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Aalen's Additive, Cox Proportional Hazards and The Cox-Aalen Model: Application to Kidney Transplant Data

(Aditif Aalen, Bahaya Berkadaran Cox dan Model Cox-Aalen: Penggunaan ke atas Data Pemindahan Buah Pinggang)

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ABSTRACT

The Cox proportional hazards model is most widely used in survival analysis for modeling censored survival data. In this model, the effect of the covariates is assumed to act multiplicatively on the baseline hazard rate and the ratio of the hazards is constant over survival time. This is an important assumption and sometimes may not hold in some survival studies. The Cox model can lead to biased results when the proportionality assumption is not satisfied. In such a situation, the additive hazards regression models have been an alternative to proportional hazards models. The Aalen model allows for time-varying covariate effects. In some situations, some covariate effects may be constant but the others may not. In such cases, the Cox-Aalen model is a better alternative since it allows to combine both kinds of covariates in the same model. In this study the Cox proportional hazards model, Aalen's additive hazards model and the Cox-Aalen model have been considered. These models have been applied to kidney transplant data and the differences in estimates of the unknown parameters obtained by the Aalen's model, the Cox model and the Cox-Aalen model are investigated.

Keywords: Aalen's additive hazards model; Cox-Aalen model; Cox proportional hazards model; kidney transplant data; survival analysis

ABSTRAK

Model bahaya berkadaran Cox paling meluas digunakan dalam analisis kemandirian untuk pemodelan data tertapis kemandirian. Dalam model ini, kesan kovariat diandaikan bertindak secara berdaya darab atas garis dasar kadar bahaya dan nisbah bahaya adalah malar dari masa kemandirian. Ini adalah suatu andaian yang penting dan kadang-kala tidak benar dalam beberapa kajian kemandirian. Model Cox boleh membawa kepada keputusan yang pincang apabila andaian perkadaran tidak dipenuhi. Dalam keadaan sedemikian, model regresi bahaya aditif menjadi alternatif kepada model bahaya berkadaran. Model Aalen membenarkan kesan kovariat masa yang berbeza. Dalam sesetengah keadaan, beberapa kesan kovariat adalah malar tetapi yang lain tidak. Dalam situasi tersebut, model Cox-Aalen adalah alternatif yang lebih baik kerana ia membolehkan penggabungan kedua-dua jenis kovariat dalam model yang sama. Dalam kajian ini, model bahaya berkadaran Cox, model bahaya aditif Aalen dan model Cox-Aalen telah diambil kira. Model-model ini telah digunakan untuk data pemindahan buah pinggang dan perbezaan dalam anggaran parameter tidak diketahui yang diperoleh pada model Aalen, model Cox dan model Cox-Aalen telah dikaji.

Kata kunci: Analisis penakatan; data pemindahan buah pinggang; model bahaya berkadaran Cox; model bahaya aditif Aalen; model Cox-Aalen

INTRODUCTION

Life history studies collect information on events and other outcomes during people's lifetimes (Lawless 2013). Thus gender, age, family diagnostics, lifestyles typically could be important covariates that have an impact on the ssurvival time T. As will be discussed in more detail in example, we also observed some covariates have significant impacts on the lifetime of the transplanted kidneys.

In analyzing censored survival data it is important to ascertain the relationship between the survival time T and the covariates by a suitable hazards regression models. There are mainly two approaches to the modeling of covariate effects on survival time. The first approach is the classical linear regression approach. The second approach to modeling the effects of covariates on survival is to model the conditional hazard rate as a function of the covariates. There are two classes of models that are used. The first class is known as multiplicative hazards regression models and the second is known as additive hazards regression models.

In the multiplicative hazards regression models, the conditional hazard rate of an individual is a product of a baseline hazard rate and a non-negative function of the covariate. Let the random variable T denote the survival time of an individual and X is a vector of covariates. In the multiplicative hazards models, the conditional hazard function $\lambda(t \mid X)$ of a survival time T associated with covariates is defined as,

$$\lambda(t \mid X) = \lambda_0(t) r(X^T \beta),$$

where $\lambda_0(t)$ is the baseline hazard and it may have a specified parametric form or may be left as an arbitrary non-negative function. In the second part of the model, $r(X^T \beta)$ characterizes the structure of the hazard function and describes how the hazard function changes as a function of the covariates. Under these model, the ratio of the hazard functions for two individual are called hazard ratio and it depends only on the function $r(X^T \beta)$. In the multiplicative hazards models, the effect of the covariates act multiplicatively on the baseline hazard rate and the hazard for each covariate is assumed to be constant over time (Klein & Moeschberger 2003). This assumption may not be satisfied in some censored survival data set. In such situations, the additive hazards regression models are alternative to multiplicative hazards models. In the additive models, the covariates are assumed to act in an additive manner on an unspecified baseline hazard rate and conditional hazard function $\lambda(t \mid X)$ are given by,

$$\lambda(t \mid X) = \beta_0(t) + X_1\beta_1(t) + \ldots + X_p\beta_p(t),$$

where $\beta(t)$ is a $(p + 1 \times 1)$ vector of regression coefficients and X is a $(p \times 1)$ vector of covariates. The additive model is useful when the main interest is risk difference rather than relative risk and the model allows covariate effects to vary with time. Additive hazards model specifies a different aspect of the association between the survival time and covariates and is more appropriate than proportional hazards model in some applications. The model provides a simple and easy approach for adding flexibility into models (Cortese et al. 2010; Martinussen & Vansteelandt 2013).

Although the additive models allow the effects of the covariates to change over time, some covariate effects can be well described with constant relative risk. In this situation, the effects of covariates estimated by either additive or multiplicative model are not well and it is the best way to combine the additive and multiplicative models. These models that are called additive-multiplicative models are more flexible and useful models. For these models, some covariate effects have been described multiplicative manner whereas the other covariates have been described additive manner (Martinussen & Scheike 2006).

In this study, the Cox proportional hazards model which is the most popular model of multiplicative models, Aalen's additive hazards model which is one of the important additive models and Cox-Aalen model which is the more flexible model of additive-multiplicative model have been considered.

The survival time data are conveniently studied by using of counting process. Although the censoring is a major characteristic of survival data, censoring structure can easily insert into counting process methods. An important contribution to the counting processes and martingale theory formulation is given by Aalen (1993, 1989, 1980) and Aalen et al. (2008). The considered models are discussed in the context of counting processes and martingale theory. In the next section, the counting process approach to survival analysis is introduced and some definitions are given. After that Cox proportional hazards model, Aalen's additive model and Cox-Aalen model are summarized and these models have been applied to kidney transplant data, which measured transplanted kidney's lifetime. In last section, the results are discussed in connection of related models. The estimates of models have been obtained using R package.

Counting Process

A counting process $[N(t), t \geq 0]$ is a stochastic process that satisfies $N(t = 0) = 0$, $N(t) < \infty$ with probability one $N(t)$ right-continuous, non-decreasing with jumps of size one. $N(t)$, can be decomposed into two parts which is referred to as a compensator $\Lambda(t)$ and a martingale $M(t)$. The martingale part is thought of as an error term of the model,

$$N(t) = \Lambda(t) + M(t).$$

These two parts are also functions of time and they have stochastic structure. $\Lambda(t)$ is called also cumulative intensity process and defined by,

$$\Lambda(t) = \int_0^t \lambda(s)ds,$$

where intensity process $\lambda(t)$ is a predictable process and it is related to the risk process $Y(t)$. The risk process $Y(t)$ is a stochastic process which $Y(t)$ is a function of the number of individuals at risk at a given time. $Y(t)$ is a left-continuous, non-increasing step function with step of size one (Fleming & Harrington 1991).

The survival time data consist of observing the occurrence of events over time. These processes may be described by counting processes. Suppose we observed n i.i.d. (T_i, δ_i, X_i), where T_i is the event time of individual; δ_i is the indicator function which determined right censoring time ($\delta_i = 0$) or failure time ($\delta_i = 1$) of i'th individual; and X_i is a vector of covariates of i'th individual.

The function $N_i(t)$ is zero until the i'th individual's failure time and then jumps to one,

$$N_i(t) = I\,[T_i \leq t, \delta_i = 1].$$

Similarly the risk process fall down at both failure and censoring times, and is defined as,

$$Y_i(t) = I\,[T_i \geq t].$$

The process $N(t) = \sum_{i=1}^{n} N_i(t)$ and $Y(t) = \sum_{i=1}^{n} Y_i(t)$ are also a counting process. The chance of an event at time t, given history just prior t, is given by,

$$\Pr[t \leq T_i < t + dt, \delta_i = 1 \mid T_i \geq t] = \lambda(t)dt,$$

where $\lambda(t)$ is the hazard function. For a given counting process, $dN(t)$ is defined as the change in process $N(t)$

over a short time interval [t, t + dt). The expected number of failure in the time interval [t, t + dt), given history just prior t, is given by,

$$E[dN(t) \mid T_i \geq t] = Y(t)\lambda(t)dt,$$

where $Y(t)$ is the at risk indicator and $\lambda(t)$ is the hazard function. The cumulative intensity process can be defined as,

$$\Lambda(t) = \int_0^t Y(s)\lambda(s)ds.$$

COX PROPORTIONAL HAZARDS REGRESSION MODELS

The Cox proportional hazards model proposed by Cox (1972) is the most popular semi-parametric regression model and by far the most used statistical tool for censored survival data. The model is an extremely useful and powerful model, simple to fit and the results are easy to explain. The Cox model has great flexibility because of two reasons. Firstly, the exponential form of function of covariates assures non-negative rates and secondly, no assumptions are made for the baseline hazard, which makes it a generally applicable model. The Cox model is popular especially in settings where the covariates effects are estimated (Oakes 2013).

Andersen and Gill (1982) extended the Cox model to the counting processes framework. The model assumes that the intensity is of the form,

$$\lambda(t \mid X) = Y(t)\lambda_0(t)exp(X^T\beta),$$

where $\lambda_0(t)$ is a nonparametric baseline hazard function; β is a ($p\times1$) vector of regression coefficients; X is a ($p\times1$) vector of covariates and $Y(t)$ is an at risk indicator. The covariates are organized into a design matrix ($n\times p$), $X(t) = (Y_1(t)X_1, \ldots, Y_n(t)X_n)^T$, and the model can be written in differential form,

$$dN(t) = \lambda(t)dt + dM(t).$$

Statistical inference in the Cox model is based on maximum partial likelihood (Andersen & Gill 1982; Cox 1975). Let $T_1 < T_2 < \ldots$ denote the event time and $R_i = \{l \mid Y_l(T_i) = 1\}$ denote the risk set at time T_i. The partial likelihood is written in the form

$$L(\beta) = \prod_{i=1}^{n} \frac{\exp\left(X_i^T\beta\right)}{\sum_{l\in R_i}\exp\left(X_l^T\beta\right)}$$

and maximum likelihood estimator $\hat{\beta}$ is the value of β that maximizes $L(\beta)$.

The proportionality assumption of the model corresponds to assuming that the hazard functions are multiplicatively related to each other and their ratio is constant over time. This is an important assumption and it may not hold in some survival data where the impact of a covariate on hazards may change over time. When the proportional hazards assumption is violated there are several methods to overcome this problem (Champbell & Dean 2014). In some cases, it may be more convenient to use the model in which the effect of covariates has an additive measure rather than a relative measure.

THE AALEN'S ADDITIVE HAZARDS REGRESSION MODELS

Aalen's additive hazards model is a useful alternative to the Cox model. The model was first suggested by Aalen (1980). Aalen's model is non-parametric and values of regression coefficients are allowed to vary over time. The advantage of this model is that, being linear in covariates and changes in coefficient can easily be detected at each distinct survival time (Henderson & Milner 1991). In Aalen's additive hazards model, the conditional hazard function $\lambda(t \mid X)$ of a survival time T associated with covariates is defined as,

$$\lambda(t \mid X) = Y(t)X(t)^T\alpha(t),$$

where $Y(t)$ is the at risk indicator; $\alpha(t)$ is a ($p\times1$) vector of regression coefficients; $X(t)$ is a ($p\times1$) vector of covariates. The cumulative regression coefficients are easier to estimate than the regression coefficients themselves. Sometimes it is called cumulative risk function and is defined by,

$$A(t) = \int_0^t \alpha(s)ds.$$

The covariates are organized into a design matrix ($n\times p$), $X(t) = (Y_1(t)X_1(t), \ldots, Y_n(t)X_n(t))^T$, and it can be written,

$$dN(t) = \lambda(t)dt + dM(t) = X(t)dA(t) + dM(t).$$

The problem of estimation, testing and model fitting were discussed in Aalen (1993, 1989). Aalen introduced ordinary least square estimation of integrated coefficient and it is given by,

$$d\hat{A}(t) = (X(t)^TX(t))^{-1}X(t)^TdN(t),$$

where $X(t)$ has full rank. Accumulating the increments over the event times, it is obtained the estimator $\hat{A}(t)$ for the vector of cumulative regression function. Huffer and McKeague (1991) and McKeague (1988) have developed weighted least square estimator. Vansteelandt et al. (2014) showed that Aalen's least square estimator is unbiased when treatment is randomized.

The cumulative regression functions are plotted against time give a description of how the covariates influence the survival over time. The Aalen's plots are obtained by estimating the instantaneous contributions of covariates to the hazard function at each distinct survival time and estimates are obtained by summing up these contribution. The slope of plots indicates whether a specific covariate has a constant effect or a time-dependent effect. Positive

slopes occur when increasing the covariate increases the hazard; negative slopes occur when increasing the covariate decreases the hazard during periods. The Aalen model provides a graphical method to check the time dependence of covariate effect and also used to provide an informal assessment of the adequacy of proportional hazards assumption in the Cox model (Aalen 1993; Lim & Zhang 2009).

COX-AALEN HAZARDS REGRESSION MODELS

The additive and multiplicative models discussed above represent different relationships between the hazard function and the covariates and sometimes it will not be clear which model is suitable for a specific application. In this situation it is the best way to combine the models. These models may be combined several ways. Lin and Ying (1995, 1994), Martinussen and Scheike (2002), Scheike and Zhang (2003, 2002) suggested different models.

Cox-Aalen regression model proposed by Scheike and Zhang (2002) is more flexible model than the other additive-multiplicative models. This model based on an additive structure on the basis of multiplication model. In the Cox-Aalen model, the covariates are partitioned into two parts, some covariate effects work additively on the intensity and other covariate effects to act multiplicatively. It is a more flexible and potentially useful model which is defined by,

$$\lambda(t \mid x) = Y(t)[X(t)^T \alpha(t)]exp(Z(t)^T\beta)$$

where $Y(t)$ is the at risk indicator; $(X(t), Z(t))$ is a $(p+q\times1)$ vector of covariates; $\alpha(t)$ is a $(p\times1)$ vector of time-varying regression coefficients and β is a $(q\times1)$vector of relative risk regression coefficients. The model allows some covariate effects to be additive nonparametric and time-varying $(X(t))$ and other covariates $(Z(t))$ to have constant multiplicative effects. The model provides a simple way of including time-varying covariate effects.

For this model estimation procedure consist of two steps and the key quantities are $A(t) = \int_0^t \alpha(s)ds$ and β. Estimation is based on solving the score equations of the model to obtain $\hat{\beta}$. Estimate $dA(t)$ by weighted least squares principle by,

$$d\hat{A}(t) = \bar{Y}(\hat{\beta}, t)dN(t).$$

The weights depend on β and are equivalent to maximum likelihood weights. One advantage of these weights is reduced to the score for the partial likelihood in the case of the Cox model. The derived estimator is efficient and has large sample properties. For a detailed description of the estimation procedures is given Scheike and Zhang (2002).

EXAMPLE

The data have been collected from register of patients at Başkent University Hospital between January 1, 1990 and November 30, 1992 (Başar 1993). In this period of time, 156 patients were operated with kidney transplantation and the lifetimes of the transplanted kidney are measured in days, until the kidney's death or censoring occurs. Thirty-four failures had been observed in the period of that study. Several covariates which have impact on the kidney's lifetime have been collected and six of them are included in this study. These are gender, patient age, donor age, verapamil, donor type and cold ischemic time. Fifty four patients were given verapamil after the operation and the others were not given; and have been observed 4 and 30 failure, respectively. Donor type of 43 patients has been cadaveric and the others have been live and have been observed 16 and 18 failure, respectively.

Firstly the Cox model is applied to the data and the results are given in Table 1. Three covariates turned to be significant. These are donor age, verapamil (0=not given, 1=given) and donor type (0=live, 1=cadaver). The exponential coefficients or the relative risks are interpretable as multiplicative effects on the hazard function. The risk for a patient with cadaver donor is 3.99 times greater than the risk for a patient with live donor while the other covariates are constant. The risk for a patient that is given verapamil is 0.204 times smaller than the risk for a patient that is not given. The overall fit of the Cox model is investigated by the likelihood-ratio, Wald and score tests. These tests are statistically very highly significant with p-values 0.0002, 0.0004, 0.0002, respectively. When three significant covariates are included in the model, the relative risks for three covariates are almost same. The overall test of the model is also statistically very highly significant for the likelihood-ratio, Wald and score tests.

When the proportional hazards assumption is investigated by examining scaled Schoenfeld residuals

TABLE 1. Estimation of regression coefficient, relative risk, standard error, z and p-value from the Cox model

Covariate	Coeff.	R.Risk	SE	z	p-value
Gender	0.35391	1.425	0.4079	0.868	0.3856
Patient age	-0.00404	0.996	0.0154	-0.262	0.7933
Donor age	0.03294	1.033	0.0124	2.654	0.0079
Verapamil	-1.58763	0.204	0.5492	-2.891	0.0038
Donor type	1.38404	3.991	0.3645	3.797	0.0001
Cold I. time	0.01608	1.016	0.0118	1.362	0.1732

and Grambsch and Therneau test (Therneau & Grambsch 2000), proportionality of covariate effects is satisfied for donor age and verapamil but there is a little evidence for donor type, resulting in p-value 0.095. The global test indicated that there is a little evidence departure from the standard Cox model (p-value = 0.104). The test results are given in Table 2. The Cox-Snell residuals are used for assessing the fit of the Cox model. If a model fits well to the data, the plot of the residuals should follow the straight line with an intercept zero and slope one. Figure 1 shows a plot of the Cox-Snell residual versus the estimated cumulative hazards of residuals. The plot is suggested that the model is not fit exactly.

TABLE 2. Test of proportional hazards assumption

	Rho	Chisq	p-value
Donor age	-0.125	0.632	0.4266
Verapamil	0.201	1.430	0.2318
Donor type	0.285	2.784	0.0952
GLOBAL	–	6.161	0.1040

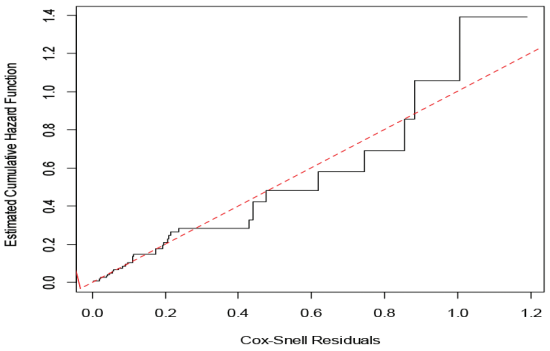

FIGURE 1. Cox-Snell residual plot

A simple graphical test of the proportionality assumption can be made by looking at the hazard functions curves. When the hazard functions for the levels of covariate are crossed, the proportionality assumption is violated. The hazard function curves for donor type are given in Figure 2. It is clear that the impact of donor type

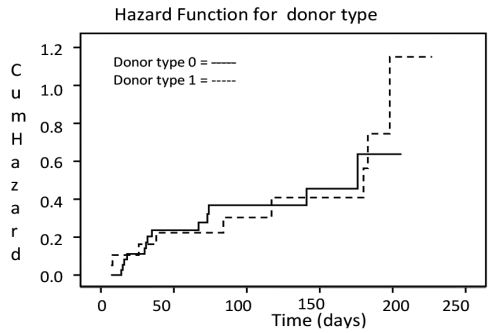

FIGURE 2. Cumulative hazard functions for donor type for only the first 200 days

on hazard is non-proportional for the first 200 days. A case like this has not been observed for the verapamil.

The plot of the scaled Schoenfeld residuals is useful diagnostic tools. A non-zero slope is an indication of a violation of the proportional hazard assumption. The proportional hazards assumption is satisfied for donor age and verapamil but it seems there is not exactly satisfied for donor type. The graphs of the Schoenfeld residuals are presented in Figure 3.

Secondly, the Aalen's additive model is fitted to the data and with the same covariates, namely donor age, verapamil and donor type, turned to be statistically significant at the level of $\alpha = 0.05$. The other covariates have no effects on the kidney's lifetime. The overall test of Aalen's additive model has p-value = 0.013. The plots of estimated cumulative regression functions are obtained to see the effect of covariate over time. The estimated cumulative regression coefficients for covariates with 95% pointwise confidence intervals are shown in Figure 4.

The slope of an estimated cumulative regression function is positive when covariate increases and this fact correspond to an increasing hazard rate. On the other hand, if the slope is negative while the covariate increases, then this fact points to a decreasing hazard rate. If the slope of cumulative sums approaches zero then a covariate has no effect on the hazard. Figure 4 indicates that the estimates of cumulative regression function for gender patient age and cold ischemic time are constant at a level of zero and hence omitted. The estimated cumulative regression

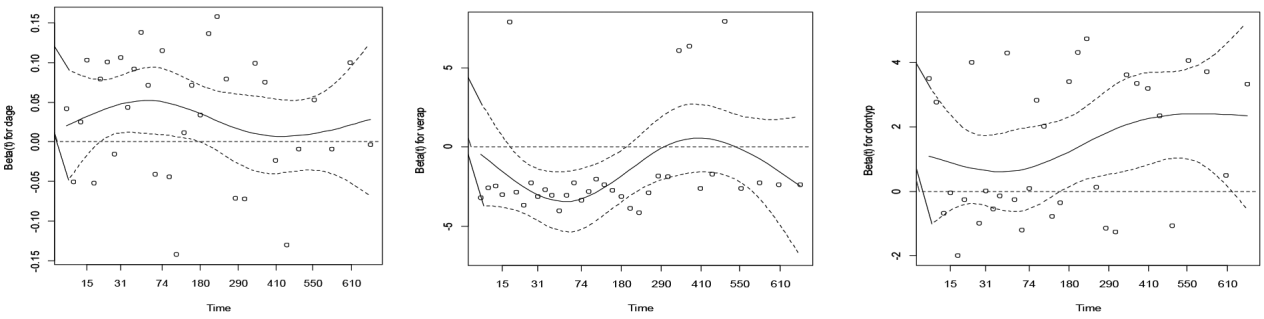

FIGURE 3. Smoothed scaled Schoenfeld residual plots with 95% pointwise confidence intervals for donor age, verapamil and donor type

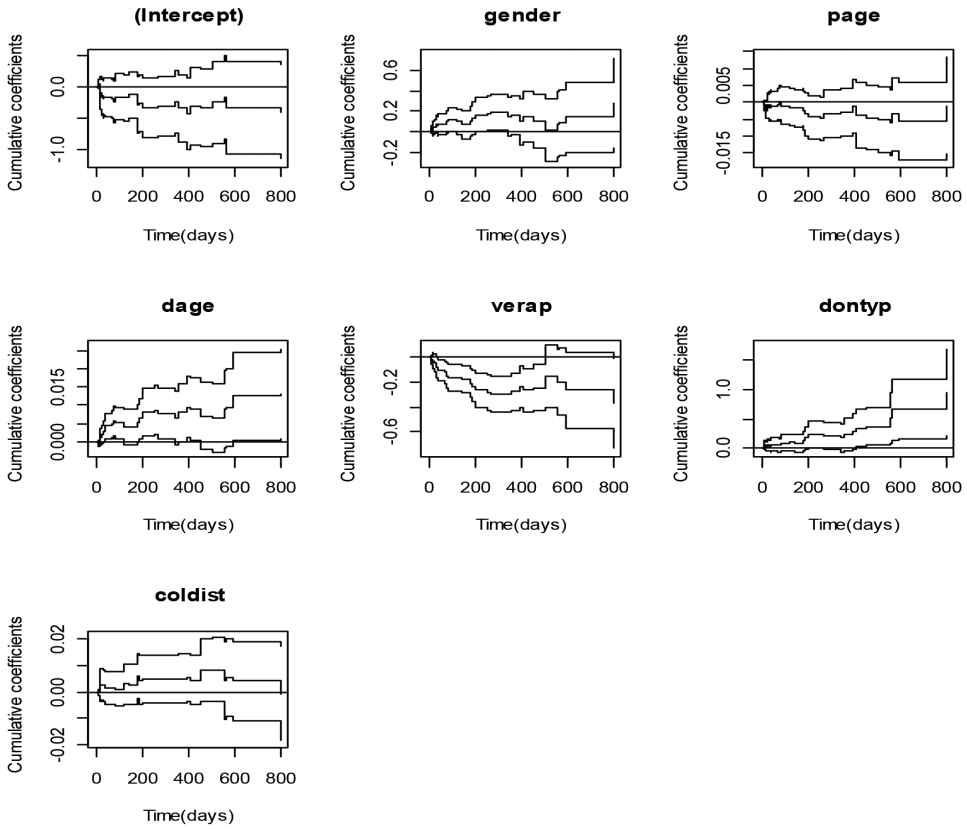

FIGURE 4. Estimated cumulative regression functions with 95% pointwise confidence intervals based on Aalen's additive model

function plot for donor age is increased rapidly only over the first few days and after this it is increased very slowly and linearly. The regression function plot for verapamil has a significant and fairly constant decreasing effect during about the first 400 days and after this point its effect was reduced. Few failures were observed when patients receiving verapamil and therefore this plot should be interpreted with caution. The slope of estimated cumulative coefficient for donor type is almost zero during the first 200 days and then it was increased. It seems that the donor type has a time-varying effect and the risk increases as the time goes on.

Thirdly the Cox-Aalen model is fitted to the data. The Cox and Aalen model show that the effects of donor age and verapamil were well described by constant coefficients. Therefore, these effects have been included in the multiplicative part of the Cox-Aalen model. When donor type known to have time-varying effect, it was included in the additive part of the model, thus allowing it to be time-varying. The results of multiplicative part of the Cox-Aalen model are given in Table 3. The multiplicative part of the model suggested that the relative risk of donor age is 1.037 and the relative risk of verapamil is 0.219. These results are similar to the Cox model. In order to evaluate the goodness of fit of the covariates included in the multiplicative part of the Cox-Aalen model, it is considered cumulative score processes (Scheike & Zhang 2003). The score processes to test proportionality for donor age and verapamil are given in Figure 5 with 100 random realizations under the null hypothesis of constant multiplicative effects. Figure 5 indicates that constant multiplicative effect is satisfied for these covariates. In the additive part of the Cox-Aalen model, the estimated cumulative regression coefficient of donor type with 95% pointwise confidence intervals is shown in Figure 6. The donor type seems to be an insignificant factor in the initial stage of 200 days. However in the following days there appear to be a strong positive effect on the kidney lifetime. We therefore concluded that the Cox-Aalen model captured better data characteristic.

TABLE 3. Estimation of regression coefficient, relative risk, standard error, z and *p*-value for multiplicative part of Cox-Aalen model

Covariate	Coeff.	R.Risk	SE	z	*p-value*
Donor age	0.0359	1.037	0.0138	2.61	0.0091
Verapamil	-1.5200	0.219	0.5300	-2.87	0.0041

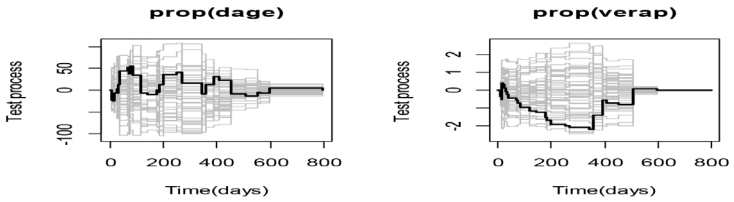

FIGURE 5. Score test for constant multiplicative effect for donor age and verapamil in Cox-Aalen model with 100 randomly chosen score processes under the null of a constant multiplicative effect

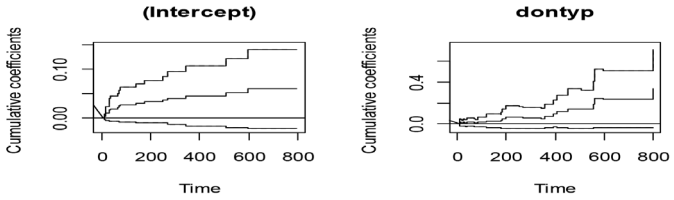

FIGURE 6. Estimated cumulative regression functions for additive part of Cox-Aalen model with 95% pointwise confidence intervals

CONCLUSION

In this study the Cox proportional hazards model and the Aalen's additive model and Cox-Aalen model were applied to a kidney transplant data. The Cox and the Aalen's model resulted in the same covariates which have significant effect on the hazard function. However, although they agree on which covariates are effective, it is not obvious to distinguish whether they are additively or multiplicatively effective. The covariates of the Cox model have multiplicative effects on unknown baseline hazard, but the covariates of the Aalen's model have additive effects. In other words, the relationship between the covariates and survival time is different at the models above. The Aalen model allows for time-varying covariate effects, while the Cox model allows only a common time-dependence through the baseline.

The Aalen's model provides a graphical method to check on a time dependence of covariate effects and it may be used for the significance test of Cox's model. Although the Aalen's model provides more details in terms of all covariate effects over time, the simple interpretation of effects is not possible. The Cox and the Aalen's model provide different aspects of the relationship between risk factors and time to failure and may be used to complement each other. In this sense, two models are not alternatives to each other and together provide different summary measures and a better understanding of data. The combined Cox-Aalen model can handle the time-varying effects more easily. This model has an advantage that allows to include both the additive and multiplicative covariate effects in the same model. Thus the Cox-Aalen model would provide a better prediction for the cumulative incidence probabilities. The model is more flexible and has a wider application for survival data.

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