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The Use of Cox and Piecewise Exponential Models in the Determination of Renal Failure

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Abstract. Cox Proportional hazards model has played a great role in epidemiological and clinical researches in examining the influence of covariates on hazard distributions when no specification of the baseline hazard is made. It is a robust model irrespective of the nature of baseline hazard distribution. However, it is less popular when it is of primary interest to estimate the hazard function. The purpose of this study is to fit and compare piecewise exponential and Cox models using renal failure data. For the piecewise exponential model, the hospital admission duration of the patients was split into various non-overlapping time intervals such that the hazard rates were assumed to be constant within each interval but not necessarily constant across the entire time duration. The results were compared with the standard Cox proportional hazards model. It was found under both models that age of the patients, diagnosis (categorized as chronic or acute), and blood pressure (systolic and diastolic) significantly influenced mortality from renal failure among the patients under study. However, based on AIC, piecewise exponential model showed superiority over Cox proportional hazards model and improved as the length of the intervals increased.

Keywords: Cox model, AIC, time to event, piecewise exponential model.

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1. Introduction

Renal disease, also known as Kidney disease is a common disease worldwide and is associated with high rates of morbidity and mortality (Goldberg and Krause, 2016). A number of studies have been carried out on kidney disease in the literature. Goldberg and Krause (2016) discussed several aspects of the relationship between gender and kidney disease, and it was shown that gender had an important influence on several aspects of the disease. Neugarten *et al.* (2000) performed a meta-analysis using studies that met defined criteria to evaluate the effect of gender on the progression of non-diabetic chronic renal disease. The results indicated that men with chronic renal disease of various etiologies showed a more rapid decline in renal function with time than do women.

Khalil *et al.* (2018) applied logistic regression analysis to examine factors associated with increased mortality of patients with acute kidney disease. Only a few studies have been carried out on kidney disease using survival analysis approach. The current study therefore aims to apply Cox proportional hazards and Piecewise exponential models to data on renal failures among patients and examines the factors that influence its mortality.

The popular Cox proportional hazards model proposed by Cox (1972) is a semiparametric survival model and it has intensive applications in the fields of social, medical, behavioral and public health sciences (Pourhoseingholi *et al.,* 2007; Samawi *et al.,* 2020). It is so widely used by researchers because of its few assumptions (Pourhoseingholi et al., 2007). The model is based on assumption that the hazards be constant across the entire time line. Some of the recent Cox related studies include: Zucker *et al.* (2018) developed a new method for covariate error correction in the Cox survival regression model, and the method was applied to data from the Health Professionals Follow-Up Study (HPFS) on the effect of diet on incidence of diabetes. Amico *et al.* (2019) applied the single-index/Cox mixture cure model to breast cancer data set

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using maximum likelihood method of estimation. It was found that the model compared favourably with the model that assumed the mixing probabilities in a logistic model framework. Yang *et al.* (2020) proposed G-estimation and artificial censoring for estimating the model parameters in the presence of time-dependent confounding and administrative censoring. By using the semiparametric efficiency theory, they derived the first semiparametric doubly robust estimators, which are consistent when the model for the treatment process or the failure time model, but not necessarily both, is correctly specified. However, the appropriateness of the Cox proportional hazards model is limited if proportionality assumption is not met. Another drawback of Cox model is its difficulty in computing the hazard rate across the interval.

Piece-wise exponential model (PEM), according to (Breslow, 1974), is an extension of the exponential proportional hazards model used in modelling time-to-event data. It appears to be more flexible than the popular standard Cox model in matters of hypothesis testing. Another advantage of PEM over Cox model is that, it is possible to compute the hazard rate within each interval. Given series of time intervals, the baseline hazards are known to be constant within each interval, but not necessarily constant across the different intervals defined by the change-points (Allison, 2010). The model has been widely used for the analysis of time-to-event data in different contexts, including reliability engineering (Kim and Proschan, 1991; Gamerman, 1994), clinical situations such as heart transplant data (Aitkin *et al.,* 1983), hospital mortality rate data (Clark and Ryan, 2002), economics (Bastos and Gamerman, 2006) and cancer studies including leukemia (Breslow, 1974). Piecewise exponential model with random time grid was proposed by Demarqui, *et al.* (2012). The study considered a class of correlated Gamma prior distributions for the failure rates.

The model has been recognized as a simple and flexible tool in survival analysis. For example, Berry *et al.* (2004) built a piecewise baseline hazard function in their Bayesian model, allowing the hazard rate to vary in each of the follow-up years. Hoos *et al.* (2010) emphasized that piecewise exponential models are valuable in cancer immunotherapy trials. Edwards and Bartlett (2005) identified a sudden reduction in the mortality rates for prostate cancer, which implied that a model with piecewise constant hazard assumption would be particularly useful for interpreting cancer survival and facilitate treatments and diagnoses.

Goodman *et al.* (2011) proposed the detection of multiple change-points in piecewise constant hazard function using a Wald-type test based on maximum likelihood estimates (MLE) and a forward selection sequential testing procedure. The method allowed them to estimate not only the number of change points in the hazard function but where those changes occurred. They then tested for change points in prostate cancer mortality rates using the NCI surveillance, epidemiology, and end results dataset. The major challenge in using the piecewise exponential model is to identify significant change-points in the failure rate over time. A number of articles have been published on detecting the change-points with piecewise constant exponential models. Demarqui *et al.* (2008) introduced a full Bayesian approach for the piecewise exponential model in which the grid of time-points (and, consequently, the endpoints and the number of intervals) is random. They estimated the failure rates using the proposed procedure and compare the results with the non-parametric piecewise exponential estimates. Cai *et al.* (2017) proposed an alternative approach based the linear approximation to study the change-point problem in the piecewise linear failure rate function. They proposed the test statistic based on the modified information criterion and the consistency as well as the asymptotic null distribution of the test were established. For other articles published in this direction, see Nguyen et al. (1984), Hawkins (2001), Dupuy(2009), Qian and Zhang (2014).

2. Material and methods

2.1 *The survival and hazard functions*

Suppose that T is a continuous random variable representing the length of time until the occurrence of failure event and we define the cumulative distribution function $F(t)$ as the probability that an individual experiences the event before or at time t, expressed as $F(t) = Pr(T \leq t)$, then the survival function denoted $S(t)$, is the probability that an individual survives longer than t and is expressed as $S(t) = Pr(T > t)$, where $S(t) = 1 - F(t)$.

The hazard function describes the conditional probability that failure event occurs to an individual in the interval $(t, t + dt)$, given survival up to time t and it is expressed as

$$\alpha(t) = \lim_{dt \to 0} Pr \left\{ \frac{t \leq T < t + dt \backslash T \geq t}{dt} \right\} \tag{1}$$

2.2 *Cox proportional hazard model*

Suppose that $\alpha_i(t, Z_i)$ is the hazard function of the time-to-failure T given the covariate Z_i, then the Cox (1972) proportional hazards model is given as.

$$\alpha_i(t, Z_i) = \alpha(t)\exp(Z_i^{'}\gamma) \tag{2}$$

where $\alpha(t)$ is an arbitrary baseline hazard which is independent of the covariates, but depends on time t and γ is a vector of parameters. If proportional hazards assumption is true, then for any $Z(.)$ and $Z_0(.)$, the hazard ratio can be written as

$$HR = \frac{\alpha(t)\exp(Z_i^{'}\gamma)}{\alpha(t)\exp(Z_{i0}^{'}\gamma)} = k \tag{3}$$

The expression in (3) implies that the hazard ratio of two individuals with covariate vectors $Z(.)$ and $Z_0(.)$ is constant over the entire duration with constant term k. (Kleinbaum and Klein, 2012)

2.3 *Parameter estimation of Cox model*

Cox model utilizes partial likelihood method in which estimates for the parameter of interest γ can be found by maximizing the partial likelihood $L(\gamma)$. Suppose that the censoring indicator for individual i, $i = 1, 2, 3, \ldots, n$ with observed time t_i and covariate vector Z_i, is defined by

$$d_i = \begin{cases} 1, & \text{if the } i^{th} \text{ individual } dies \text{ at time } t_i\ , \\ 0, & \text{if the individual } is \text{ censored at time } t_i \end{cases}$$

then the partial likelihood can be given (Cox, 1972; 1975)

$$L(\gamma) = \prod_{i=1}^{n}\left[\frac{\exp(Z_i^{'}\gamma)}{\sum_{s\in R_i}\exp(Z_s^{'}\gamma)}\right]^{d_i} \tag{4}$$

2.4 *Piecewise exponential model (PEM)*

The basic idea underlying the PEM is to divide the duration time into q non-overlapping intervals, $t_0 < t_1 < \cdots < t_q$ and define the $k-th$ interval as $[t_{k-1}, t_k)$, extending from the $(k-1)-th$ boundary to the $k-th$ and including the former but not the latter. Let t_{ik} denote the time lived by the $i-th$ individual in the $k-th$ interval, that is, between τ_{k-1} and τ_k. If the individual lived beyond the end of the interval, so that $t_i > \tau_k$, then the time lived in the interval equals the width of the interval and $t_{ik} = \tau_k - \tau_{k-1}$. If the individual died or was censored in the interval, i.e. if $\tau_{k-1} < t_i < \tau_k$, then the time lived in the interval is $t_{ik} = t_i - \tau_{k-1}$, which is the difference between the total time lived and the lower boundary of the interval. We only consider intervals actually visited, but obviously the time lived in an interval would be zero if the individual had died before the start of the interval and $t_i < \tau_{k-1}$. The baseline hazard is then assumed to be constant within each interval, where the baseline hazard within the k^{th} interval can be written as

$$\alpha(t) = \alpha_k, \qquad t \in [\tau_{k-1}, \tau_k) \tag{5}$$

Consequently, hazard rates within each interval (Goodman *et al.,* 2011)will be expressed as follows:

$$\alpha(t; \alpha_k, \tau_1, \tau_2) = \begin{cases} \alpha_1, & 0 \le t < \tau_1 \\ \alpha_2, & \tau_1 \le t < \tau_2 \\ \ldots & \ldots\ldots\ldots\ldots \\ \alpha_k, & t > \tau_k \end{cases} \tag{6}$$

Since the hazard is assumed to be piece-wise constant, the corresponding survival function is also piece-wise exponential (Friedman, 1978), and this is given as

$$S(t;\alpha_k,\tau_1,\tau_2)=\begin{cases}\exp(-\alpha_1 t), & 0\le t<\tau_1\\ \exp(-\alpha_1\tau_1-\alpha_2(t-\tau_1)), & \tau_1\le t<\tau_2\\ \exp(-\alpha_1\tau_1-\alpha_2(t-\tau_1)-\alpha_3(t-\tau_2)), & t>\tau_2\end{cases} \tag{7}$$

The hazards can be obtained simultaneously along with the estimates of the regression parameters which express the effects of the covariates on the hazards. If we consider fitting the proportional hazards model of the usual form given in (2), then under relatively mild assumption that the baseline hazard $\alpha_0(t)=\alpha_k$ is piece-wise constant, the proportional hazards model in the context of (5) and (6), given the covariates Z_i can be given as

$$\alpha_{ik}=\alpha_k\exp(Z_i^{'}\gamma) \tag{8}$$

where α_{ik} is the hazard corresponding to individual i in interval k, α_k is the baseline hazard for interval k, and $\exp(Z_i^{'}\gamma)$ is the hazard ratio for an individual with covariate vector Z_i in the interval.

2.5 *Parameter estimation of piecewise exponential model*

A discussion on the likelihood function is presented in Friedman (1982). Maximum likelihood estimates of the underlying hazards rates under the piecewise exponential model can be obtained simultaneously with the parameter estimates. After some simple calculation, Holford (1980), Laird and Oliver (1981) noted that the piecewise exponential model was equivalent to a certain Poisson regression model.

Suppose that the censoring indicator is defined as $d_{ik}=1$ if subject i is observed to fail in interval k and $d_{ik}=0$ if the subject is censored. Suppose we define

$$y_{ik}=\begin{cases}1, & \text{if } t_i\in[t_{k-1},t_k),\ d_{ik}=1,\\ 0, & \text{otherwise}\end{cases} \tag{9}$$

and

$$\mu_{ik}=\begin{cases}t_i-t_k, & t_k<t_i,\\ t_k-t_{k-1}, & t_{k-1}<t_i\le t_k,\\ 0, & t_i\le t_{k-1}\end{cases} \tag{10}$$

where y_{ik} is a Poisson response variable and $\mu_{ik}^{'}=\log\mu_{ik}$ is an offset term, then the likelihood construction for subject i in the interval k of PEM model is proportional to Poisson likelihood with response y_{ik} with predictor $\eta_{ik}=Z_i^{'}\gamma$ and offset term $\mu_{ik}^{'}$.

2.6 *Model comparison*

A common criterion for model comparison is the Akaike Information Criterion (AIC) (Akaike, 1974), which is expressed as

$$AIC=-2\ln L(\hat{\gamma})+2p \tag{11}$$

where $L(\hat{\gamma})$ is the likelihood of the estimated model, p denotes the number of estimated parameters and n is the number of observations. A model with smaller AIC value is the preferred model for the data.

3. Results

As an illustration, we applied the proposed methods to renal failure data. The data were collected from the Renal Care Centre, University of Ilorin Teaching Hospital. Survival time was the length of time (in days) stayed in the hospital before death. The covariates collected included the sex of the patients, age on admission, occupation, diagnosis of the disease and blood pressure (systolic and diastolic). Kaplan-Meier estimates of survival probabilities were computed and the associated curves were plotted for the dichotomous or dichotomized covariates. Also the log-rank test of equality of survival probabilities $S_1(t) = S_2(t)$ were carried out. For the study, the following dichotomous covariates were defined. sex: 1 for male and 2 for female (reference), age: 1 for less than 40 years (reference) and 2 for 40 years or older, diagnosis: 1 for chronic renal failure and 2 for acute renal failure (reference), occupation: 1 for government/business and 2 for others (reference), systolic BP: 1 for greater than 120 and 2 for 120 or less (reference) and for diastolic BP: 1 for greater than 80 and 2 for 80 or less (reference). The minimum survival time was 1 day and the maximum was 103 days. The results of log-rank test at 5 per cent level of significance are summarized in Table 1. As observed from the table, the difference between the survival probabilities of male and female patients was not significant.

Table 1: Results of log-rank test of equality of survival probabilities at 5 per cent level of significance

Covariates	Chi-square	p-value
Sex	0.16	0.3856
Age	3.02	0.0001**
Diagnosis	7.71	0.0055 **
Occupation	2.62	0.0158 **
Systolic	0.1	0.8000
Diastolic	0.7	0.4000

However the Kaplan-Meier curve in Figure 1 (a) revealed that male patients had a slightly higher probability of survival than their female counterparts, with median survival times of 20 days and 18 days respectively. The results of the log-rank test also revealed that there was a significant difference between the survival experiences of patients aged less than 40 years and those 40 years or older $(p < 0.0001)$, and as observed in Figure 1(b), patients less than 40 years of age had higher survival probability than those aged 40 years or older, with median survival times of 19 years and 14 days respectively. Also, patients diagnosed with chronic renal failure had significantly higher survival experience, with median survival time of 22 days compared to their counterparts who were diagnosed with acute renal failure, having median survival time of 13 days. The median survival times for patients who were government workers was 25 days, with a significantly higher survival experience than those in other occupations, having median survival time of 17 days. The median survival times for patient with systolic BP of 120 or less and those with BP greater than 120 were the same (19 days). However the survival probability was slightly higher in favour of patients with BP 120 or less. The survival probabilities of patients had similar pattern for diastolic BP, with median survival time of 20 days for patients with diastolic BP less or equal to 80 and 16 days for patients having diastolic BP greater than 80.

3.1 *Cox proportional hazards model*

The results of Cox proportional hazards models were presented in Table 2, showing the estimated coefficients, standard errors and the p-values. As observed, age, diagnosis, systolic and diastolic blood pressures were significant predictors of hazards of renal failure mortality at 5 percent level of significance. Increased age of the patients increased the hazards, patients age 40 years or more were 16 percent more likely to die from renal failure compared to those less than 40 years of age. Female patients were 15 percent less likely to die from renal failure relative to the male patients. Patients above normal systolic and diastolic blood pressures had higher risk of mortality due to kidney failure than those within the normal range.

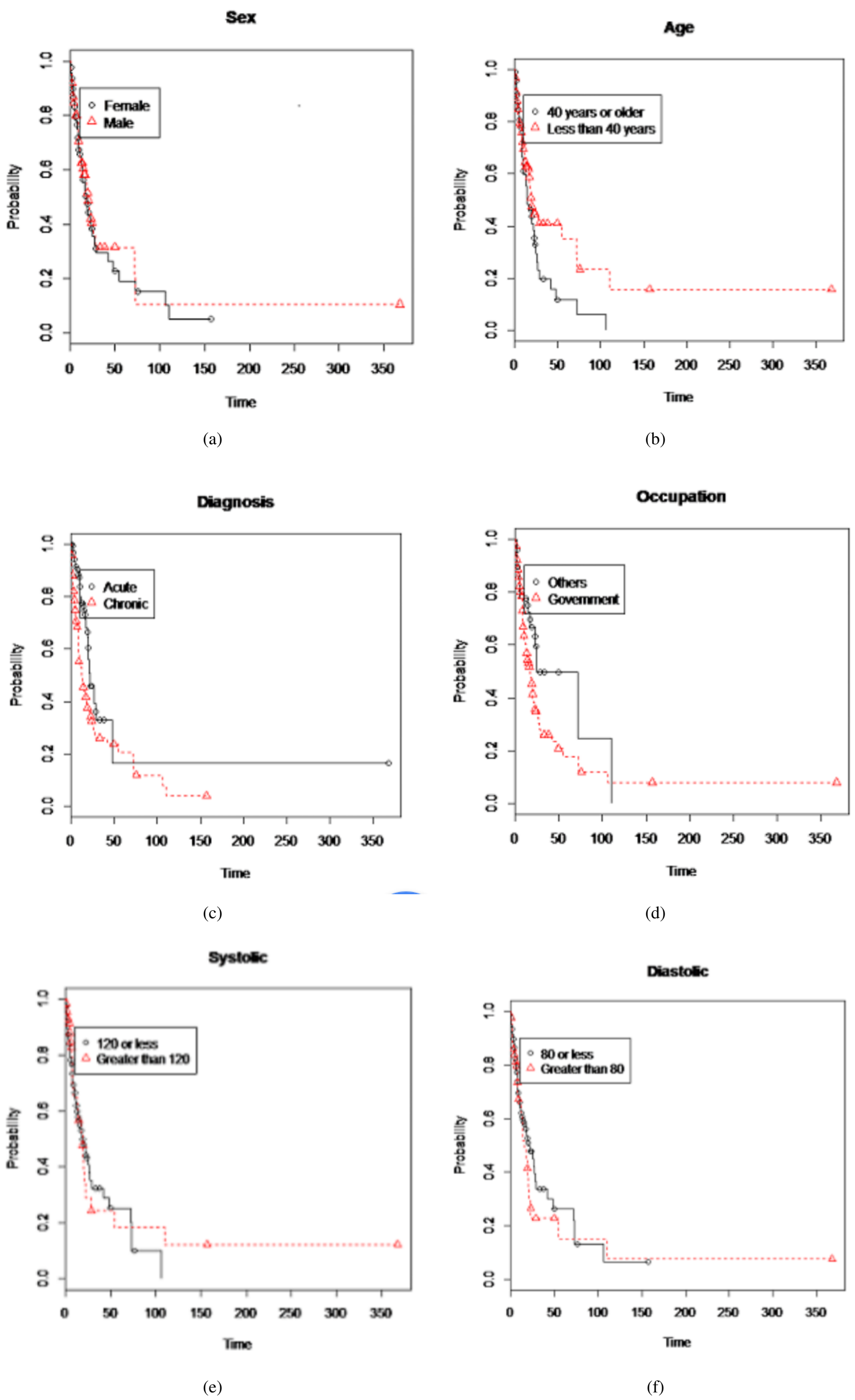

Figure 1: Kaplan Meier-curves: (a) sex (b) age (c) diagnosis (d) occupation (e) systolic (f) diastolic.

3.2 *Piecewise exponential model*

The whole follow-up period was broken up into 15 intervals of length 7 days each and the hazard was assumed to be constant within each interval. A new dataset was created with multiple records for each person. The time variable was defined as the length of time from the start of the interval until death. The 7-day interval piece-wise exponential model was then fitted to the data. As observed, the model included 22 parameters: 1 intercept and 21 in the linear predictor (15 hazard parameters for the baseline hazard function and 6 for the regression coefficients).

The estimated hazard rate for the i^{th} person in the kth interval from the PEM with 7-day intervals was calculated from equation (8), where $k_1, k_2, \ldots, k_{15}$ are indicators for the intervals. For example, when k_1, is equal to 1 and $k_2, \ldots, k_{15}$ are set to 0, we could obtain the hazard rate estimate for the second interval

Table 2: Cox-proportional hazard model for renal failure patients

Covariate	Coefficient Beta	Hazard Ratio	Std. Error	p-value
Age				
$<$ 40 years	0	1.000		
$\geq$ 40 years	0.145	1.156	0.306	0.0480
Sex				
Female	0	1.000		
Male	-0.168	0.845	0.245	0.8190
Occupation				
Others	0	1.000		
Government	0.044	1.045	0.082	0.5888
Diagnosis				
Acute	0	1.000		
Chronic	0.826	2.284	0.257	0.0013**
Systolic BP				
$\leq$ 120	0	1.000		
$>$ 120	0.101	1.106	0.006	0.0040**
Diastolic BP				
$\leq$80	0	1.000		
$>$ 80	0.115	1.122	0.011	0.0120**

($7 - 14^{th}$ day), which is the seventh day to the fourteenth day. The complete results of PEM are shown in Table 3.

As observed, the factor effects of diagnosis, systolic and diastolic blood pressures were significant at 5 percent similar to Cox model. The hazard ratio of diagnosis is $\exp(0.8717) = 2.391$ $(p - value < 0.0001)$, indicating that the risk of dying by patients diagnosed with chronic renal failure was about 2.4 times higher compared to those diagnosed with acute renal failure. Also, both systolic and diastolic blood pressures increased the risk of death from renal failure with relative risks of $\exp(0.712) = 2.0380$ $(p - value = 0.0008)$ and $\exp(0.110) = 1.1162$ $(p - value = 0.0002)$ respectively.

The 15-interval piecewise exponential hazard rate can generally be expressed as

$$\begin{aligned}\lambda(t) &= \exp(-5.260 + 0.110j_1 + 0.141j_2 + 0.008j_3 - 1.589j_4 - 1.488j_5 - 1.353j_6 \\ &- 1.130j_7 - 15.890j_8 - 15.890j_9 + 0.351j_{10} - 0.334j_{11} - 0.195j_{12} - 15.823j_{13} \\ &- 15.823j_{14} - 1.084j_{15}) \times \exp(0.006age - 0.024sex + 0.047occupation \\ &+ 0.872diagnosis + 0.007BPU + 0.001BPL) \qquad (12)\end{aligned}$$

In computing the hazard rate within each interval, using the formula in (12) above, the hazard rate for a 42-year-old, male govt-employed/self- employed with diastolic blood pressure of 80 and systolic blood pressure of 120, diagnosed of chronic renal failure in the first time interval ($0 - 7^{th}$ day) and tenth time interval ($70 - 77^{th}$ day) are computed as follows.

3.2.1 First time interval ($0 - 7^{th}$ day)

$$\begin{aligned}\lambda_1 &= \exp(-5.260 + 0.110j_1) \times \exp(0.006age - 0.024sex + 0.047occupation \\ &+ 0.872diagnosis + 0.007BPU - 0.001BPL) \\ &= \exp(-5.260 + 0.110 * 1) \times \exp(0.006 * 42 - 0.024 * 1 + 0.047 * 1 + 0.872 * 1 \\ &+ 0.007 * 120 + 0.001 * 80) = 0.046 \qquad (13)\end{aligned}$$

Table 3: Piece-wise exponential model for renal failure data with 7-day interval

Covariate	Estimate	Std. Error	z value	p-value
(Intercept)	-5.260	0.986	-5.33	$<$ 0.0001**
j_1	0.110	0.291	0.381	0.7028
j_2	0.141	0.334	0.420	0.6741
j_3	0.008	0.422	0.020	0.9840
j_4	-1.589	1.018	-1.562	0.1184
j_5	-1.488	1.019	-1.461	0.1439
j_6	-1.353	1.018	-1.329	0.1839
j_7	-1.130	1.021	-1.107	0.2670
j_8	-15.890	1.019	-0.016	0.9875
j_9	-15.890	1.019	-0.016	0.9875
j_{10}	0.351	0.610	0.575	0.5651
j_{11}	-0.334	1.023	-0.327	0.7439
j_{12}	-0.195	1.024	-0.191	0.8483
j_{13}	-15.823	1.551	-0.010	0.9918
j_{14}	-15.823	1.551	-0.010	0.9918
j_{15}	-1.084	0.762	-1.422	0.1550
Age	0.006	0.007	0.701	0.4835
Sex	-0.024	0.246	-0.096	0.9238
Occupation	0.047	0.083	0.564	0.5724
Diagnosis	0.872	0.258	3.369	<0.0001 **
Systolic BP	0.007	0.006	2.657	0.0008 **
Diastolic BP	0.001	0.011	-0.094	0.0002 **

3.2.2 *Tenth time interval ($70 - 77^{th}$ day)*

$$\begin{aligned}\lambda_{10} &= \exp(-5.260 + 0.351 j_{10}) \times \exp(0.006 age - 0.024 sex + 0.047 occupation \\ &\quad + 0.872 diagnosis + 0.007 BPU - 0.001 BPL) \\ &= \exp(-5.260 + 0.110 * 42) \times \exp(0.006 * 42 - 0.024 * 1 + 0.047 * 1 + 0.872 * 1 \\ &\quad + 0.007 * 120 + 0.001 * 80) = 0.058 \end{aligned} \tag{14}$$

3.3 *Sensitivity analysis and model comparison*

The PEM was re-estimated with the division of the timeline into intervals of 3, 5 and 10 days. Table 4 shows the values of AIC for PEM at different time intervals as well as for the Cox model. As observed, irrespective of the time interval, PEM outperformed Cox model in terms of AIC. It is also observed that PEM improved as the length of time interval increased. In other words, for the data under study, the model gives a better fit when the interval is smaller. Thus the piecewise exponential model is preferred over Cox in modeling the survival rate of renal patients.

Table 4: Table comparing AIC values of the models

Model	AIC
PEM	
3-week interval	658.63
5-week interval	588
7-week interval	572
10-week interval	500.48
COX Model	**644.23**

4. Conclusion

Piecewise exponential and Cox proportional hazards models were applied to data on renal failure patients. For the piecewise exponential model, the entire time line was divided into series of non-overlapping intervals. The choice of the cut-points in the piecewise exponential models allowed one to reasonably approximate the baseline hazards at each interval, using closely-spaced boundaries where the hazard varied rapidly and wider intervals where the hazard changed more slowly. Among the factors selected for the analysis, the two approaches found that patients' age, diagnosis and blood pressure (systolic and diastolic) were significantly associated with death from renal failure. Results from AIC indicated that Piecewise exponential model was better in predicting the death from the renal failure data as compared to Cox model. The adequacy of the model was found to be better as the length of interval increases. The current study demonstrated that piecewise exponential model offered the flexibility of modeling changes in the hazard of renal failure with ease in interpretation. It is particularly useful in the context in which the baseline hazard is of primary interest, which Cox proportional hazards model could not achieve. While Cox model demonstrated that the death from renal failure across the entire time line matters, it did not provide a simple characterization of the change in hazard. This limitation is addressed by the use of Piecewise exponential model.

References

Aitkin, M., Laird, N. and Francis, B. (1983). A reanalysis of the Stanford heart transplant data with discussion. J. Am. Stat. Assoc., **19**78: 264–292.

Akaike, H. (1974). A new look at statistical model identification. IEEE Trans. Automatic Control, **19**: 716–723.

Allison P.D. (2010). Survival analysis using SAS: a practical guide (2nd ed.). SAS Institution Inc., Cary, NC, USA.

Amico, M., Keilegom, I . V. and Legrand, C. (2019). The single-index/Cox mixture cure model. Biometrics, **75**(2): 452–462.

Bastos, L. S., Gamerman, D. (2006). Dynamic survival models with spatial frailty. Lifetime Data Anal., **12**: 441–460.

Berry, S.M., Berry, D.A. and Natarajan, K. (2004). Bayesian survival analysis with nonproportional hazards: Meta-analysis of pravastatin-aspirin. Journal of the American Statistical Association, **99**: 36–44.

Breslow, N. E. (1974). Covariance analysis of censored survival data. Biometrics, **30**: 89–99.

Cai, X., Tian, Y and Ning, W. (2017). Modified information approach for detecting change points in piecewise linear failure rate function. Statistics and Probability Letters, **125**: 130–140.

Clark, D. E. and Ryan, L. M. (2002). Concurrent prediction of hospital mortality and length of stay from risk factors on admission. Health Services Res., **37**: 631–645.

Cox D.R. (1972). Regression models and life-tables (with discussion). J. Roy. Statist. Soc. Ser. B., **34**: 187–220.

Cox D.R. (1975). Partial likelihood. Biometrika, **62**(2): 269–276.

Demarqui, F. N., Loschi, and Colosimo, E. A (2008). Estimating the grid of time-points for the piecewise exponential model. Lifetime Data Anal., **142**: 333–356. DOI 10.1007/s10985-008-9086-0

Demarqui, F., Loschi, R., Dey, D. and Colosimo, E. (2012). A class of dynamic piecewise exponential models with random time grid. Journal of Statistical Planning and Inference, **142**: 728–742.

Dupuy, J. F. (2009). Detecting change in a hazard regression model with right censoring. Journal of Statistical Planning and Inference, **139**: 1578–1586.

Edwards, J. and Bartlett, J. M. S. (2005). The androgen receptor and signal-transduction pathways in hormone-refractory prostate cancer. Part 2: androgen-receptor cofactors and bypass pathways. BJU International, **95**(9): 1327–1335.

Friedman M.(1982). Piecewise exponential models for survival data with covariates. The Annals of Statistics, **10**: 101–113.

Gamerman, D. (1994). Bayes estimation of the piece-wise exponential distribution. IEEE Trans Reliab., **43**: 128–131.

Goldberg, I. and Krause, I. (2016). The role of gender in chronic kidney disease. EMJ, **2**: 58–62.

Goodman, M. S., Yi, L. and Tiwari, R. C. (2011). Detecting multiple change points in piecewise constant hazard functions. Journal of Applied Statistics, **38**(11): 2523–2532. DOI: 10.1080/02664763.2011.559209.

Holford, T. R. (1980). The analysis of rates and of survivorship using log-linear models. Biometrics, **36**(2): 299–305.

Hoos, A., Eggermont, A. M. M., Janetzki, S., et al. (2010). Improved Endpoints for Cancer Immunotherapy Trials. Journal of the National Cancer Institute, **102**(18): 1388–1397. doi.org/10.1093/jnci/djq310.

Kim, J. and Proschan, F. (1991). Piecewise exponential estimator of the survival function. IEEE Trans Reliab., **40**: 134–139.

Kleinbaum, D. G and Klein, M. (2012). Statistics for Biology and Health. Springer New York, Dordrecht.

Laird, N. and Olivier, D. (1981). Covariance Analysis of Censored Survival Data using Log-Linear Analysis Techniques. Journal of the American Statistical Association, **76**: 231–240.

Neugarten, J., Acharya, A. and Silbiger, S. R. (2000). Effect of gender on the progression of nondiabetic renal disease. J. Am. Soc. Nephrol., **11**: 319–329.

Nguyen, H. T., Rogers, G. S. and Walker, E. A. (1984). Estimation in change-point hazard rate models. Biometrika, **71**: 299–304.

Pourhoseingholi, M. A., Ebrahim Hajizadeh, E., Dehkordi, B. M. (2007). Comparing Cox Regression and Parametric Models for Survival of Patients with Gastric Carcinoma. Asian Pacific Journal of Cancer Prevention, **8**: 412–416.

Qian L., Zhang W. (2014). Multiple Change-Point Detection in Piecewise Exponential Hazard Regression Models with Long-Term Survivors and Right Censoring. In: Lahiri S., Schick A., SenGupta A., Sriram T. (eds) Contemporary Developments in Statistical Theory, Springer Proceedings in Mathematics and Statistics, **68**, Springer, Cham.

Samawi, H. M., Yu, L., Rochani, H. and Vogel, R. (2020). Reducing sample size needed for cox-proportional hazards model analysis using more efficient sampling method. Communications in Statistics - Theory and Methods, **49**6: 1281–1298, DOI: 10.1080/03610926.2018.1554141.

Yang, S., Pieper, K and Cools, K. (2020). Semiparametric estimation of structural failure time models in continuous-time processes. Biometrika, **107**(1): 123–136. doi.org/10.1093/biom
et/asz057.

Zucker, D. M., Zhou, X., Liao, X. (2018). A modified partial likelihood score method for Cox regression with covariate error under the internal validation design. Biometrics, **75**(2): 414–427. doi.org/10.1111/biom.13012.