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A COMPARISON OF MULTIPLICATIVE AND ADDITIVE HAZARD MODELS USING THE HAZARD AND SURVIVAL RATIO

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Abstract: The Cox multiplicative hazards regression and Aalen additive hazards regression models are widely used for survival data analysis. While the Cox model emphasizes hazard ratios or relative risks, the Aalen model focuses on relative survival or excess risks. This study compares the performance of these models through simulations of biomedical survival data. Results reveal no clear dominance of one model over the other, suggesting that both models should be employed to have a more thorough survival analysis.

1. INTRODUCTION

Survival data or time-to-event data frequently arise in many applications including biomedical investigations, actuarial science, epidemiology, demography, and so forth (Başar, 2017; Cook & Lawless, 2014; Emmerson & Brown, 2021; Haberman & Sibbett, 2024; Kragh Andersen et al., 2021; Wuryandari & Kartiko, 2018) . Two competing models to analyze survival data are the Cox proportional hazards model, which is also known as the multiplicative hazards model; and the Aalen additive hazards model. Simple and rough bibliometric analysis using Scopus in 2023 with keywords related to the multiplicative hazards model; and keywords related to the additive hazards model showed that the published papers with keywords related to the multiplicative hazards model have increased exponentially since the seminal paper by Cox in 1972 (Kalbfleisch & Schaubel, 2023) and gave total hits of about 108,276. The additive hazards model also started gaining popularity since Aalen's Dissertation in 1975 (Aalen et al., 2020) and reached 2,643 hits.

The interpretation of the Cox proportional hazards model in terms of hazard ratio is intuitive to the users. It is similar to the relative risk and odds ratio in the logistic regression. However, misspecification in the Cox model often occurs when the effect of covariate changes over time, causing biased parameter estimates (Martinussen & Peng, 2016). Aalen et al. (2008) and Aalen et al. (2015) argued that the additive models are useful. The reason is, among others, (1) the model may be the actual relationship governing the data, (2) the model has a similar interpretation as risk difference, excess risk, or attributable risk that measures public health importance of risk factors, (3) the Additive hazard model fits very nicely with the Martingale theory, (4) the models may be developed and implemented for dynamic covariates and causality. Despite their frequent use in many applications, one question remains: which one should be used?

It is well known that the multiplicative hazard models, such as the Cox proportional hazards model, are closely related to the hazard ratio or relative risk (Kalbfleisch &

Schaubel, 2023). Whereas the additive hazards models, such as the Aalen regression models, are closely related to the relative survival or excess risk (Aalen et al, 2008). Therefore, a comparison of the two models may be studied through the behavior of the hazard ratio and survival ratio (relative survival). In this paper, such a comparison will be discussed and implemented in a simulation study with the main scenario in the application of biomedical survival data analysis, for example, in cancer studies and clinical trials. The principle and the methods for comparison will be discussed in the next section. A simulation study will be performed in Section 3, and the discussion and conclusion follow in Section 4.

2. MODELS AND METHOD FOR COMPARISON

The multiplicative hazards model or the Cox regression model assumes that the covariates modify the baseline hazard in a multiplicative time-independent way given by

$$h(t|\psi) = h_0(t)\psi \tag{1}$$

where $h_0(t)$ is the baseline hazard, common to all individuals; ψ is the parametric function of covariates, independent of time. Since the hazard must be non-negative, then ψ has to be. Therefore, typically ψ is in the form of the exponential function of covariates and the regression parameters. The ratio between hazards of two groups or individuals, e.g., $h(t|\psi_1)$ and $h(t|\psi_2)$ given (1), will be constant ψ_2/ψ_2 over time. Given this property, this model is also known as the proportional hazards model.

The additive hazards model takes the hazard function as

$$h(t|\psi\,) = h_0(t) + \psi(t) \tag{2}$$

where the $\psi(t)$ is the parametric function of covariates, dependent on time. Model (2) assumes that the covariate modifies the baseline hazard additively. The $\psi(t)$ here is parametrically defined as the linear combination of covariates and the regression coefficients. In this model $\psi(t) \leq h_0(t)$.

As an illustration, suppose the multiplicative hazards model is specified as in (1) and the additive hazards model specified as (2) but with $\psi(t) = \theta$, a constant over time. Using the functional relationship between $S(t)$ and $\psi H(t)$, the survival function of the multiplicative hazards model can be written as

$$\begin{aligned} S(t|\psi\,) &= \exp\left(-H(t\,|\psi)\right) \\ &= \exp\left(\int_0^t h_0(t)\psi\, du\right) \\ &= \exp\left(-\psi\, \int_0^t h_0(t)\, du\right) \\ &= \exp\left(-H_0(t)\psi\right) \\ &= S_0(t)^{\psi} \end{aligned} \tag{3}$$

where $S_0(t)$ is the baseline survival. The additive hazards model is specified in the same way

$$\begin{aligned} S(t|\theta) &= exp(-H(t|\theta)) \\ &= exp\left(-\int_0^t [h_0\,(t)\, + \theta]\, du\right) \\ &= exp(-H_0(t)\, -\, \theta t) \\ &= S_0\,(t)\, exp(-\theta t) \end{aligned} \tag{4}$$

Figure 1a and Figure 1b show the picture of survival functions (3) and (4), taking $S_0(t)$ as an exponential distribution with parameter unity. When the $\psi = \theta \geq 1$ both survival curves are lower than the baseline survival, with the additive one being the lowest. Both multiplicative and additive curves will coincide when $\psi = \theta$ close to infinity. On the other side, given the values $\psi = \theta < 1$, the survival curve of the multiplicative hazards will be higher than the baseline, whereas the survival curve of the additive hazards is always lower than the baseline.

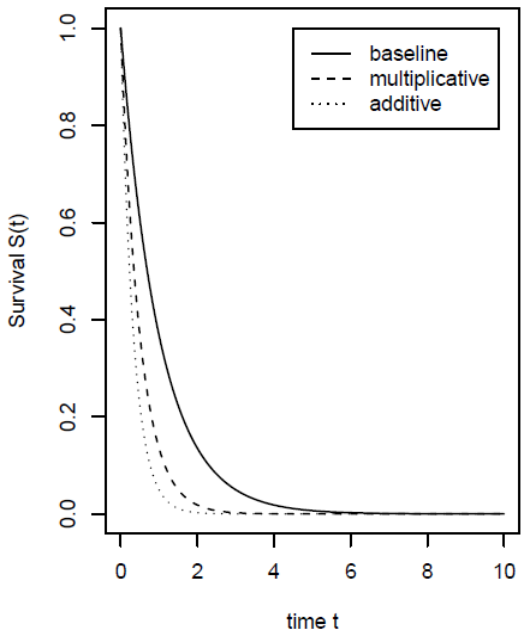


Figure 1a. Survival curve with the value of $\psi = \theta \geq 1$

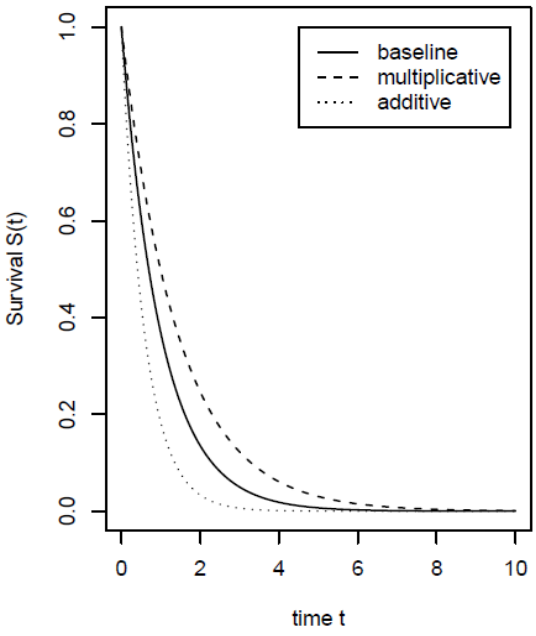


Figure 1b. Survival curve with the value of $\psi = \theta < 1$

Of course, the values of ψ and θ do not have to be the same. When θ is negative, the survival curve of the additive hazards model will be larger than the baseline. Values of ψ and θ give the same survival curve for both the multiplicative and the additive model. For example, given the $S_0(t)$ is exponentially distributed with a unit parameter, $\psi = 2.25$ and $\theta = 1.25$ will give the same survival curve; also, when $\psi = 0.8$ and $\theta = -0.2$. There are infinite numbers of ψ and θ which will give the same survival curve. When this happens, it does not matter which one is used, the multiplicative hazards or the additive hazards model will give the same result.

The models considered here are not parametric but semi or non-parametric models, in which the baseline survival curve, and the corresponding baseline hazard, are not known. Therefore, analytical comparison by investigating hazard or survival function as discussed previously is not possible. However, comparison by disregarding the baseline survival and the corresponding baseline hazard is still possible by looking at the hazard ratio and survival ratio. In the multiplicative hazards model (1), the hazard ratio between two groups or individuals will disregard the baseline hazard, since, by proportional hazards assumption, the baseline hazard will be canceled out in the hazard ratio. Whereas in the additive hazards model (2) the survival ratio (or the relative survival) between two groups or individuals will be equal to the exponential of the negative cumulative risk function which can be estimated non-parametrically. Therefore, the comparison will be performed based on the estimated hazard ratio and survival ratio obtained from both models by a simulation study. The

methods for estimating hazard and survival function from each model as the basis for the simulation study are discussed in the following.

For the multiplicative hazards model (1), the hazard model for each individual is specified as

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

where $\boldsymbol{x} = (x_1, \dots, x_p)$ is a $1 \times p$ vector of covariates for one individual, $\boldsymbol{\beta} = (\beta_1, \dots, \beta_p)$ is a $p \times 1$ vector of regression coefficient. When considering all $i = 1, \dots, n$ individuals, $\boldsymbol{X}$, an $n \times p$ matrix of covariates of all individuals, is used in place of $\boldsymbol{x}$. The estimation method for $\boldsymbol{\beta}$ is based on the partial likelihood function (Collett, 2023; van Houwelingen & Stijnen, 2016).

The survival function of Model (5) can be estimated using the functional relationship between the survival function $S(t)$ and the cumulative hazard function as discussed in the early paragraph of this section. The baseline cumulative hazard itself can be estimated by the Nelson-Aalen estimator or Breslow estimator,

$$\widehat{H_0}(t) = \sum_{t_i \le t} \frac{d_i}{Y_i} \tag{6}$$

where d_i is the number of events, which gives the value of unity in the case of no ties in the time-to-event data and Y_i be the number of individuals who are at risk at time t_i.

The estimated conditional survival function is conditional to the covariates and the parameter is given by

$$\hat{S}(t|\boldsymbol{X},\boldsymbol{\beta}) = \hat{S}_0(t)^{\exp(\boldsymbol{X}\boldsymbol{\beta})} \tag{7}$$

where $\hat{S}_0(t) = \exp\left(\widehat{H}_0(t)\right)$

The additive hazards model (2) has the following function,

$$h(t|x(t)) = h_0(t) + x(t)\,\beta(t) \tag{8}$$

where the covariates are time-dependent. It is also possible that not all the coefficients are time-dependent which is known as the semiparametric additive hazards model (Martinussen & Scheike, 2006).

The cumulative hazard for Model (8) is obtained by integrating $h(t|\boldsymbol{X}(t))$ over time

$$\begin{aligned} H(t|\boldsymbol{X}(t)) &= \int_0^t (h_0(u) + \boldsymbol{X}(u)\boldsymbol{\beta}(u))du \\ &= H_0(t) + \boldsymbol{X}(u)\boldsymbol{B}(t) \end{aligned} \tag{9}$$

Here, the matrix notations $\boldsymbol{X}$ is used for convenience. The $\boldsymbol{B}(t)$ is the cumulative regression coefficient $\boldsymbol{B}(t) = (B_1(t), \dots, B_p(t)$, where $B_j = \int_0^t B_j(u)\,du$, $j = 1, \dots, p$. The method of estimation for $\boldsymbol{B}(t)$ in Model (8) follows that in (Martinussen & Scheike, 2006).

To estimate the survival function under model (8), the functional relationship $S(t) = \exp(-H(t))$ is again used.

$$\begin{aligned} \hat{S}(t \mid \boldsymbol{X}(t)) &= \exp(-\widehat{H}_0(t) - \boldsymbol{X}(t)\widehat{\boldsymbol{B}}(t)) \\ &= S_0(t)\exp(-\boldsymbol{X}(t)\widehat{\boldsymbol{B}}(t)) \end{aligned} \tag{10}$$

where the $\widehat{\boldsymbol{B}}(t)$ is the estimate of $\boldsymbol{B}(t)$ as specified in Model (9).

The estimation functions of (6), (7), and (10) can be used to calculate the hazard ratio and survival ratio between two groups or individuals. The hazard ratio is formulated as,

$$\widehat{HR}(t) = \frac{\hat{H}_1(t)}{\hat{H}_2(t)} \tag{11}$$

where index 1 and index 2 denote the different groups or individuals. For the multiplicative hazards model of (5), the hazard ratio $\widehat{HR}(t)$ will be constant through time, whereas it is not necessary in the additive hazards model of (8). In the case of dichotomous covariates, with the estimated regression coefficient $\hat{\beta}$, the adjusted hazard ratio in Model (5) will be $\exp(\hat{\beta})$, by adjusting means all values for other variables are kept the same in both groups.

The survival ratio is defined as

$$\widehat{SR}(t) = \frac{\hat{S}_1(t)}{\hat{S}_2(t)} \tag{12}$$

where in the additive hazards model (8), the estimation (12) will be equal to $\exp\left(-\left(\widehat{\boldsymbol{B}}(t)\right)\right)$, which is also known as the adjusted relative function of covariates (Aalen et al., 2008b).

As it has been mentioned earlier, a comparison between the two models will be performed through a simulation study. The comparison is based on the performance of the estimated survival function given a certain Data Generating Process (DGP) for the survival random variable T. Three data DGPs are considered here: (1) the multiplicative hazards model; (2) the additive hazards model, with time-independent coefficient on the main covariate of interest; (3) the additive hazards model, with time-dependent coefficients on the main covariates of interest.

Often, the main interest in biomedical applications is the comparison of survival curves for two or more competing groups. For example, comparing the survival curve between treatment and control groups. Therefore, the multiplicative and additive models in the simulation study accommodate this kind of survival data. Two covariates were considered here, one is a zero-one covariate representing the treatment and control group usually used in biomedical applications; the other one is a continuous covariate, representing a potential confounding variable. The main models were the multiplicative hazards model and additive hazards model as follows.

1. Specification for the multiplicative hazards model

   $$h(t|x) = 0.05 \exp(\beta_1 X_1 + \beta_2 X_2) \tag{13}$$

   where X_1 are independent Bernoulli distribution with mean value of 0.5; X_2 are independent Uniform distribution; β_1 = 1.44 and β_2 = 0.16. Other distributions can be specified, as long as it is a discrete distribution for X_1, and a continuous distribution for X_2.

2. Specification for the additive hazards model with time-independent effect on the main variable of interest

   $$h(t|x) = \beta_1 + \beta_2 X_1 + \beta_3 X_2 \tag{14}$$

   where X_1 are independent Bernoulli distribution with mean value of 0.5; X_2 are independent Uniform distribution; β_1 = 0.07, β_2 = 0.14 and β_3 = 0.04.

3. Specification for the additive hazards model, with time-dependent effects on the main variable of interest

$$h(t|x) = 0.05 + \frac{1}{\log(1+t)} X_1 + \beta_2 X_2 \quad (15)$$

where X_1 are independent Bernoulli distribution with mean value of 0.5; X_2 are independent Uniform distribution; β_1 = 0.07, the $\frac{1}{\log(1+t)}$ is mimicking the decreasing time-varying effect of X_1; and β_2 = 0.04.

For each DGP, samples of size n = 100, 200 were generated using the method based on the data generation given hazard rate. For each sample set, several statistical quantities were obtained from the estimated models as the basis for the comparison analysis as described below.

1. The estimated coefficients of the Cox multiplicative hazards Regression.
   These quantities were estimated using the Partial Likelihood and were compared with the true values of Model (13)
2. The test for the proportional hazard assumption.
   The data generated by the additive hazards model will likely violate the proportionality assumptions of the Model (13). In this simulation, the behavior of the *p*-values obtained from the *R* replication was investigated. As random variables, *p*-values will be uniformly distributed if they are not significant.
3. The hazard ratios.
   For the Cox regression methods, these values were calculated from the estimated coefficients of the main variable (X_1 in the DGP); for the Aalen regression, these quantities were calculated from the estimated cumulative hazard for X_1=1,

   $$\widehat{H}(t\,|X_1 = 1) = \widehat{\boldsymbol{B}}_0(t) + \widehat{\boldsymbol{B}}_1(t)X_1 + \widehat{\boldsymbol{B}}_2(t)\,\tilde{X}_2 \quad (16)$$

   and for $X_1 = 0$

   $$\widehat{H}(t|X_1 = 0) = \widehat{\boldsymbol{B}}_0(t) + \widehat{\boldsymbol{B}}_2(t)\tilde{X}_2 \quad (17)$$

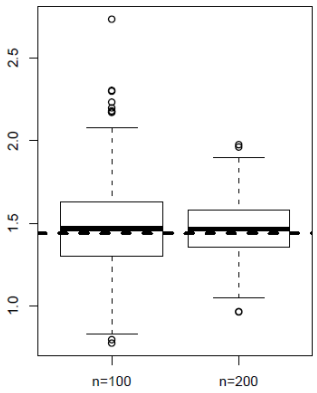
   with $\tilde{X}_2$= 0.5 which is the mean of random uniform(0,1), the underlying distribution of X_2 as specified by the DGPs above. The hazard ratios are $\widehat{H}(t)|X_1 = 1/\widehat{H}(t)|X_1 = 0$. The similar calculation is applicable for the hazard ratios of the DGP under additive hazards models (14) and (15), replacing the estimate of $B_1(t)$ and B_2 with the true values under the models. The average differences between estimated hazard ratios and the true hazard ratios for the whole times (the times were taken from each the generated models) were calculated for *R* replications.
4. The survival ratios.
   For the Cox regression methods, the ratios were calculated from exp(exp($-\hat{\beta}_1$)*t*) and replacing $\hat{\beta}_1$with β_1 for the DGP of Model (13). For the Aalen model, the ratio is exp($-\hat{\beta}_1(t)$) and replacing $\hat{B}_1(t)$ with $B_1(t)$ for the DGP under Model (14) and (15). The average differences between estimated survival ratios and the true survival ratios for the whole time were calculated for *R* replications.

For each combination of DGP, sample sizes, and their statistical quantities, an *R* = 500 replications were performed. The computations were performed using **R** (R Core Team, 2024) and library **survival** (Therneau, 2024) and **timereg** (Martinussen & Scheike, 2006). The next section shows the simulation results.

3. SIMULATION RESULT

a. DGP under the Multiplicative Hazards Models

The estimates of β_1, as the main effect to be studied, using the Cox regression model is as expected. The estimations were reasonably good. The $\hat{\beta}_1$'s were very close to the true value $\beta_1 = 1.44$. As the sample size increased, the precision is also increased. (Figure 2). The same behavior were also found for the other estimated parameter β_2's, in which the estimations were very close to the true value. Under the multiplicative hazards model, the test for proportionality assumptions were accepted. The medians and means for the *p*-values of 500 replications gave values near 0.5, showing that the proportionality assumptions were not rejected. The results also showed that the estimated hazard ratio , i.e., the exponential of the Cox regression's coefficients were very close to the true hazard ratio, even if the baseline hazard in the Model (13) is a constant hazard of 0.05, whereas in the estimation this baseline hazard was not specified.



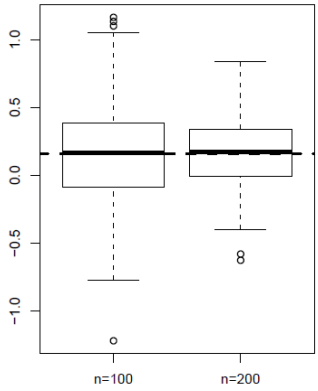


Figure 2a. The Boxplot of the $\hat{\beta}_1$ **Figure 2b**. The Boxplot of the $\hat{\beta}_2$

The hazard ratios calculated from the Aalen model are compared to the true hazard ratio, exp(1.44), using the mean difference between. The result shows that Aalen's hazard ratios and the true Cox's hazard ratio are close but they have very high variability (Figure 3). This pattern is the same for the larger sample size (n = 200). The mean differences between the survival ratio calculated by the Cox multiplicative hazards $\exp(\exp(-\hat{\beta}_1)t)$ and the true survival ratio $\exp(\exp(-0.14)t)$ for the available time were close, for n = 100 and n = 200. Whereas for the Aalen model, the mean differences were slightly downward (Figure 4).

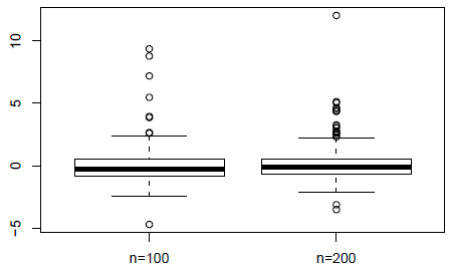


Figure 3. The boxplot of the mean difference between the estimated hazards ratios using the Aalen additive hazards model with the true hazard ratio from the Cox model

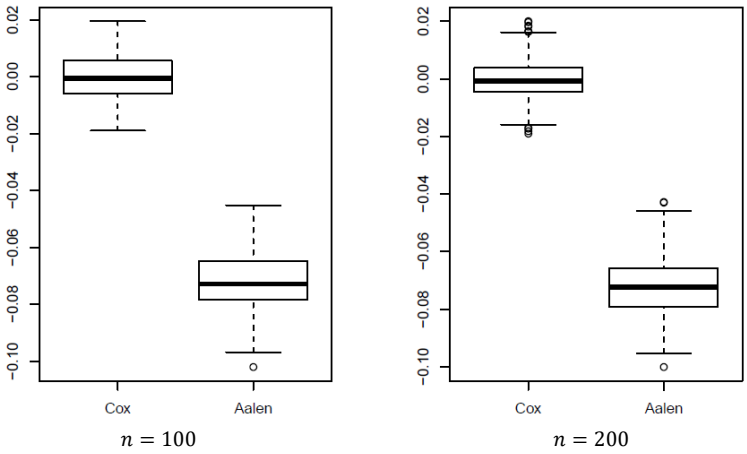


Figure 4. The boxplot of the mean difference between the estimated survival ratios using the Cox multiplicative hazard and the Aalen additive hazards model with the true survival ratio from the Cox model.

b. DGP under the Additive Hazards Models with Time Independent Effect on X_1

The hazard ratio of Model (15) is independent in time and can be calculated as (0.07+ 0.14+ 0.04 × 0.5)/(0.07+ 0.04 × 0.5) = 2.55. This value is comparable with the Cox model. The estimation of $\beta 1$ for the R = 500 replication gave the median value of 0.993 (n = 100) or hazard ratio exp(0.993) = 2.699; and 0.944 (n = 200) or exp(0.944) = 2.570, where these values are close to the 2.55 from the true additive model. The test for hazard proportionality for the given model estimated from the additive model was not rejected either. Using the Cox model in this time independent additive hazards model seems reasonable. However, when analyzing the survival ratio, the estimated survival ratios obtained from the Cox model were biased downward (Figure 5).

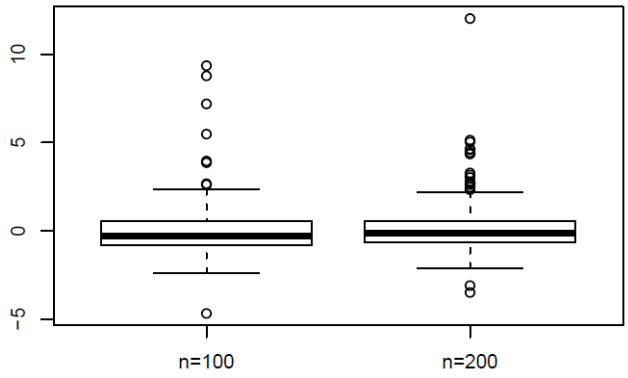


Figure 5. The boxplot of the mean difference between the estimated survival ratios using the Cox multiplicative hazards model with the true hazard ratio from the Aalen model

c. DGP under the Additive Hazards Models with Time-Dependent Effect on X_1

In this time-dependent additive model, the estimated hazard ratios were far from the time dependent hazard ratios from the true additive hazards model. The estimated β_1 using the Cox model gave a median of 1.4 (n = 200, R = 500). When it is plotted as a cumulative hazard function and compared to the true cumulative hazard function of Model (15), the result were quite different (Figure 6). The test of proportional hazard assumption were significantly rejected for the β_1, (n = 100 and n = 200). The estimated survival ratio obtained from the Cox model were also biased downward.

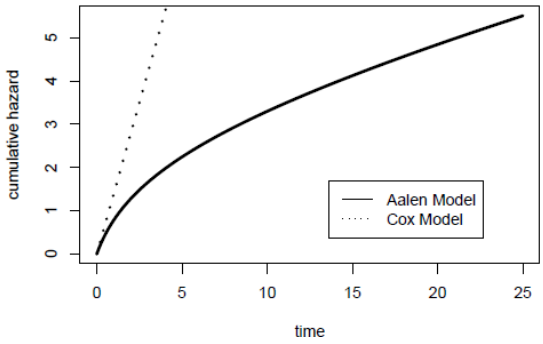


Figure 6. The cumulative hazard plotted from the estimated β_1 and the true cumulative hazard from the Aalen model

3. CONCLUSION

The main aim of this study is to investigate the performance of multiplicative hazards and additive hazards under the miss-specified models, in which the data-generating process from the Aalen additive models was analyzed by the Cox multiplicative hazards model and vice versa. To study their performances, the hazard ratio and survival ratio, which may be estimated semi- or non-parametrically from the data, were used. Generally, the Cox multiplicative hazards regression is good when the DGPs are multiplicative hazards models or time-independent additive hazards models, both in terms of hazard ratio or survival ratio. However, it is severely biased under time-independent additive hazard models. The Aalen additive hazards regression is good under time-independent or time-dependent additive hazards models, but severely biased in representing hazard ratio under the multiplicative hazards model. In the simulation study, several replications under the Aalen additive regression failed, suggesting this method is sometimes computationally problematic. The result of the simulation studies confirms the previous study, suggesting that each model does not dominate the other (Aalen et al., 2008; Martinussen & Scheike, 2006). Both models should be employed to have a more thorough survival analysis.

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