ANALYSIS OF PARAMETRIC FRAILTY MODELS TO ESTIMATE THE RISK OF AMPUTATION

Ivette Raíces*, Vivian Sistachs**, Hannelore Liero***, Isis Yera*, Liset Martínez*
*Center for Genetic Engineering and Biotechnology, Cuba.
**University of Havana, Cuba.
***University of Potsdam, Germany.

ABSTRACT
With the goal of knowing what variables might influence in the occurrence time of amputation in medical practice we used multivariate parametric frailty models. Specifically we used two models where the baseline hazard function follows a Weibull distribution and the frailty term has a Gamma and inverse Gaussian distribution respectively. The data set contains observations of 69 patients with diabetic foot ulcers from a retrospective study. We used **parfm** package from statistical software **R 3.1.3**. As result, we obtained in both models that Etiopatogenia variable has statistically significance in the occurrence of amputation.

KEYWORDS: Survival analysis, Parametric Frailty Models, Weibull distribution, Gamma distribution, inverse Gaussian distribution.

MSC: 62P10

RESUMEN
Con el objetivo de conocer que variables influencian en el tiempo la ocurrencia de amputación en la práctica médica habitual, se utilizaron modelos *frailty* paramétricos multivariados. Específicamente se emplearon dos modelos donde la función de riesgo inicial tiene distribución Weibull y el término *frailty* tiene distribución Gamma e inversa Gaussiana respectivamente. La muestra esta constituida por 69 pacientes con úlcera de pie diabético pertenecientes a un estudio retrospectivo. Se utilizó el paquete **parfm** del software estadístico **R 3.1.3**. Como resultado se obtuvo que la variable Etiopatogenia tiene significación estadística en la ocurrencia de amputación.

PALABRAS CLAVE: Análisis de sobrevida, modelos Parametric Frailty, distribución de Weibull, distribución Gamma, distribución inversa Gaussiana.

1. INTRODUCTION

Frailty models have been used frequently to model the multivariate dependence in time of an interest event for more details we refer to [1], [5] and [6]. Usually dependency is generated because subjects from the same group are either related or because multiple recurrent events occur in the same subject. In this case the traditional proportional hazard model could not be applied. One possible solution to this problem is to use the conditional proportional hazard model taking into account frailty terms. In this model the variability has two different sources: the natural variability, included in the baseline hazard function and the other which is given by a frailty term that represents the unobserved variability from the covariates, see [5]. In this model is assumed that a given frailty term, the risk of each survival time follows a proportional hazard model, where the frailty term has a multiplicative effect on the baseline hazard function and also the covariates. For that reason we have to specify the assumed distribution for baseline hazard function and frailty term.
Recently frailty models have been more used, because they allow to consider the individual heterogeneity from each subject or group either from a disease or interest event. Frailty is an unobserved quantity modeled as a random variable over the population of individuals, with a high (low) value of the frailty term associated with a large (small) risk of acquiring the disease or the occurrence of an interest event.
The aim of this work is to analyze the influence of variables in the occurrence of amputation in a sample constituted by 69 patients with diabetic foot ulcers. In this study we analyzed the time until the occurrence of

amputation or treatment ending after two cycles with Heberprot-P. We used **parfm** package from statistical software **R 3.1.3**.
This paper is structured as follows: In Section 2, the frailty model is explained, including how to estimate its parameters and the predict frailties. Finally, in Section 3, the results are presented and discussed.

2. MATERIALS AND METHODS

In this section we give some details about parametric frailty models, further information can be found in [3] and [5].

2.1. FRAILTY MODELS

The basic model is the proportional hazards model of the form:

$$h_0(t)\exp(x^T\beta),$$

where h_0 denotes the baseline hazard rate, assumed to be unique for all individuals in the population, x is the value of the p-dimensional vector of the covariate values and $\beta \in \mathbb{R}^p$ is the unknown regression parameter. This model can be applied for independent observations; if we have to model lifetimes of individuals which are related to each other or they are result of repeated measurements the following approach is useful. The dependence is taken into account by introducing a frailty variable U. The variable U is a random variable with a density f which will be specified later.
Suppose there are G groups or clusters. We define the conditional hazard rate of individual j in group i, given the covariate takes the value x_{ij} and the frailty variable the value u_i by

$$h_i(t|u_i, x_{ij}) = u_i h_0(t)\exp(x_{ij}^T\beta) \tag{1}$$

with $i \in I = \{1,\ldots,G\}$ and $j \in J_i = \{1,\ldots,n_i\}$. Notice, a shared frailty model is assumed that all individuals in the same cluster share the same frailty value.
In survival analysis is important to know the probability of an individual to survive time t, which is given by:

$$S(t) = P(T > t),\ T \text{ non-negative.}$$

Also it is important to mention the relation between survival function and the cumulative hazard function, $H(t)$ which is given by:

$$S(t) = \exp\{-H(t)\} \text{ where } H_0(t) = \int_0^t h_0(z)dz.$$

Now, considered the conditional survival function given the covariates and the frailty term the expresion is:

$$S(t|U,x) = \exp\left\{-UH_0(t)\exp(x^T\beta)\right\},$$

where $H_0(t) = \int_0^t h_0(z)dz$ is the cumulative baseline hazard. The conditional survival function $S(t|x)$ given the covariates may be obtained by taking the expectation respect U:

$$S(t|x) = \mathsf{E}_U[S(t|U,x)] = \mathsf{E}_U[\exp\left\{-UH_0(t)\exp(x^T\beta)\right\}].$$

Now, introducing the Laplace transform of the frailty variable $\mathcal{L}(s) = \mathsf{E}\left[\exp(-sU)\right]$ we see immediately that $S(t|x)$ is the Laplace transform at the value $H_0(t)\exp(x^T\beta)$, being the expression:

$$S(t|x) = \mathcal{L}(H_0(t)\exp(x^T\beta)).$$

It is assumed that the frailty causes dependence between individuals from the same group, but given the frailty, all individuals within the group are independent. Thus, for one group of n individuals, the conditional

join survival distribution of failures times $T_1, T_2, \ldots, T_n$ given the frailty U and let $\boldsymbol{X} = (X_1, \ldots, X_n)$ the covariates:

$$\begin{aligned} S(t_1, \ldots, t_n | u, \boldsymbol{x}) &= \mathsf{P}(T_1 > t_1, \ldots, T_n > t_n | \boldsymbol{X} = \boldsymbol{x}, U = u) \\ &= \mathsf{P}(T_1 > t_1 | \boldsymbol{X} = \boldsymbol{x}, U = u) \ldots \mathsf{P}(T_n > t_n | \boldsymbol{X} = \boldsymbol{x}, U = u) \\ &= S(t_1 | u, \boldsymbol{x}) \ldots S(t_n | u, \boldsymbol{x}) \\ &= \exp\left\{ -u \sum_{j=1}^{n} H_0(t_j) \exp(x_j^T \beta) \right\}. \end{aligned}$$

The above joint conditional survival distribution holds for any group. Integrating the frailty out, we get the join survival function given the covariates for this group as:

$$\begin{aligned} S(t_1, \ldots, t_n | \boldsymbol{x}) &= \mathsf{P}(T_1 > t_1, \ldots, T_n > t_n | \boldsymbol{X} = \boldsymbol{x}) \\ &= \int_0^\infty \mathsf{P}(T_1 > t_1, \ldots, T_n > t_n | \boldsymbol{x}, u) f(u) du \\ &= \int_0^\infty \exp\left\{ -u \sum_{j=1}^{n} H_0(t_j) \exp(x_j^T \beta) f(u) du \right\} \\ &= \mathcal{L}\left[\sum_{j=1}^{n} H_0(t_j) \exp(x_j^T \beta) \right], \end{aligned}$$

Since the dependence in a cluster is expressed by the frailty, we have, given the frailty, independence. And from definition (1) we obtain the conditional multivariate survival function of the subjects of group i. Let $\boldsymbol{X}_i = (X_{i1}, \ldots, X_{in_i})$ be the $p \times n_i$ matrix of the covariates and $\boldsymbol{x}_i$ the corresponding value.

$$\begin{aligned} S_i(t_1, \ldots, t_{n_i} | u_i, \boldsymbol{x}_i) &= \mathsf{P}(T_{i1} > t_1, \ldots, T_{in_i} > t_{n_i} | \boldsymbol{X}_i = \boldsymbol{x}_i, U_i = u_i) \\ &= \prod_{j=1}^{n_i} S_{ij}(t_j | u_i, \boldsymbol{x}_i) \\ &= \exp\left(-u_i \sum_{j=1}^{n_i} H_0(t_j) \exp(x_{ij}^T \beta) \right). \end{aligned}$$

We obtain the "usual" survival distribution, that is the conditional survival distribution given the covariate, by

$$S_i(t_1, \ldots, t_{n_i} | \boldsymbol{x}_i) = \int S_i(t_1, \ldots, t_{n_i} | u, \boldsymbol{x}_i) f(u) \, \mathrm{d}u,$$

in other words, by taking the expectation of the conditional survival function with respect to U. We can write

$$\begin{aligned} S_i(t_1, \ldots, t_{n_i} | \boldsymbol{x}_i) &= \mathsf{E}_{U_i}\left[S_i(t_1, \ldots, t_{n_i} | U_i, \boldsymbol{x}_i) \right] \\ &= \mathsf{E}_{U_i}\left[\exp\left(-U_i \sum_{j=1}^{n_i} H_0(t_j) \exp(x_{ij}^T \beta) \right) \right] \\ &= \mathcal{L}\left(\sum_{j=1}^{n_i} H_0(t_j) \exp(x_{ij}^T \beta) \right). \end{aligned}$$

The joint survival function for all event-time data is the product of survival function of all the groups because of the assumption about independence between groups.

$$\begin{aligned} & S(t_{11},\ldots,t_{Gn_G}|\boldsymbol{x}_1,\ldots,\boldsymbol{x}_G) \\ = \; & \mathsf{P}(T_{11}>t_{11},\ldots,T_{Gn_G}>t_{Gn_G}|\boldsymbol{X}_i=\boldsymbol{x}_i, i=1,\ldots,G) \\ = \; & \prod_{i=1}^{G}\mathcal{L}\left(\sum_{j=1}^{n_i}H_0(t_{ij})\exp(x_{ij}^T\beta)\right). \end{aligned}$$

For the model estimation, a parametric approach is considered and the parameters of the models are estimated using **parfm** package which do that through the maximisation of the marginal log-likelihood. Also using this package is estimated the predicted frailty value for each patient into the study, for more details see [4].

2.2. BASELINE HAZARD FUNCTION

For the approach that we consider, the baseline hazard function is defined as a parametric function and the vector of its parameters are estimated with the regression coefficients and frailty term. Different distributions have been proposed for baseline hazard function for instance, see [5]. In this work we consider Weibull distribution, which is denoted by:

$$T\sim Weibull(\lambda,\rho),\ \lambda>0,\rho>0,$$

the probability density function of T is:

$$f(t)=\begin{cases}\lambda\rho t^{\rho-1}\exp(-\lambda t^{\rho}) & t\geq 0\\ 0 & t<0\end{cases}$$

the hazard function is:

$$h(t)=\lambda\rho t^{\rho-1},$$

and the cumulative hazard function:

$$H(t)=\lambda t^{\rho}.$$

2.3. FRAILTY DISTRIBUTION

The frailty parameter u_i is an unobservable realization of a random variable U with probability density function $f(\cdot)$ the frailty distribution. Since u_i multiplies the hazard function, U has to be non-negative. Several distributions have been proposed for frailty distributions, see [1] and [5]. In this work, we use Gamma distribution considering its properties and also the inverse Gaussian distribution as an alternative for Gamma distribution. Sometimes inverse Gaussian distribution has convergence issues, in our case that do not happen. We compare the results between them.
Next, is presented the frailty distributions used in this model. First, Gamma distribution appears, which is denoted by:

$$U\sim\ \text{Ga}\ \left(\frac{1}{\theta},\frac{1}{\theta}\right),\ \theta>0,$$

and has probability density function:

$$f(u)=\begin{cases}\frac{\theta^{-\frac{1}{\theta}}u^{\frac{1}{\theta}-1}\exp\left(-\frac{u}{\theta}\right)}{\Gamma\left(\frac{1}{\theta}\right)} & \theta>0\\ 0 & \theta\leq 0\end{cases}$$

where $\Gamma(\cdot)$ is the gamma function, therefore $E(U) = 1$ and $Var(U) = \theta$. Besides the corresponding Laplace transform is given by:

$$\mathcal{L}(s) = (1 + \theta s)^{-\frac{1}{\theta}}, \ s \geq 0,$$

The multivariate survival function for the i group correspond to:

$$S_i(t_1, \ldots, t_{n_i} | \boldsymbol{x}_i) = \left[1 + \theta \sum_{j=1}^{n_i} H_0(t_j) \exp\left(x_{ij}^T \beta\right) \right]^{-\frac{1}{\theta}} \tag{2}$$

There are different ways of expressing dependence in a frailty model. One of them is to use Kendall's tau to quantify dependence because it is independent of transformation on the time scale and the frailty model used. Kendall's tau measures the association between any two events times from the same cluster in the multivariate case, this can be consulted in [2]. For the Gamma distribution is:

$$\tau = \frac{\theta}{\theta + 2} \in (0, 1)\,.$$

The other frailty distribution used in this work is inverse Gaussian distribution which is given by:

$$U \sim \text{ IG } (\theta)\,,$$

and the probability density function is:

$$f(u) = \frac{1}{\sqrt{2\pi\theta}} u^{-\frac{3}{2}} \exp\left(-\frac{(u-1)^2}{2\theta u} \right), \ s \geq 0,$$

with mean and variance 1 and θ respectively.
For this distribution the associated Laplace transform is given by:

$$\mathcal{L}(s) = \exp\left(\frac{1}{\theta} \left(1 - \sqrt{1 + 2\theta s} \right) \right), s \geq 0.$$

Then, the multivariate survival function for the i group is given by:

$$S_i(t_1, \ldots, t_{n_i} | \boldsymbol{x}_i) = \exp\left\{ \frac{1}{\theta} \left[1 - \sqrt{1 + 2\theta \sum_{j=1}^{n_i} H_0(t_j) \exp\left(x_{ij}^T \beta\right)} \right] \right\} \tag{3}$$

for this distribution Kendall's tau is:

$$\tau = \frac{1}{2} - \frac{1}{\theta} + 2 \frac{\exp\left(\frac{2}{\theta}\right)}{\theta^2} \int_{\frac{2}{\theta}}^{\infty} \frac{\exp(-u)}{u} du \in \left(0, \frac{1}{2}\right).$$

2.4. ESTIMATION OF THE PARAMETERS

The data in our case study are right-censored, the observation for individual j, $j = 1, \ldots, n_i$ in group $i \in I$ is the triple $(y_{ij}, \delta_{ij}, x_{ij})$, where x_{ij} denotes the vector of covariates, and

$$y_{ij} = \min(t_{ij}, c_{ij}) \qquad \delta_{ij} = I(t_{ij} \leq c_{ij}).$$

Here c_{ij} are censoring times and I denotes the event indicator. We assume that we have non informative censoring, that is given the covariates, the survival times and the censoring times are independent. Furthermore, the frailty variable is independent from censoring.

Since we assume a parametric model we can derive the conditional likelihood function: The contribution of the individuals of the group i (given the frailty u_i) to the likelihood function is given by:

$$\prod_{j=1}^{n_i}(u_i h_0(y_{ij}\exp(\beta^T x_{ij}))^{\delta_{ij}}\exp(-u_i H_0(y_{ij})\exp(\beta^T x_{ij})).$$

Since the frailty is not observable we take the expectation with respect to U_i and obtain the marginal likelihood

$$\begin{aligned}&\prod_{j=1}^{n_i}(h_0(y_{ij}\exp(\beta^T x_{ij}))^{\delta_{ij}})\, E_{U_i}(U_i^{\sum_j \delta_{ij}}\exp(-U_i\sum_{j=1}^{n_i}H_0(y_{ij})\exp(\beta^T x_{ij})))\\ =\;&\prod_{j=1}^{n_i}(h_0(y_{ij}\exp(\beta^T x_{ij}))^{\delta_{ij}})\,(-1)^{d_i}\mathcal{L}^{(d_i)}(\sum_{j=1}^{n_i}(H_0(y_{ij})\exp(\beta^T x_{ij}))).\end{aligned}$$

Here $d_i=\sum_{j=1}^{n_i}\delta_{ij}$ is the number of uncensored observations in group i, and $\mathcal{L}^{(r)}$ is the r-th derivative of the Laplace transform. Summarizing, we obtain the marginal log-likelihood function as:

$$\begin{aligned}\ell(\beta,\theta,\psi) \;=\; &\sum_{i=1}^{G}\Big[\sum_{j=1}^{n_i}\delta_{ij}(\log(h_0(y_{ij}))+\beta^T x_{ij})\\ &+\log\Big((-1)^{d_i}\mathcal{L}^{(d_i)}\big(\sum_{j=1}^{n_i}H_0(y_{ij})\exp(\beta^T x_{ij})\big)\Big)\Big] \qquad (4)\end{aligned}$$

The parameter ψ characterizes the baseline distribution.
The estimators of the parameters β, θ and ψ are the maximizers of $\ell(\beta,\theta,\psi)$. The maximization is carried out by a numerical procedure.
Also the predict frailties for the individuals were estimated. The prediction of the unobservable frailty term u_i is defined as the conditional expectation of the random variable U_i given the data $(y_{ij},\delta_{ij},x_{ij})$ and the estimates $\hat{\beta}$, $\hat{\theta}$ and $\hat{\psi}$, i.e.

$$\widehat{u}_i = E(U_i|\hat{\beta},\hat{\theta},\hat{\psi},y_{ij},\delta_{ij},x_{ij},j=1,\ldots,n_i).$$

In [4] it is shown that:

$$E(U_i|\beta,\theta,\psi,y_{ij},\delta_{ij},x_{ij},j=1,\ldots,n_i)=\frac{\mathcal{L}^{(d_i+1)}\big(\sum_{j=1}^{n_i}H_0(y_{ij})\exp(\beta^T x_{ij})\big)}{\mathcal{L}^{(d_i)}\big(\sum_{j=1}^{n_i}H_0(y_{ij})\exp(\beta^T x_{ij})\big)}.$$

3. RESULTS AND DISCUSSIONS

We want to know what variables might influence the amputation risk occurrence in time. With this goal, we used a data set which contains observation of 69 patients holding diabetic foot ulcer from one of the studies of Clinical Trial department from the Center for Genetic Engineering and Biotechnology (CIGB). In this study we analyzed the time until either the occurrence of amputation or end of treatment in patients who do not have amputation. Here each patient received two cycles of treatments, it may happen that the same patient is amputated at different times, this is a case of recurrent events. We used **parfm** package from the statistical software **R 3.1.3**.
The data of the first three patients from the study appear in Table 1. The first column indicates the cycle of treatment received for the patients. Second column provides the unique patient identification number (cluster). Variable time measures time (in days) until the occurrence of amputation or end of treatment and variable amputation indicates the ocurrence of amputation. Also there are three covariates available in the data set: sex (1 Female, 2 Male), localization (1 Simple, 2 Complex, 3 Calcaneous) and etiopatogenia (1 Ischemic, 2 Neuropathic).

We have the special case: $n_i = 2$ for $i = 1, \ldots, G = 69$. The first data in the table are all censored. In the data there are 122 censored case and 16 amputation events.

Table 1: Data of first three patients of the study

cycle	**id_pac**	**time**	**amputation**	**sex**	**localization**	**etiopatogenia**
1	1	71	0	1	2	1
2	1	15	0	1	2	1
1	2	180	0	1	2	1
2	2	180	0	1	2	1
1	3	29	0	1	2	2
2	3	12	0	1	1	2

Firstly, we analyze the model with Weibull hazard function and Gamma frailty.
In other words, the (unconditional) survival function given in (2) has the form

$$\begin{aligned} & S_i(t_1, t_2|\boldsymbol{x}_i) \\ = \; & [1 + \theta\lambda \exp(\text{sex}_i\beta_1)(t_1^\rho \exp(\text{et}_{i1}\beta_2 + \text{loc}_{i1}\beta_3) + t_2^\rho \exp(\text{et}_{i2}\beta_2 + \text{loc}_{i2}\beta_3))]^{-\frac{1}{\theta}} \end{aligned}$$

with $\boldsymbol{x}_i = (\text{sex}_i, \text{et}_{i1}, \text{et}_{i2}, \text{loc}_{i1}, \text{loc}_{i2})$.

Table 2: Model with Weibull baseline hazard distribution and Gamma frailty distribution

	Estimate	**SE**	**p − val**
theta	0.303	0.911	
rho	1.258	0.279	
lambda	0.008	0.015	
sex	−0.175	0.583	0.764
etiopatogenia	−1.334	0.710	0.060
localization	−0.071	0.357	0.843
Kendall's Tau:	0.132		
Loglikelihood:	−108.231		

The variable with statistic signification on the hazard of amputation is etiopatogenia. The hazard of amputation for a neuropathic patient at any time t compared to an ischemic patients is $\exp(-1.334) = 0.263$ provided all other things-the covariates sex and localization and the value of the frailty-are equal. As for the frailty term θ, it is estimated to be 0.303, that reveal the presence of unobserved heterogeneity. Also Kendall's tau equal to 0.132 is estimated, which indicate the presence of a low association between the amputation time in patients. Also the baseline hazard function is estimated $\lambda = 0.008$ and $\rho = 1.258$, which indicate the hazard increase with time, see Table 2.
The covariates sex and localization have not statistical significant influence, but the corresponding likelihood ratio test for the comparison of the models with one and three covariates leads to the acceptance of the null hypothesis that the data do not contradict the smaller model. However, because from the viewpoint if application it seems to useful to include these covariates in the model.
On the other hand, we consider a model with Weibull hazard function and inverse Gaussian frailty, which the (unconditional) survival function given in (3) is:

$$\begin{aligned} & S_i(t_1, t_2|\boldsymbol{x}_i) \\ = \; & \exp\left(\frac{1}{\theta}\left[1 - \sqrt{1 + 2\theta\lambda \exp(\text{sex}_i\beta_1)\left[t_1^\rho \exp(\text{et}_{i1}\beta_2 + \text{loc}_{i1}\beta_3) + t_2^\rho \exp(\text{et}_{i2}\beta_2 + \text{loc}_{i2}\beta_3)\right]}\right]\right) \end{aligned}$$

with $\boldsymbol{x}_i = (\text{sex}_i, \text{et}_{i1}, \text{et}_{i2}, \text{loc}_{i1}, \text{loc}_{i2})$.

Table 3: Model with Weibull baseline hazard distribution and inverse Gaussian frailty distribution

	Estimate	**SE**	**p − val**
theta	0.359	1.307	
rho	1.260	0.287	
lambda	0.008	0.015	
sex	−0.171	0.582	0.770
etiopatogenia	−1.336	0.718	0.063
localization	−0.075	0.368	0.839
Kendall's Tau:	0.121		
Loglikelihood:	−108.232		

Here we obtained similar results as in the previous model. The variable with statistical signification on the hazard of amputation is etiopatogenia too, see Table 3.
Prediction of frailty terms for each group (in this case are 69 patients) assumming a Gamma and inverse Gaussian distributions respectively are presented in Figures 1 and 2.
Figure 1 shows a group of patients (42%) who have predict frailty close to 1, however in 58% of the patients is posible to infer if the risk of amputation is either high or low. This result is useful because it allow to take preventive actions in patients who have higher risk.

Figura 1: Gamma frailty model with Weibull baseline

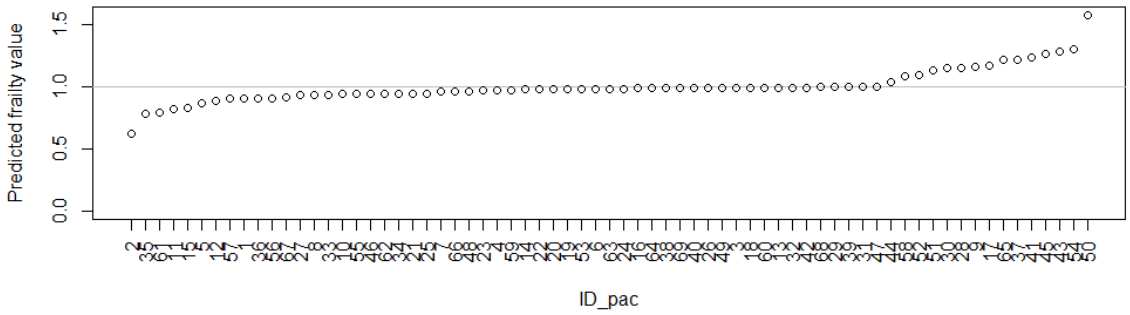
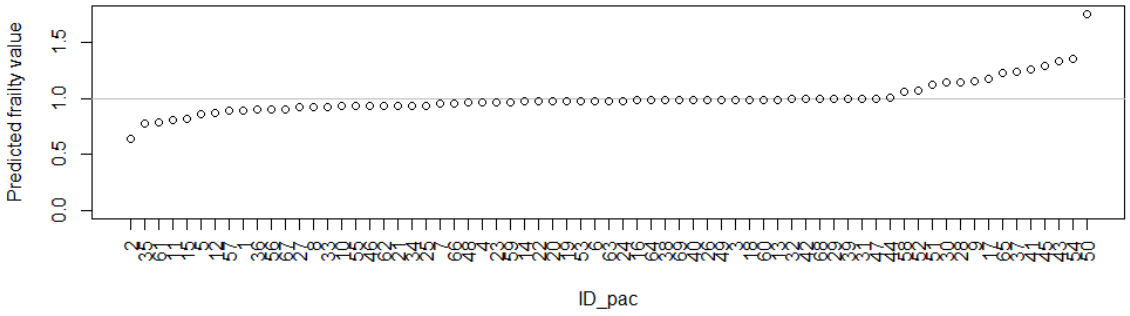


Figure 2 shows similar results as Figure 1.

Figura 2: Inverse Gaussian frailty model with Weibull baseline



We checked the convergence of the used methods for estimating the model parameter. Also we used a model selection criterion: AIC and BIC, see Table 4. We obtained that model with Gamma frailty had less value with both criterion, we should highlight the difference was small, beside the results obtained with both model were similar.

Table 4: Model Selection Criterion

Models	AIC	BIC
$Weibull + Gamma\ frailty$	228.462	246.025
$Weibull + inverse\ Gaussian\ frailty$	228.465	246.028

4. CONCLUSIONS

Frailty models can be used when survival data are clustered in groups. Also allow to incoporate a term to a model that considers unobserved heterogeneity which affects the risk estimation. We obtained in both models that etiopatogenia variable has statistically significance in the occurrence of amputation.

RECEIVED: NOVEMBER, 2016
REVISED: MARCH, 2017

REFERENCES

[1] GUTIERREZ, R. [2002]: Parametric frailty and shared frailty survival models **The Stata Journal**, 1.

[2] HOUGAARD, P. [2000]: **Analysis of Multivariate Survival Data** Springer-Verlag.

[3] KLEIN, J.P., H. C. HOUWELINGEN, J. G. IBRAHIM and T. H. SCHEIKE [2014]: **Handbook of Survival Analysis** Chapman Hall/CRC.

[4] MUNDA, M., F. ROTOLO and C. LEGRAND [2012]: Parametric frailty models in R **Journal of Statistical Software**, 51 http://www.jstatsoft.org/.

[5] WIENKE, A. [2010]: **Frailty Models in survival Analysis** Chapman Hall/CRC.

[6] ZARULLI, V., C. MARINACCI and G. COSTA et al [2013]: Mortality by education level at late-adult ages in Turin: a survival analysis using frailty models with period and cohort approaches **BMJ Open.** 2013;3:e002841. doi:10.1136/bmjopen-2013-002841.