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A NEW APPROACH FOR ANALYSING SURVIVAL MODELS: THE MODIFIED GAMMA FRAILTY DISTRIBUTION

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Abstract: Survival analysis examines and models the time it takes for events to occur. The prototypical such event is death, from which the name 'survival analysis' and much of its terminology derives, but the ambit of application of survival analysis is much broader.Frailty models is effective in formulating the effects of covariates on potentially censored failure times and in the joint modelling of incomplete repeated measures and failure times in longitudinal studies. Survival data are often subject to right censoring and to a subsequent loss of information about the effect of explanatory variables. Three frailty models are used to analyze bivariate time-to-event data. Each approach accommodates right censored lifetime data and account for heterogeneity in the study population. A Modified Gamma Frailty [MGF] Model is compared with two existing Frailty Models. The newly derived MGF is more robust when sample size is more than forty.The MGF model performs better than the existing models in the presence of clustering. However the CGF is preferable in the absence of clusters in a given data set.

Keywords: Frailty Models, Censorship, Proportional hazard model, Survival Analysis, Correlated Gamma Frailty Models, Random effects

INTRODUCTION

survival modeling examines the relationship between survival and one or more predictors, usually termed covariates in the survival-analysis literature.Hazard models have become widespread in their use for the analysis of duration time data in many scientific disciplines, including biology and medicine (e.g., Cox, 1972; Kalbfleisch and Prentice, 1980), sociology (e.g., Petersen, 1995, Vermunt 1996), marketing research (e.g., Vilcassim and Jain, 1991; Wedel et al., 1995), and economics (e.g., Kiefer, 1988; Lancaster, 1990). These models overcome the problems of accounting for censored observations of duration and time-varying explanatory variables, that arise in applying standard regression type models to duration data. The basic concept in hazard models is the probability of the occurrence of an event during a certain time interval, say t to $t+\Delta t$, given that it has not occurred before t, specified as:

$$\lambda(t|N_i(t-),Z_i(t)) = \lim_{\Delta t \to 0} \Pr\left(t \le T_i, Ni(t-)+1 < t+\Delta t | N_i(t-), Z_i(t)\right)/\Delta t$$

$$= \lim_{\Delta t \to 0} \Pr\left(\Delta N_i(t) = 1 | N_i(t-), Z_i(t)\right)/\Delta t$$

The Cox proportional hazards model (Cox, 1972) is commonly used in the analysis of survival time data. An often unstated assumption of the proportional hazards model and of traditional frailty models (with the exception of those that use the compound Poisson distribution (Aalen, 1988, Aalen, 1992)) is that all individuals will experience the event of interest. However, in some situations a fraction of individuals is not expected to experience the event of interest; that is, these individuals are not at risk. The terminology to describe the never-at-risk group varies from field to field, but includes 'long-term survivors' or 'cured' in epidemiology, 'non-susceptible' in toxicology, 'stayers' in finite Markov transition models of occupational mobility, the 'non-fecundable' in fertility models, and 'non-recidivists' among convicted criminals. In

epidemiology and medicine, researchers may be interested in analyzing the occurrence of a disease. Many individuals may never experience that disease; therefore, there exists a fraction in the population that is protected. Cure models are survival models which allow for a cured fraction in the study population. These models extend the understanding of time-to-event data by allowing for the formulation of more accurate and informative conclusions than previously made. These conclusions would otherwise be unobtainable from an analysis that fails to account for a cured fraction in the population. If a cured component is not present, the analysis reduces to standard approaches of survival analysis. In cure models, the population is divided into two sub-populations so that an individual is either cured with probability $1-\varphi$, or has a proper survival function $S(t)$, with probability φ. Here, proper survival function means $\lim_{t\to\infty} S(t) = 0$. Individuals regarded as cured will never experience the event of interest and their survival time will be defined as infinity. Therefore, the hazard and survival functions of cured individuals are set to zero and one, respectively, for all finite values of t.

Longini and Halloran (1996) have proposed frailty cure models that extend standard frailty models. The frailty random variable in the former has point mass at zero with probability 1 - φ while heterogeneity among those experiencing the event of interest is modelled via a continuous distribution with probability φ. Price and Manatunga (2001) gave an excellent introduction to this area and applied leukaemia remission data to different cure, frailty and frailty cure models. They found that frailty models are useful in modelling data with a cured fraction and that the gamma frailty cure model provides a better fit to their remission data compared to the standard cure model. In the next section we describe the existing models and a proposed model, then provide an application of the models to an existing data on occupational exposure tagged – HEBRON data.

STATISTICAL MODELS

Cox PH models

The notation used for Cox PH models (Cox, 1972) with one more subscript to capture multiple events is generalized. Let T_{ik} be the total time of the k^{th} event for the i^{th} subject, C_{ik} be the censoring time of the k^{th} event for the i^{th} subject. Let U_{ik} be the observation time, that is, $U_{ik} = \min(T_{ik};C_{ik})$, and $\delta_{ik} = I(T_{ik} \le C_{ik})$ is an indicator of observed k^{th} failure time for subject i. $Z_{ik} = (Z_{1ik}; \ldots ;Z_{pik})'$ is the covariate vector for the i^{th} subject with respect to the k^{th} event, and $Z_i = (Z'_{i1};\ldots ;Z'_{ik})$ denotes the covariate vector for the i^{th} subject, where K is the maximum number of events within a subject. $\beta = (\beta_1; \ldots \beta_p)$ is a p x 1 vector of unknown parameters. Denote $h_k(t|Z_i(t))$ as the hazard function for the k^{th} event of the i^{th} subject at time t. This is in the context of competing risk. In general, the hazard function at time t for a subject is defined as the instantaneous probability of failure at time t given the survivorship prior to time t and the covariates:

$$h_{k+1}(t \mid Z_i(t)) = \lim_{\Delta t \to 0} \Pr(t \le T_{i,k+1} < t + \Delta t \mid T_{i,k+1} \ge t, Z_i(t)) / \Delta t. \qquad (2.1)$$

Note that Cox PH model for the k^{th} event time T_k is

$$h_k(t|Z_i(t)) = h_{0,k}(t) \exp\{\beta' Z_i(t)\}. \qquad (2.2)$$

Correlated Gamma Frailty (CGF) Model

This model was introduced by Yashin and Iachine (1995a,b, 1997, 1999a,b) and applied to related lifetimes in many different settings. Examples are found in Pickles et al. (1994), Yashin

et al. (1996), Iachine et al. (1998), Iachine (2002), Petersen (1998), Wienke et al. (2000, 2001, 2002, 2003a,b, 2004, 2005), Zdravkovic et al. (2002, 2004).

Let k_0, k_1, k_2 be some real positive values. Set $\lambda_1 = k_0 + k_1$ and $\lambda_2 = k_0 + k_2$.
Let Y_0, Y_1, Y_2 be independently gamma distributed random variables with

$$Y_0 \sim \Gamma(k_0, \lambda_0),\ Y_1 \sim \Gamma(k_1, \lambda_1),\ Y_2 \sim \Gamma(k_2, \lambda_2). \quad . \quad . \quad . \quad (2.3)$$

Consequently,

$$Z_1 = \frac{\lambda_0}{\lambda_1} Y_0 + Y_1 \sim \Gamma(k_0 + k_1, \lambda_1) \quad (2.4)$$

$$Z_2 = \frac{\lambda_0}{\lambda_2} Y_0 + Y_2 \sim \Gamma(k_0 + k_2, \lambda_2) \quad (2.5)$$

$$\begin{aligned} \textit{and} \quad & E(Z_1) = E(Z_2) = 1, \\ & V(Z_1) = \frac{1}{\lambda_1} := \sigma_1^2, \\ & V(Z_2) = \frac{1}{\lambda_2} := \sigma_2^2. \end{aligned} \quad (2.6)$$

The following relation holds

$$\begin{aligned} E(Y_0^2) &= V(Y_0) + (E(Y_0))^2 \\ &= \frac{k_0}{\lambda_0^2} + \left(\frac{k_0}{\lambda_0}\right)^2 \\ &= \frac{k_0^2 + k_0}{\lambda_0^2} \end{aligned} \quad (2.7)$$

$$\begin{aligned} E(Z_1 Z_2) &= E\left(\frac{\lambda_0}{\lambda_1} Y_0 + Y_1\right)\left(\frac{\lambda_0}{\lambda_2} Y_0 + Y_2\right) \\ &= E\left(\frac{\lambda_0^2}{\lambda_1 \lambda_2} Y_0^2 + \frac{\lambda_0}{\lambda_1} Y_0 Y_2 + \frac{\lambda_0}{\lambda_2} Y_0 Y_1 + Y_1 Y_2\right) \\ &= \frac{\lambda_0^2}{\lambda_1 \lambda_2} \frac{k^2 + k_0}{\lambda_0^2} + \frac{\lambda_0 k_0 k_2}{\lambda_1 \lambda_0 \lambda_2} + \frac{\lambda_0 k_0 k_1}{\lambda_2 \lambda_0 \lambda_1} + \frac{k_1 k_2}{\lambda_1 \lambda_2} \\ &= \frac{k_0 + (k_0 + k_1)(k_0 + k_2)}{\lambda_1 \lambda_2} \\ &= \frac{k_0}{(k_0 + k_1)(k_0 + k_2)} + 1 \end{aligned} \quad (2.8)$$

$$\begin{aligned} Cov(Z_1, Z_2) &= E(Z_1 Z_2) - E(Z_1) E(Z_2) \\ &= \frac{k_0}{(k_0 + k_1)(k_0 + k_2)}, \end{aligned} \quad (2.9)$$

This leads to the correlation

$$\rho = \frac{\operatorname{cov}(Z_1, Z_2)}{\sqrt{V(Z_1)V(Z_2)}} = \frac{k_0}{\sqrt{(k_0 + k_1)(k_0 + k_2)}} \tag{2.10}$$

Consequently, because of relation

$k_0 + k_1 =$ □□

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It holds that

$$k_0 = \frac{\rho}{\sigma_1 \sigma_2} \tag{2.11}$$

And

$$k_i = \frac{1}{\sigma_i^2} - k_0 = \frac{1 - \frac{\sigma_i}{\sigma_j}\rho}{\sigma_i^2} \qquad (i, j = 1,2; i \neq j). \tag{2.12}$$

To derive the unconditional model, the Laplace transform of gamma distributed random variables is applied. Hence,

$$\begin{aligned}
S(t_1, t_2) &= E\left\{ S(t_1, t_2 \mid Z_1, Z_2) \right\} \\
&= E\left\{ S_1(t_1 \mid Z_1) S_2(t_2 \mid Z_2) \right\} \\
&= E\left\{ e^{-Z_1 \Lambda_1(t_1)} e^{-Z_2 \Lambda_2(t_2)} \right\} \\
&= E\left\{ e^{-\left(\frac{\lambda_0}{\lambda_1} Y_0 + Y_1\right)\Lambda_1(t_1)} e^{-\left(\frac{\lambda_0}{\lambda_2} Y_0 + Y_2\right)\Lambda_2(t_2)} \right\} \\
&= E\left\{ e^{-Y_0\left(\frac{\lambda_0}{\lambda_1}\Lambda_1(t_1) + \frac{\lambda_0}{\lambda_2}\Lambda_2(t_2) - Y_1 \Lambda_1(t_1) - Y_2 \Lambda_2(t_2)\right)} \right\} \\
&= \left(1 + \frac{1}{\lambda_0}\left(\frac{\lambda_0}{\lambda_1}\Lambda_1(t_1) + \frac{\lambda_0}{\lambda_2}\Lambda_2(t_2)\right)\right)^{-k0} \left(1 + \frac{1}{\lambda_1}\Lambda_1(t_1)\right)^{-k_1} \left(1 + \frac{1}{\lambda_2}\Lambda_2(t_2)\right)^{-k_2} \\
&= \left(1 + \sigma_1^2 \Lambda_1(t_1) + \sigma_2^2 \Lambda_2(t_2)\right)^{\frac{-\rho}{\sigma_1 \sigma_2}} \left(1 + \sigma_1^2 \Lambda_1(t_1)\right)^{\frac{-1 + \frac{\sigma_1}{\sigma_2}\rho}{\sigma_1^2}} \left(1 + \sigma_2^2 \Lambda_2(t_2)\right)^{\frac{-1 + \frac{\sigma_2}{\sigma_1}\rho}{\sigma_2^2}}
\end{aligned} \tag{2.13}$$

Which results in the representation of the Correlated Gamma Frailty model given as

$$S(t_1,t_2)=\frac{S_1(t_1)^{1-\frac{\sigma_1}{\sigma_2}\rho}\,S_2(t_2)^{1-\frac{\sigma_2}{\sigma_1}\rho}\,e^{\beta x_{ij}}}{\left(S_1(t_1)^{\sigma_1^2}+S_2(t_2)^{\sigma_2^2}-1\right)^{\frac{\rho}{\sigma_1\sigma_2}}}, \tag{2.14}$$

The Proposed Model – Modified Gamma Frailty (MGF) Model

In order to include heterogeneity in the model, we assume a correlated gamma frailty model. Let Z_j (j = 1; 2) be the frailties, and X_j (j = 1; 2) vectors of observable covariates of the two individuals of a twin pair. Assume that their individual hazards are represented by the proportional hazards model.

$$\lambda(t)=Z_j\lambda_0(t)\exp\{\beta^T X_j\} \qquad (j=1,2) \tag{2.15}$$

With a baseline hazard function $\lambda_0(t)$ describing the risk of respiratory infection as a function of age and β denotes the vector of regression parameters. Let the lifetimes of the two twin partners be conditionally independent given their frailties Z_1 and Z_2. Because frailties Z_j (j = 1; 2) are usually unobservable, their correlation coefficient used cannot be estimated directly from the empirical data. So a bivariate lifetime model which allows indirect calculation of the parameters is needed. The unconditional bivariate survival function of the correlated gamma frailty model with observed covariates is given by:

$$S(t_1,t_2|X_1,X_2)=S(t_1|X_1)^{1-\rho}S(t_2|X_2)^{1-\rho}S(t_1|X_1)^{-\sigma^2}+\{S(t_2|X_2)^{-\sigma^2}-1\}^{-\frac{\rho}{\sigma^2}} \tag{2.16}$$

Where $S(t|X)$ denotes the marginal univariate survival function, assumed to be equal for both partners in a twin pair. Using a parametric approach we fit a model to the data, such that

$$S(t|X_{ijk})=\left(1+[(1+\sigma_1^2\frac{a}{b}(e^{bt}-1))^{\frac{\sigma_2^2}{\sigma_1^2}\rho}-1]\right)^{-\frac{1}{\sigma_1^2}}e^{\beta_k X_{ijk}} \tag{2.17}$$

Where a, b, σ_1^2, σ_2^2, β and ρ are parameters to be estimated.

The lifetimes are assumed to be independently censored from the right by independent and identically distributed pairs of non-negative random variables, which are independent of the lifetimes. Thus, observe

$$(T_{i1}, T_{i2}, \delta_{i1}, \delta_{i2}, X_{i1}, X_{i2}) \tag{2.18}$$

With δ_{ij} (i = 1, ...n; j = 1; 2) as a binary variable with values 1 (event) and 0 (no event). Let the lifetimes follow a distribution (dependent on covariates X_1,X_2) given by the bivariate survival function

$$S(t_1,t_2|X_1,X_2)=P(T_{i1}>t_1,\ T_{i2}>t_2|X_1,X_2) \tag{2.19}$$

Starting from this model, we are able to derive the likelihood function given by

$$L(t_1,t_2,\delta_1,\delta_2,X_1,X_2)=\delta_1\delta_2 S_{t_1t_2}(t_1,t_2\mid \mathrm{X}_1,\mathrm{X}_2)-\delta_1(1-\delta_2)S_{t_1}(t_1,t_2\mid \mathrm{X}_1,X_2)- (1-\delta_1)\delta_2 S_{t_2}(t_1,t_2\mid \mathrm{X}_1,X_2)+(1-\delta_1)(1-\delta_2)S(t_1,t_2\mid \mathrm{X}_1,X_2)\,.\,. \quad (2.20)$$

Partial derivatives of the marginal survival functions are given by

$$S_{t_j}(t_1,t_2)=\frac{\partial S(t_1,t_2)}{\partial t_j} \quad (\mathrm{j}=1,\,2) \quad (2.21)$$

and

$$S_{t_1,t_2}(t_1,t_2)=\frac{\partial S(t_1,t_2)}{\partial t_1\partial t_2}\,. \quad (2.22)$$

The model is called the **Modified Gamma Frailty** (MGF) Model.

NUMERICAL ILLUSTRATION

We demonstrate here an application of the models to an existing data on occupational exposure tagged – HEBRON data. Relationships between occupational exposures and morbidity, morbidity and job category were analyzed using proportional hazard analysis, allowing for exposure status (never exposed, ever smoked and ever exposed) until the time of carrying out the study. The survival-analysis was performed using the SPSS VERSION 15. The discrete algorithm was used, since the time-scale (person-years) was discrete. All exposures were first analyzed separately, allowing for age and smoking habits. Two-sided p-values < 0.05 were considered as statistically significant. The relationship between occupational exposures and morbidity was also analyzed simultaneously. Using the stepwise option of SPSS, and allowing for age and smoking habits, specific exposures were included and excluded until the following conditions were met: the significance of the residual Chi-squared was less than 0.25, and the significance of the relative risks was less than 0.10. Using the standard error of the regression coefficient, the 95% confidence intervals were estimated. The Matlab software and R was also applied in analyzing the Correlated Gamma Frailty Model and the Modified Gamma Frailty Model. Hazard function and survival functions for the exposure data for large and small samples were estimated.

RESULTS

Tables 4.1 – 4.4 shows the results of analysis of the Hebron data and the goodness of fit table . In table 4.1, holding the other covariates constant, an additional year of age increases the yearly hazard of exposure of worker by a factor of e^{β} = 1.047389 on average – that is, by 4.7 percent. Similarly, each FVC factor increases the hazard by a factor of 1.405088 or 40.5 percent. The Body Mass Index (**BMI**), exposure status (never exposed, exposed and ever smoked), Jobcategory and pack years smoked is considered to be insignificant for the Hebron data using the Cox Model. The CGF captures the exposure status and Job category to be insignificant for the Hebron data while the proposed MGF considers all the variables to be significant for the Hebron data.

Table 4.1: Regression Coefficients in the Cox Model for the Hebron Study

Covariate	coeff(β)	Exp(coeff(β)	Std error coeff(β)	Z	P	95% C.I for coeff(β)
AGE	0.0463	1.047389	0.0217	2.133641	0.0001	1.0023 - 1.0982
BMI	- 0.3567	0.699982	0.1911	-1.86656	0.0667*	0.3608 -1.08163
EXPOSURE STATUS	-0.0461	0.954946	0.0219	-2.10502	0.3171*	0.0061 - 1.0118
JOB CATEGORY	-0.0253	0.975017	0.2014	-0.12562	0.6777*	0.2306 -1.2009
SYST B P	- 0.0657	0.936412	0.1847	-0.35571	0.0065	0.0021 - 0.9833
PACK YRS SMOKED	0.0861	1.089915	0.0271	3.177122	0.5169*	0.023 - 1.1328
FVC	0.3401	1.405088	0.3011	1.129525	0.0085	1.0144 - 1.6449
FEV_1	0.0793	1.082529	0.0384	2.065104	0.0001	1.0045 - 1.1429

* Not significant.

Table 4.2: Regression Coefficients in the Correlated Gamma Frailty Model for the Hebron Study

Covariate	coeff(β)	Exp(coeff(β))	Std error coeff(β)	Z	P	95% C.I for coeff(β)
AGE	0.0470	1.048122	0.0226	2.079646	0.0041	1.0076 -1.2552
BMI	- 0.3075	0.735283	0.1141	-2.6950	0.0026	0.0448 - 0.9263
EXPOSURE STATUS	-0.0468	0.954278	0.0536	-1.87313	0.3174*	0.002 - 1.0158
JOB CATEGORY	-0.0126	0.987479	0.2034	-0.06195	0.6787	0.0686 -0.9979
SYST B P	- 0.0687	0.933607	0.1713	-0.40105	0.2867	0.0621 - 0.9843
PACK YRS SMOKED	0.0861	1.089915	0.0157	5.484076	0.0015*	0.028 - 1.1428
FVC	0.3521	1.422051	0.3121	1.128164	0.4418	1.0146 - 1.8453
FEV_1	- 0.1963	0.821766	0.0815	-2.40859	0.0027	0.0135 - 0.9433

* Not significant.

Table 4.3: Regression Coefficients in the Modified Gamma Frailty Model for the Hebron Study

Covariate	coeff(β)	Exp(coeff(β))	Std error coeff(β)	Z	P	95% C.I for coeff(β)
AGE	0.0437	1.044669	0.0137	3.189781	0.0001	1.0875 - 1.1552
BMI	- 0.2075	0.812613	0.1041	-1.99328	0.0038	0.6448 -0.9263
EXPOSURE STATUS	-0.0456	0.955424	0.0239	-1.90795	0.7321	0.5626 - 0.9738
JOB CATEGORY	-0.0226	0.977653	0.2058	-0.10982	0.5777	0.6316 - 0.9929
SYST B P	- 0.0737	0.92895	0.1722	-0.42799	0.2869	0.7825 - 0.9623
PACK YRS SMOKED	0.0868	1.090679	0.0263	3.30038	0.0056	1.0023 - 1.2328
FVC	0.3511	1.420629	0.1411	2.488306	0.0015	1.0144 - 1.8449
FEV_1	- 0.2856	0.751563	0.1046	-2.7304	0.0027	0.0138 - 0.8529

* Not significant.

Table 4.4: Prognostic Factors of Occupational Exposure using Cox and frailty Models for Hebron Study

Prognostic factors	Cox regression HR† (CI§ 95%)	Correlated Gamma Frailty HR (CI 95%)	Modified Gamma Frailty HR (CI 95%)
Age	1.0474(1.0023 - 1.0982)	1.048122(1.0076 -1.2552)	1.044669(1.0875 - 1.1552)
BMI	0.7000(0.3608 -1.08163)*	0.735283(0.0448 - 0.9263)	0.812613(0.6448 - 0.9263)
EXPOSURE STATUS	0.9550(0.0061 - 1.0118)*	0.954278(0.0020 - 1.0158)*	0.955424(0.5626 - 0.9738)
JOB CATEGORY	0.9750 (0.2306 -1.2009)*	0.987479(0.0686 -0.9979)	0.977653(0.6316 - 0.9929)
SYST B P	0.9364 (0.0021 - 0.9833)	0.933607(0.0621 - 0.9843)	0.92895(0.7825 - 0.9623)
PACK YRS SMOKED	1.0899 (0.023 - 1.1328) *	1.089915(0.028 0- 1.1428)*	1.090679(1.0023 - 1.2328)
FVC	1.4051(1.0144 - 1.6449)	1.42205(1.0146 - 1.8453)	1.420629(1.0144 - 1.8449)
FEV_1	1.0825 (1.0045 - 1.1429)	0.821766(0.0135 - 0.9433)	0.751563(0.0138 - 0.8529)
AIC#	1357	968	722

† Hazard Ratio § Confidence interval * Not significant # Akaike Information Criterion

Figures 4.1 – 4.3 shows the survival function and hazard function for the Hebron study

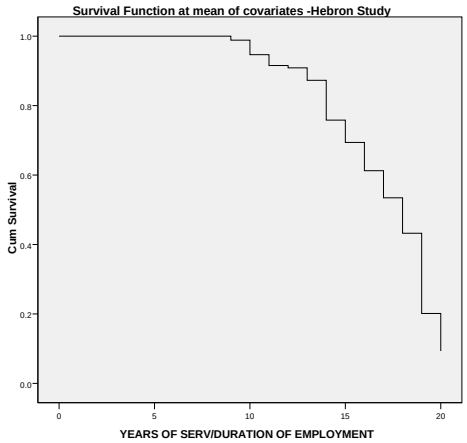

Fig.4.1 Survival Function at mean of covariates - Hebron Study

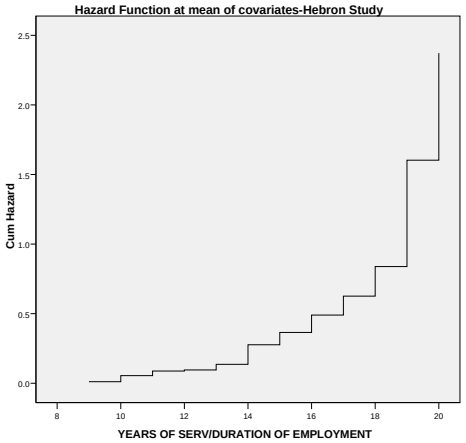

Fig. 4.2: Hazard Function at mean of covariates - Hebron Study

CONCLUSION

Interestingly, parameter estimates are quite different depending on distribution of the base-line hazard function. The newly introduced Modified Gamma frailty model offers a very elegant approach to integrate the concept of clusters into frailty modelling. The survival function is explicitly available and of easy form which allows traditional maximum likelihood parameter estimation. This is the most important advantage of the suggested model compared to the model introduced by Moger and Aalen (2005). The present work contributes to three aspects of Frailty models with censored data. First, we present several important extensions of the existing models. Secondly, we develop a general asymptotic theory for the Frailty models. Thirdly, we provide simple and efficient numerical method to implement the corresponding inference procedures. We hope that our work will facilitate further development and applications of Frailty models. We have demonstrated that the MGF is a very general and powerful approach to the analysis of Frailty models with censored data. This approach can be used to study many other problems. Of great interest would be a non-parametric version of the correlated compound Poisson frailty model, where the baseline hazard functions are not specified. A part of future research is envisaged in this direction. Another aspect that will be of interest for further research is the problem of identifiability. The identifiability problem is growing with increased censoring, but is reduced by the parametric modelling of the baseline hazard.

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