10926	0.480
100	1.5	0.30	0.5	**0.11055**	0.972	0.58544	0.668	1.01643	0.000	1.00579	0.000
100	1.5	0.30	0.7	**0.07722**	0.974	0.35858	0.764	0.52822	0.000	0.50707	0.000
100	1.5	0.30	0.9	**0.05295**	0.986	0.20407	0.844	0.12964	0.498	0.10675	0.618
100	1.5	0.60	0.5	**0.16500**	0.964	0.46575	0.766	1.04010	0.000	1.02290	0.000
100	1.5	0.60	0.7	**0.12501**	0.954	0.31382	0.754	0.56659	0.040	0.53415	0.064
100	1.5	0.60	0.9	**0.08740**	0.968	0.19414	0.758	0.17423	0.628	0.14393	0.712

ABG-CRM: adjusted Bayesian method with gamma prior, ABP-CRM: adjusted Bayesian method with polygonal prior, B-CRM: Bayesian Cox regression model, CRM: Cox regression model, MSE: Mean square error, CP: Coverage probability of the 95% credible/confidence interval, n: sample size.

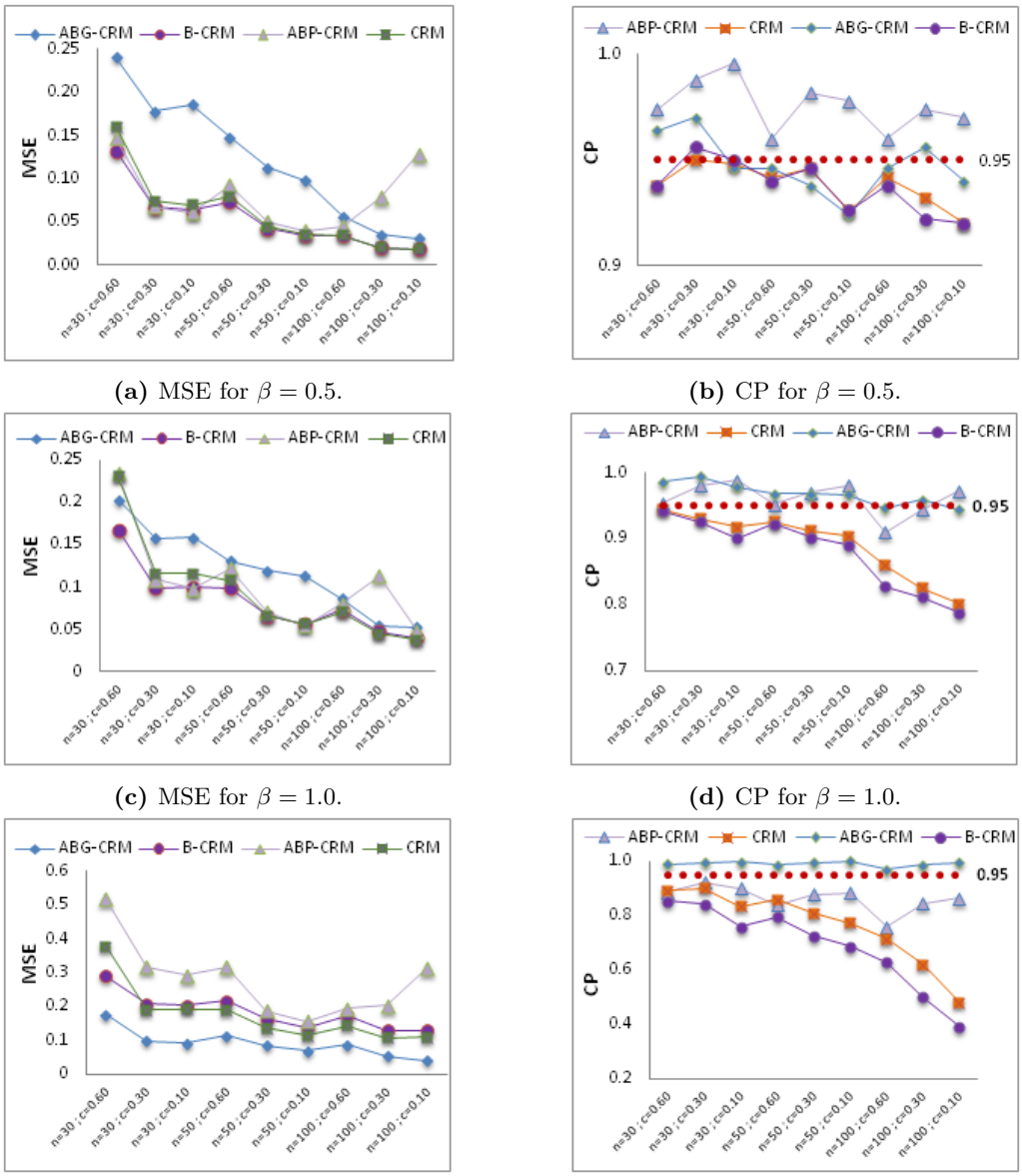
MSE with the CP for the 95% nominal level is shown in Table 3 for the regression parameter 1.0. In the low and medium reliability levels, B-CRM and CRM were biased with larger MSE and smaller coverage probability compared with adjusted models. Except for 0.60 and 0.10 censored rate of 100 sample size ABG-CRM has smaller MSE in all scenarios. MSE results were obtained close in ABG-CRM and ABP-CRM for 0.60 and 0.10 censored rate of 100 sample size but poorer CP in ABP-CRM for 0.60 censored rate. In the high reliability except for 0.60 censored rate of 30 sample size and 0.30 censored rate of 100 sample size B-CRM, CRM, and proposed method have similar results in terms of MSE but CP decreased under of nominal level with increasing sample size in B-CRM and CRM.

MSE with the CP for the 95% nominal level is shown in Table 4 for the regression parameter 1.5. ABG-CRM performs well with smaller MSE and the coverage probability was maintained at or above the nominal level under all the scenarios considered. The coverage probability was mostly far below the nominal level in all other considered models. In particular, the estimated 95% confidence intervals for the low and medium reliability with 50 and 100 sample size rarely or never contained the true coefficient in B-CRM and CRM.

4. Application to PBC data

To illustrate the applicability of the analyses, we analyze a set of real data which is known as the Primary Biliary Cirrhosis (PBC) data obtained from the Mayo Clinic study between 1974 and 1984. During this ten-year interval, a total of 424 PBC patients who were referred to Mayo Clinic who met the criteria for a randomized placebo-controlled study of D-penicillin were enrolled in the study, but 312 cases including complete data were included in the randomized trial due to loss of follow-up. This clinical study aims to examine the effect of the D-penicillin drug on time to death or liver transplantation. In the study, 154 patients were taken as placebo group to see the effect of the D-penicillin drug on the disease, and the remaining 158 patients were given the drug. Besides, the

serum bilirubin levels of the patients were recorded at the entry of the study, at the end of the first 6 months, and annually thereafter throughout the study [9, 23].



(a) MSE for $\beta = 0.5$. **(b)** CP for $\beta = 0.5$.

(c) MSE for $\beta = 1.0$. **(d)** CP for $\beta = 1.0$.

(e) MSE for $\beta = 1.5$. **(f)** CP for $\beta = 1.5$.

Figure 1. Mean square error (MSE) and coverage probability (CP) for reliability=0.9 according to each regression coefficient (β) using four methods with related sample size (n) and censoring rate (c).

In our study, the log-serum bilirubin level was considered as an explanatory variable with measurement error. The measurement recorded six months later was taken as the second repeated measure of the explanatory variable with the measurement error. Our study aimed to examine the effects of the drug (variable without measurement error) and log-serum bilirubin (measurement error variable) on the survival time of PBC patients.

We estimated the regression coefficients using the naive, Bayesian methods without adjusting for measurement error and adjusting measurement error using gamma and polygonal priors with Bayesian approaches. We performed a global test of the proportional hazards assumption using the Schoenfeld residuals following fitting the Cox model. The

test indicated no evidence to reject an assumption of proportional hazards (p=0.730). Due to the lack of prior information for the Bayesian approaches, all hyperparameters were chosen to reflect noninformative priors. The standardized values of the log-serum bilirubin variable were used in the analysis to achieve faster convergence in Bayesian models. For regression coefficients, the hyperparameters of the multivariate Normal priors were set and we set the prior distributions for variance parameters similar to the simulation. The number of iterations at which convergence was achieved was determined and three chains were run for all Bayesian models. All the hyperparameters of the model showed an acceptable convergence to the stationary distribution both with the graphical method and statistical tests, Gelman- Rubin and Heidelberger-Welch convergence diagnostics. Regression coefficient and standard error with 95% confidence intervals for the Cox regression model and posterior mean estimates and standard deviations with 95% credible intervals and DIC for Bayesian models were presented in Table 5.

Table 5. Regression parameter estimates and 95% credible/confidence intervals for the PBC data.

Model	**Covariate**	**Estimate (SD)**	**95% Credible/Confidence Intervals**		**DIC**
			Lower Limit	**Upper Limit**	
ABG-CRM	Log-serum bilirubin	1.3594 (0.1264)	1.1191	1.6149	2108
	Drug	-0.2147 (0.1825)	-0.5737	0.1415	
ABP-CRM	Log-serum bilirubin	1.3149 (0.1228)	1.0807	1.5620	1949
	Drug	-0.1857 (0.1797)	-0.5399	0.1650	
B-CRM	Log-serum bilirubin	1.0901 (0.0948)	0.9053	1.2770	1760
	Drug	-0.1004 (0.1694)	-0.4324	0.2316	
CRM	Log-serum bilirubin	1.0966 (0.0949)	0.9105	1.2828	-
	Drug	-0.1032 (0.1708)	-0.4380	0.2316	

It is seen in Table 5 that the effect of log-serum bilirubin variable on death risk is high for all models. Regarding the results of the simulation scenarios, it was concluded that adjusted models also gave close MSE in large samples, although the minimum MSE was achieved for CRM only at reliability 0.90 for regression parameter 1 and 0.60 censoring rate. Since the real values of the log-serum bilirubin variable, which is the measurement error variable, can not be observed, information about its reliability can not be obtained. Therefore, it is more reliable to compare and interpret the adjusted models. So, the naive method and the Bayesian method ignoring measurement error are not taken into consideration for the comments. Comparing the adjusted models, it was concluded that ABP-CRM is a better model with a smaller DIC. Only just log-serum bilirubin effect is significant on survival time. It can be said that as the log-serum bilirubin value increases, the risk of death increases. Given the observed data, the effect of log-serum bilirubin has 95% probability of falling within the range 1.0807-1.5620.

5. Conclusions

In this paper, we have proposed a new alternative Bayesian method for adjusting measurement error covariate that reflecting also activity between adjacent intervals in cumulative hazard increases. We also compare the Bayesian adjusted models for measurement error and classic known method according to different sample sizes, censoring rates, reliability, and risk levels in order to reveal in detail the magnitude of the bias that is created by the estimation of the regression coefficient.

Especially in large samples or in cases where the risk is high, the use of classical analyses ignoring measurement error will lead the researcher to wrong conclusions while interpreting the effect of the covariate on the output variable. In cases where the reliability is low and medium, it can be said that the classical model and its Bayesian approach have low performance in terms of CP compared to the adjusted methods. Also, ABP-CRM is preferred to all other methods in terms of CP in low and medium reliability scenarios except for large sample, low censoring, and low reliability. In cases where the reliability is high, at least one of the adjusted models has been an alternative method with close MSE, although smaller MSE has been obtained for classical models. In real data analysis, the reliability of the variable containing measurement error is mostly unknown, so its reliability can not be obtained. As can be seen in the simulation study, the use of adjusted models in analysis for high reliability as well as low and medium reliability will provide more reliable results compared to classical models. The limitation of this study is that the computation time for adjusting Bayesian methods is long because of the complex structure of the Cox regression model and determines the corner points of polygonal function. Different determinations on corner points of polygonal functions that reflect accurately the activity between adjacent intervals in cumulative hazard increases can provide better results. Also, we believe better predictions can be obtained with informative prior.

While the measurement error variable, which is frequently encountered in epidemiological studies, is used in studies that require sensitive interpretation such as survival analysis, it is necessary to carefully decide on parameter estimation methods.

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