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Ajuste de modelos de fragilidade e riscos proporcionais aplicados a dados de retinopatia diabética

Adjustment of Fragility Models and Proportional Risks Applied to Diabetic Retinopathy Data

Ajuste de modelos de fragilidad y riesgos proporcionales aplicados a datos de retinopatía diabética

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Resumo

Atualmente a análise de sobrevivência é uma das áreas que mais crescem no campo da análise estatística, com uma sólida teoria para ajustar modelos de regressão para estudar certos fenômenos, os quais têm, em sua estrutura, a característica de ter observações incompletas na amostra denominada censura. Embora esses modelos possam representar eficientemente o fenômeno em estudo em muitas situações, alguns deles não levam em consideração a existência de uma variável não observável presente na maioria dos estudos, denominada fragilidade. Essa fragilidade denota a suscetibilidade do evento a ocorrer por um indivíduo ou objeto determinado sob investigação. O objetivo deste trabalho foi mostrar que, em situações em que a fragilidade está presente, o uso de modelos que capturam a variabilidade dessa variável é mais viável para a análise desses dados quando comparado aos modelos convencionais em estudos de sobrevivência. Para tanto, foi realizada uma análise comparativa entre esses modelos, ajustada para um conjunto de dados de pacientes diagnosticados com retinopatia diabética, e também foi realizado um estudo de simulação para o modelo de fragilidade gama com diferentes porcentagens de censura e heterogeneidade. Após o ajuste dos modelos, observa-se que os modelos de fragilidade tiveram melhor desempenho quando comparados ao modelo de Cox, com ênfase no modelo de fragilidade gama, que gerou o menor valor para AIC e BIC. O estudo de simulação mostrou que altas taxas de censura prejudicam o grau de previsibilidade do modelo de fragilidade e que altas taxas de heterogeneidade contribuem para estimativas de parâmetros.

Palavras-chave: Análise de sobrevivência; Modelo de cox; Heterogeneidade.

Abstract

Survival analysis is currently one of the fastest-growing areas in the field of statistical analysis, with a solid theory for adjusting regression models to study certain phenomena, which have, in their structure, the characteristic of having incomplete observations in the sample called censorship. Although such models can efficiently represent the phenomenon under study in many situations, some of them do not take into account the existence of an unobservable variable present in most studies, called frailty. This fragility denotes the susceptibility of the event to occur by a determined individual or object under investigation. The objective of this work was to show that in situations where frailty is present, the use of models that capture the variability of this variable is more viable for the analysis of these data when compared to conventional models in survival studies. For this purpose, a comparative analysis was performed between these models, adjusted for a set of data from patients

diagnosed with Diabetic Retinopathy, and a simulation study was also carried out for the gamma fragility model with different percentages of censorship and heterogeneity. After adjusting the models, it can be seen that the fragility models performed better when compared to the Cox model, with an emphasis on the gamma fragility model, which generated the lowest value for AIC and BIC. The simulation study showed that high censorship rates impair the degree of predictability of the fragility model and that high heterogeneity rates contribute to parameter estimates.

Keywords: Survival analysis; Cox model; Heterogeneity.

Resumen

El análisis de supervivencia es actualmente una de las áreas de más rápido crecimiento en el campo del análisis estadístico, con una teoría sólida para ajustar los modelos de regresión para estudiar ciertos fenómenos, que tienen, en su estructura, la característica de tener observaciones incompletas en la muestra llamada censura. Aunque tales modelos pueden representar eficientemente el fenómeno en estudio en muchas situaciones, algunos de ellos no tienen en cuenta la existencia de una variable no observable presente en la mayoría de los estudios, llamada fragilidad. Esta fragilidad denota la susceptibilidad del evento a ocurrir por un determinado individuo u objeto bajo investigación. El objetivo de este trabajo fue mostrar que en situaciones donde la fragilidad está presente, el uso de modelos que capturan la variabilidad de esta variable es más viable para el análisis de estos datos en comparación con los modelos convencionales en estudios de supervivencia. Para este propósito, se realizó un análisis comparativo entre estos modelos, ajustado por un conjunto de datos de pacientes diagnosticados con retinopatía diabética, y también se realizó un estudio de simulación para el modelo de fragilidad gamma con diferentes porcentajes de censura y heterogeneidad. Después de ajustar los modelos, se puede ver que los modelos de fragilidad funcionaron mejor en comparación con el modelo de Cox, con énfasis en el modelo de fragilidad gamma, que generó el valor más bajo para AIC y BIC. El estudio de simulación mostró que las altas tasas de censura afectan el grado de previsibilidad del modelo de fragilidad y que las altas tasas de heterogeneidad contribuyen a las estimaciones de los parámetros.

Palabras clave: Análisis de supervivência; Modelo de cox; Heterogeneidad.

1. Introdução

According to the World Health Organization (2016), Diabetes Mellitus (DM) is an endocrine disease in which the pancreas does not produce insulin, or there is a failure in the action of this hormone in the body. DM afflicts more than 400 million people worldwide, its incidence and prevalence have increased considerably in developing countries. It is estimated that in 2016, DM was the seventh leading cause of death in the world, responsible for the deaths of 1.6 million people (World Health Organization, 2016).

This disease stands out due to the severity of its complications that endanger the health of the individual, and which generate a high economic impact due to the high costs of treatments (Krug, 2016; World Health Organization, 2016). One of the severe complications of DM is the Diabetic Retinopathy (RD), a condition that causes irreversible visual loss due to neurovascular injuries (Yau et al., 2012; Krug 2016).

A survey of the worldwide prevalence of DM estimated that approximately 35% of individuals with long-term DM have Non-Proliferative Diabetic Retinopathy (RDNP), and 7% is diagnosed with Proliferative Diabetic Retinopathy (RDP) as the most severe, as it causes loss of the vision (Yau et al., 2012). Another meta-analysis study showed that of the 32.4 million cases of blindness in the world in 2010, 833,690 were due to RD, and of the 191 million cases of visually impaired, 3.7 million were due to RD (Leasher et al., 2016). DR is considered a severe public health risk (Krug, 2016).

One of the treatments commonly used in RDP is laser photocoagulation. This treatment removes areas where there is no perfusion and cauterizes micro-aneurysms. It is expected that the individual undergoing this therapy will reduce the risk of visual loss by up to 50 % (Leasher et al., 2016).

Considering that the RD depends on the time that the individual has the DM, the uncontrolled glycemic levels, arterial hypertension (Krug, 2016; Yau et al., 2012) and that these variables are different for each individual, when analyzing sample data with this variability, if necessary, the applicability of statistical models that consider such heterogeneities.

Nowadays, there is an increase in the application of statistical tools in the area of health and medical sciences. In this sense, the mechanisms of survival analysis appear with a significant impact on clinical trials and medical experiments. To verify the influence of covariables in the time until the occurrence of the event of interest, one can use the Cox Regression Model, proposed in 1972 by the British statistician David Cox (Cox, 1972).

However, when the individuals to be observed are heterogeneous for several reasons, as, in health research, it is necessary to employ an analysis of the data that considers the distinct characteristics that favor or not that the individual suffers the event. The statistical models that find this information are essential to obtain better estimates and accurate inferences. Therefore, the fragility models, extensions of the Cox model, present a theoretical basis that satisfies the presence of heterogeneity between individuals. Furthermore, in these cases, they may perform better estimates than the classic Cox model.

In this study, the main focus was to make a comparative analysis of the performance of Cox's proportional hazards model and the fragility models on the assumption of heterogeneity among the individuals under study. To this end, we performed an analysis of a data set from the study of prognosis in Diabetes by Blair et al. (1980) in Northern Ireland in 1976. In which, the time until the total blindness of patients with Diabetic Retinopathy who were being evaluated undergoing laser treatment. Besides, a simulation study was carried out with different values of censorship rate and degree of heterogeneity, assessing the degree of predictability of the Gamma fragility model for the simulated data.

Given this, the objective of this study was to demonstrate that in situations where there is a presence of heterogeneity between individuals, the fragility models behave better than Cox's proportional hazards model, which disregards the existence of this random effect in the construction of the statistical models. It leads to better estimates for fragility models, and therefore better inferences about the problem addressed.

2. Literature Review

In survival analysis, the variable of interest is always the time until the occurrence of a certain event of interest, which we call failure. Colosimo & Giolo (2006) define, T as a random, non-negative, usually continuous variable, which represents the failure time. This variable is specified in Survival Analysis by the functions probability density $f(t)$, survival $S(t)$, risk $\lambda(t)$, and cumulative risk $\Lambda(t)$.

2.1 Censoring

The main attribute in a survival study is the presence of censoring, which is partial or incomplete observations. The occurrence of these censures is because of not all individuals

under investigation experience the event of interest (outcome) for several reasons, linked or not to failure. However, censorship should be taken into account in the statistical analysis, as it provides some information about individuals.

There are three types of censoring. Type I is the one in which time is pre-established, reaching the end of the study with individuals who have not failed. In type II, a specific number of failures is established. The rest is classified as a censor at the end of the study. The last one is random censorship, which occurs when the individual understudy is removed from the experiment without observing the failure for the reason that is not linked to the event of interest.

2.2 Important Functions

The first function that we will deal with in a survival context is the probability density function, which is defined based on the event of interest when observing an individual over a period of time. It is expressed as follows

$$f(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t)}{\Delta t}, \quad (1)$$

in which, $f(t) \geq 0$ for all t, and has the area under the curve equal to 1.

According to Moore (2016), the survival function can be understood as the probability of an individual surviving over a specific time t since it has not yet suffered the event, it is mathematically defined as

$$S(t) = P(T > t) = 1 - P(T \leq t) = 1 - F(t), \quad (2)$$

this function assumes a value of 1 at time zero and decreases or remains constant over time.

Two other functions that are also very important in the context of survival analysis are the risk and accumulated risk functions. As reported by Colosimo & Giolo (2006), the risk function is the instantaneous failure rate in time t conditioned on survival until time t. The risk function is then defined as follows

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t}. \quad (3)$$

The accumulated risk function as the name suggests provides the accumulated risk or cumulative failure rate of individuals and is defined as

$$\Lambda(t) = \int_0^t \lambda(u) du. \quad (4)$$

The accumulated risk function does not have a direct interpretation, but it can be advantageous in assessing the risk function or failure rate.

2.3 Kaplan-Méier Estimator

One of the most used estimators in the literature to estimate the survival function in a non-parametric way when censored data is available and was proposed by (Kaplan & Meier, 1958). This estimator has excellent asymptotic properties and is also a maximum likelihood estimator of $S(t)$, also known as a product limit estimator and defined as follows

$$\widehat{S(t)} = \Pi_{j, t_j < t} (1 - \frac{d_j}{n_j}). \quad (5)$$

Another well-known estimator for estimating the survival function is the Nelson Aalen estimator, which is more appropriate for small samples.

2.4 Log-Rank and Peto tests

One of the goals in survival analysis is to check if there is a difference in the survival curves of specific groups; this is very common in medical studies. In this sense, many tests have been proposed in the literature to compare these curves.

In the particular case of comparing two survival functions, the following general form includes the essential criteria in the research [see (Colosimo & Giolo, 2006)]:

$$S = \frac{[\sum_{j=1}^{k} u_j (d_{2j} - w_{2j})]^2}{\sum_{j=1}^{k} u_j (v_j)^2}, \quad (6)$$

where d_{2j} characterizes the failure of individuals in group 2 at time j. w_{2j} and V_j are the mean and variance of d_{2j} , respectively; obtained from the distribution of d_{2j} , which follows a hypergeometric distribution and u_j's are the weights that specify the tests.

Under the null hypothesis that survival functions do not differ between groups, the S statistic has a chi-square distribution with 1 degree of freedom for large samples (Colosimo & Giolo, 2006). In particular, the Log-rank test is obtained when we consider that $u_j = 1$, with $j = 1,2 \dots, k$.

Peto & Peto (1972), Prentice (1978), and Colosimo & Giolo (2006) suggest using a weight function that directly depends on the past expression of survival observed from the two combined samples.

The weight function is a modification of the Kaplan-Meier estimator and is defined in such a way that its value is known before the failure occurs. The survival function estimator is given by

$$\hat{S} = \Pi_{j:t_j<t}\left(\frac{n_j+1-d_j}{n_j+1}\right) = \Pi_{j:t_j<t}\left(1-\frac{d_j}{n_j+1}\right), \quad (7)$$

and the weights used are

$$u_j = \hat{S}(t_j - 1)\frac{n_j}{n_j+1}. \quad (8)$$

This estimator is known as Peto-Prentice (Colosimo & Giolo, 2006). The main difference between the Log-rank and Peto tests are that in the Peto test, a weighting relative to the previous survival experience is made, what does not happen in the test Log-rank.

2.5 Semiparametric Cox's model

Cox's model has been widely used in survival studies due to its great flexibility, with the main assumption for its application that the risks between individuals in the groups are proportional, for this reason, it is also known as the proportional risk model and was proposed by (Cox, 1972). Colosimo & Giolo (2006) define Cox's model as follows.

Consider p covariables, so that $\mathbf{x}$ is a vector of components $= (x_1, \dots, x_p)^T$. The general expression of the model is given by

$$\lambda(t) = \lambda_0(t) g(\mathbf{x}^T \beta), \quad (9)$$

where $g(.)$ is a non-negative function such that $g(0) = 1$ usually specified as the exponential function, λ_0 is the non-parametric component of the model, also known as the base function or basal, and β is the parameter vector.

2.6 Fragility in a univariate context

Cox's model disregards the existence of an unobservable random variable, which is because a particular individual or object under study is more susceptible to suffering the event than another, which we call fragility.

Frailty enters the model as a multiplicative effect on the underlying risk function. It was proposed by Clayton (1978) who used frailty without mentioning the term in a situation of multivariate modeling, for a study of the incidence of chronic disease.

Vaupel, Manton & Stallard (1979) introduced the term frailty in a univariate context in survival models. This random variable follows a specific probability distribution that should be used to model this effect; several distributions can be used for this purpose. In this work the Gamma, Inverse Gaussian and t –Student distributions were used. With the inclusion of the fragility variable, the model is given as follows,

$$\lambda_i = z_i \lambda_0(t) exp(\mathbf{x}_i{}^T \beta), \quad (10)$$

wherein z_i is the frailty term that follows a specific probability distribution.

2.7 Probability distributions for $z_i's$

In this section, we present some probability distributions for modeling the random effect (fragility). In this sense, the t-Student, Inverse Gaussian, and Gamma distributions are discussed.

2.7.1 The t-Student distribution

This distribution is well known in Statistics and used for continuous data modeling, which has the characteristic of having tails heavier than the normal (or Gaussian) distribution. It is obtained from the ratio of two other continuous random variables, that is, normal and chi-square. A particularity of this distribution is that as we increase the sample size, the $t-$student distribution converges to a normal distribution.

We say that the fragility Z has t-Student distribution if its density function is of the form:

$$f_Z(z) = \frac{\Gamma(\frac{n+1}{2})}{\Gamma(\frac{n}{2})\sqrt{\pi n}}(1+\frac{z^2}{n})^{-(\frac{n+1}{2})}, \quad (11)$$

We denote that $Z \sim t(n)$, and we say that Z follows a t-Student distribution with n degrees of freedom.

2.7.2 The Gaussian Inverse distribution

In the inverse Gaussian distribution, it is mainly considered that the data have a high dependence at the beginning and the end of the study. This distribution has two parameters (μ, θ) and its probability density function is given by

$$f_Z(z) = \frac{1}{\sqrt{2\pi\theta}} z^{-\frac{3}{2}} \exp\left\{-\frac{(z-\mu)^2}{2\theta\mu^2 z}\right\}, \quad (12)$$

where $\mu > 0$, $\theta > 0$, and the expected value of the fragility is μ with variance $\mu^3\theta$. Since the assumptions of the fragility models imply that $E(Z) = \mu = 1$, as well as $Var(Z) = \mu^3\,\theta = \theta = \sigma^2$, then the density function happens to be as follows

$$f_Z(z) = \frac{1}{\sqrt{2\pi\theta}} z^{-\frac{3}{2}} \exp\left\{-\frac{(z-1)^2}{2\sigma^2 z}\right\}. \quad (13)$$

2.7.3 The Gamma distribution

The Gamma distribution is one of the most used in fragility modeling due to its mathematical comprehensiveness. It is beneficial for modeling data with a strong dependence on end times. The probability density function for the fragility component with Gamma distribution with parameters $\alpha > 0$ and $\beta > 0$ is given by

$$f_Z(z) = \frac{1}{\Gamma(\alpha)\beta^\alpha} z^{\alpha-1} \exp\left\{-\frac{z}{\beta}\right\}, \quad (14)$$

wherein α and β are named shape and scale parameters, respectively.

2.8 Parameter Estimation Method

The estimation of parameters in univariate fragility models is carried out employing penalized partial likelihood. However, in some cases, it is also possible to estimate the parameters using the EM (Expectation-Maximization) algorithm, as in the Gamma fragility model, for example.

According to Duchateau & Janssen (2008), in the penalized partial likelihood approach, the complete likelihood of the data consists of two parts. The first part is the conditional verisimilitude of the data given the weaknesses, while the second part corresponds to the distribution of the weaknesses. In this approach, the second part of the likelihood is considered to be a penalty term. In this context, the complete likelihood is then written as follows,

$$l_{ppl}(\boldsymbol{\gamma}, \boldsymbol{\beta}, \boldsymbol{\omega}) = l_{part}(\boldsymbol{\beta}, \boldsymbol{\omega}) - l_{pen}(\boldsymbol{\gamma}, \boldsymbol{\omega}), \quad (15)$$

in which $l_{ppl}(\boldsymbol{\gamma}, \boldsymbol{\beta}, \boldsymbol{\omega})$ is the complete likelihood of the data, $l_{part}(\boldsymbol{\beta}, \boldsymbol{\omega})$ is the conditional likelihood of the data given the weaknesses and $l_{pen}(\boldsymbol{\gamma}, \boldsymbol{\omega})$ is the penalty function. With $\eta_i = \mathbf{x}^T\boldsymbol{\beta} + \omega$ and $\boldsymbol{\eta} = (\eta_1, \dots, \eta_n)$ with $i = 1, \dots, n$. Thus, follows that

$$l_{part}(\boldsymbol{\beta}, \boldsymbol{\omega}) = \sum_{i=1}^{n} \delta_i \left[\eta_i - \log \sum_{\omega \in R(y_i)} \exp(\eta_\omega)\right], \quad (16)$$

And

$$l_{pen}(\boldsymbol{\gamma}, \boldsymbol{\omega}) = -\sum_{i=1}^{n} log f_W(\omega), \quad (17)$$

where $f_W(\omega)$ is the density function for the random effects $\omega_i's$. Note that the general shape of the complete likelihood function changes according to the choice of distribution for modeling the fragility effect; therefore, there is a change in the density function of the random effects $\omega_i's$ and, in the penalty term of the complete likelihood function.

2.9 Model Selection

This section presents the most used information criteria for selecting and choosing statistical models, that is, the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC).

The basic idea in the Akaike Information Criterion (AIC) is to adjust the model as parsimonious as possible, that is, that it has a smaller number of parameters compared to the model containing all parameters (saturated model), but that it can explain or describe the phenomenon as well or even better than the saturated model.

According to Moore (2016), one of the best ways to evaluate statistical models is through the calculation of AIC, which consists of assessing the likelihood of the model, penalized by the number of parameters. The goal is to find the model so that the quantity below is minimized. The AIC is given as follows,

$$\text{AIC} = -2l(\hat{\boldsymbol{\beta}}) + 2k, \quad (18)$$

wherein $l(\hat{\beta})$ is the model's log-likelihood and k is the number of parameters.

As reported by Klein & Moeschberger (2005), the inclusion of variables in the model causes a decrease in the value of AIC; however, at some point, the criterion starts to increase, indicating that the inclusion of particular variables is unnecessary and will not contribute to parameter estimates.

Regarding the Bayesian information criterion (BIC), there is a more significant penalty in the model by the number of parameters, that is, by the number of covariables added to the model. In general, the idea in this criterion is the same view for the AIC; we want to find the most parsimonious model possible. Therefore, we must find the model for which the quantity below is minimal.

$$\text{BIC} = -2l(\hat{\beta}) + k\log n \tag{19}$$

3. Material and Methods

This is an observational, retrospective study with a quantitative approach, as can be seen in (Pereira et al., 2018). The data set used in this work is derived from the work done by Blair et al. (1980) in Northern Ireland. The database contains 394 observations from 197 patients with diabetic retinopathy undergoing photocoagulation treatment with laser. For each patient, one eye was randomized to receive the treatment, and the other eye was taken as a control. The variables present in the database are: id (which is an individual identifying variable), eye, status, treatment, age, laser type and diabetes type. It is possible to access this data through the command data(rms) in software R (Team, 2013).

In this work, the focus was on the analysis of semiparametric fragility models in contrast to the Cox model. Kaplan-Meier survival curves, the Log-rank test were also evaluated for comparison between these curves. The analyses were performed using the statistical software R in version 3.5.0 (Team, 2013). The analyzes in the program were aided by the *survival* (Therneu, 2015; Borgan, 2000), *muhaz* (Hess & Gentleman, 2010), and *rms* (Harrel & Frank, 2019).

The software R is currently one of the most used tools for statistical analysis, covering all the techniques available in this segment. The tool also allows the modeling of fragility in

survival analysis, with implementations in the parametric and semi-parametric fragility models. For the simulation study in the R software, the *frailtySurv* (Monaco, Gorfine & Hsu, 2018), in which 10,000 values were generated in each simulation for the different combinations of censorship rate and degree of heterogeneity of the data. The settings of the values were the censorship percentages of 10, 25, 50, and 75%, combined with the degrees of heterogeneity of 10, 20, 30, 40, and 50%.

4 Results and Discussion

4.1 Descriptive Statistics

In order to verify the estimates of the probabilities of survival between the groups, the Kaplan-Meier estimator was used. In Table 1, it is possible to see some results obtained for the treated and control groups.

Table 1. Kaplan-Meier estimates for the treated and control groups.

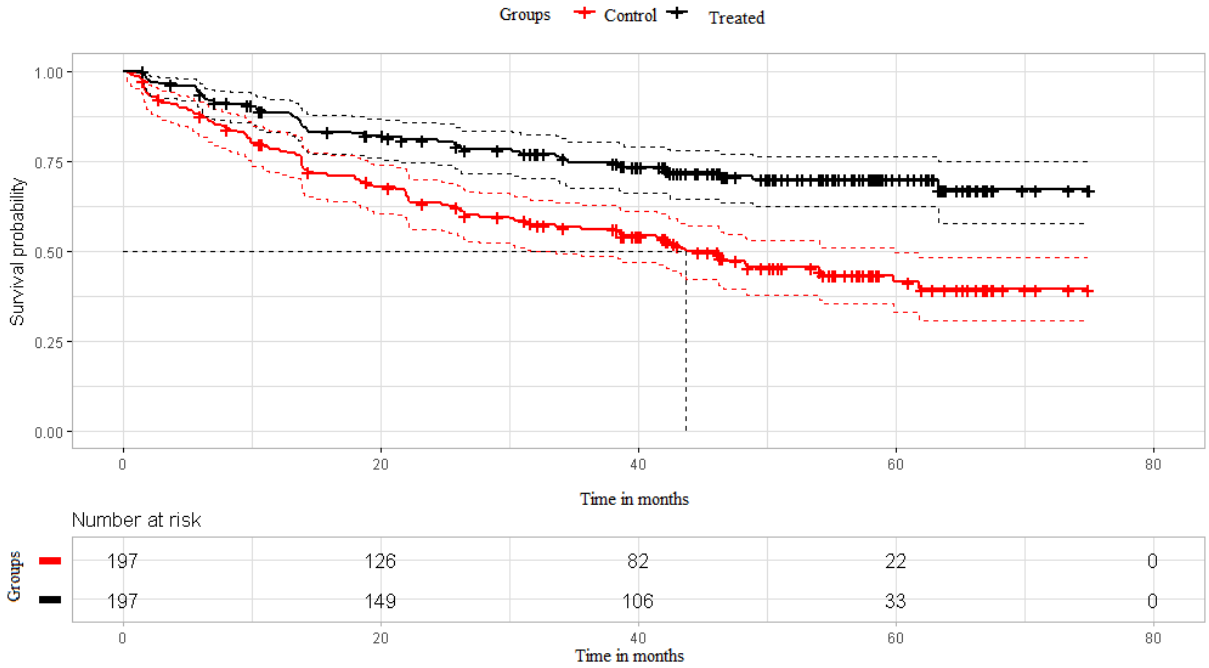
Groups	**(N=394)**	**Events**	**Median**	$IC_{95\%}$
Control	197	101	43,7	[31,6;59,8]
Treated	197	54	NA	NA

Source: Prepared by the authors.

Where, there is a possible efficacy of laser treatment for delaying blindness since, in the control group, the number of events was much higher than in the treated group.

It is noted that it was not possible to obtain the estimates for the median survival time for the treated group, this was due to the study has ended, and more than 50% of the individuals did not suffer the event (This can be seen in Figure 1).

Figure 1. Kaplan-Meier survival curves for the treated and control groups.

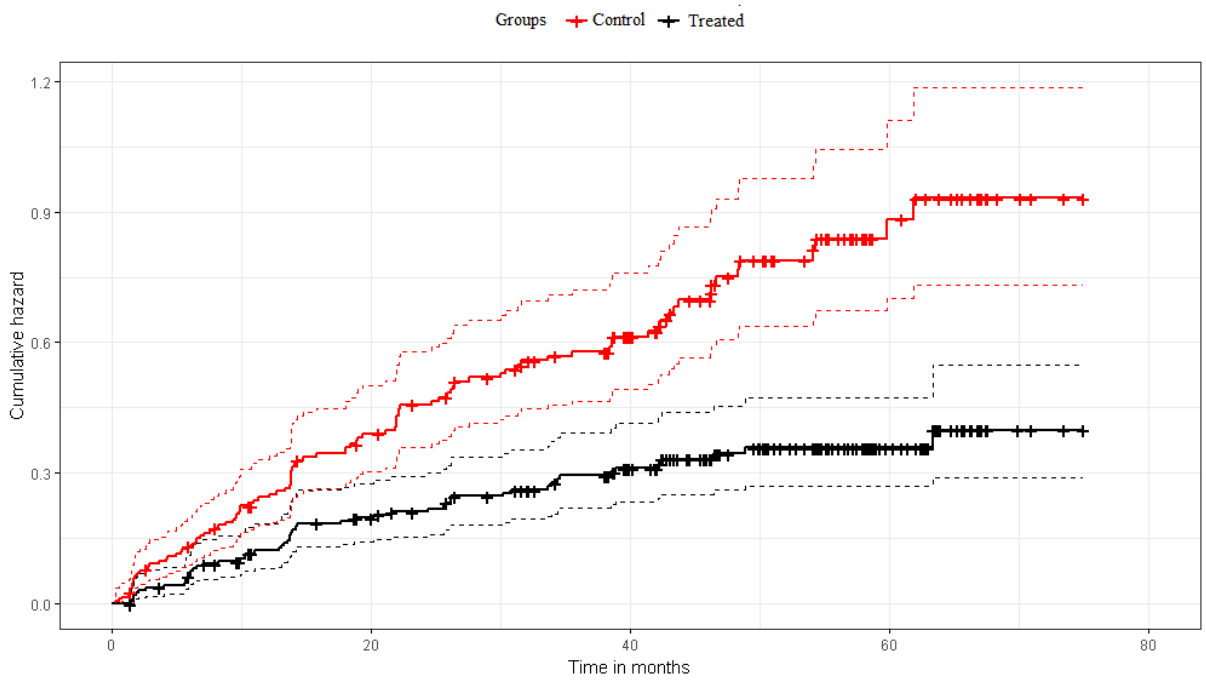


Source: Prepared by the authors.

Figure 1 shows that the survival curve obtained by the Kaplan-Meier estimator for eyes treated by photocoagulation with laser obtained a superior survival curve compared to control eyes. One can see that this is an indication that the treatment carried out using both types of lasers was effective in reducing the risk of blindness among patients.

Figure 2 displays the accumulated risk curves for the treated and control groups. As expected, it is observed that the control group has, during the entire study period, a risk curve higher than the curve of the treated group. Reinforcing the idea that treatment seems to have control under the blindness of these patients.

Figure 2. Accumulated risk curves for the treated and control groups.



Source: Prepared by the authors.

In order to certify the possible differences between the survival curves of the groups, the log-rank test shown in Table 2 was used. It can be seen that in all groups, there was a significant difference between the survival curves; thus, it can be concluded that the laser treatment performed played a decisive role in delaying the blindness of the patients. It can also be noticed that there was a difference in the type of laser, which means that one of the lasers was more effective for the treatment.

There was also a difference in the survival of patients who had type 1 and type 2 diabetes, implying that one of the two is more aggressive in terms of retinopathy blindness. It is possible to see that the treatment proved to be more efficient in one eye, with a difference in the survival curves of these groups.

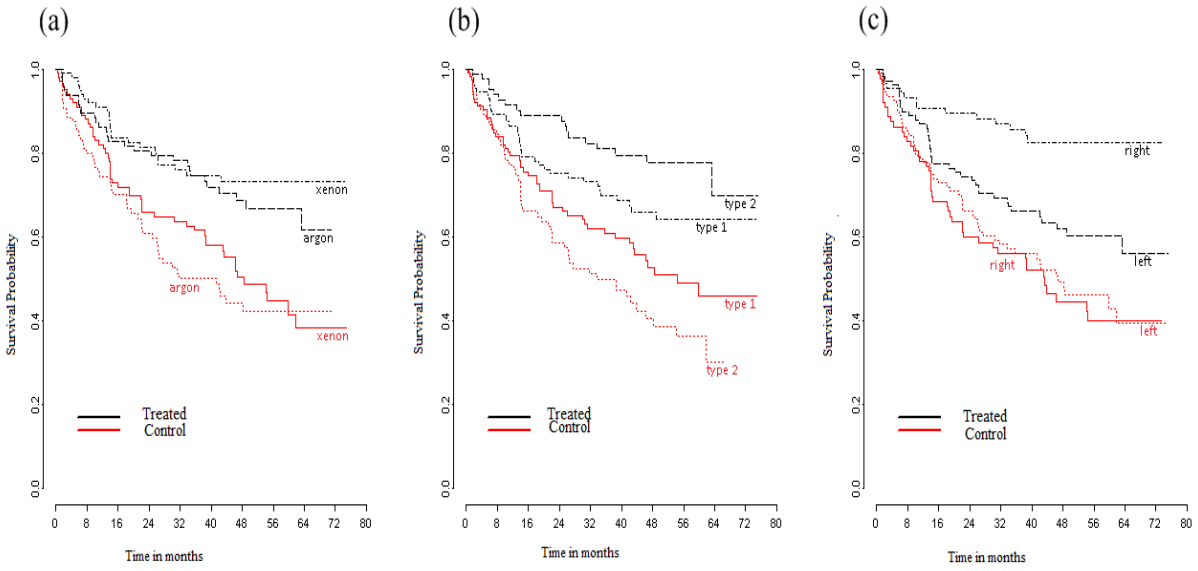
Table 2. Log-rank and Peto tests for the difference between the survival curves of the studied groups.

	Log- rank		Peto	
Group	χ^2	**p-value**	χ^2	**p-value**
Treated vs Control	22,2	<0,0001	20,7	<0,0001
Laser xenon vs Laser argon	22,4	<0,0001	20,9	<0,0001
DM type 1 vs DM type 2	22,5	<0,0001	20,8	<0,0001
Right eye vs Left eye	24	<0,0001	23,1	<0,0001

Source: Prepared by the authors.

After verifying the differences between the survival probabilities of the groups through the Log-rank test, we plotted the graphs of the survival curves of these groups to find out in which situations or in which groups presented the most significant probability of obtaining blindness. Thus, Figure 3 shows the survival curves for the groups: type of laser, type of Diabetes, and treated eye.

Figure 3. Kaplan-Meier survival curves for groups.



Source: Prepared by authors.

Looking at Figure 3 (a), it is possible to notice that patients who were undergoing treatment with the type of *xenon laser* had higher chances of survival than those treated with *argon laser* or that is *xenon laser* was more effective in reducing the risk of blindness. It can also be noted from Figure 3 (b), that type 1 diabetes was more aggressive towards the blindness of the individual when he was undergoing treatment with the laser, and when not, individuals with type 2 diabetes were more likely to have blindness.

It can also be seen in Figure 3 (c) that, when treated, the right eye was more likely to survive than the left eye. Moreover, when left untreated, the left eye remained in most of the study with a higher chance of not blinding.

Table 3 displays the adjustment of the frailty models and Cox proportional hazards models where a comparative analysis of these models was made through the values of AIC, BIC and agreement (a measure that provides the degree of predictability of the model) of the models adjusted for the different distributions of the fragilities.

Table 3. AIC and BIC values for the adjusted models for the Diabetic Retinopathy data set.

Models	**AIC**	**BIC**	**Agreement**
Classic Cox	1707,931	1720,105	0,638
Gamma Fragility	1436,263	1437,715	0,881
Inv. Gaussian Fragility	1541,557	1543,742	0,841
t-Student Fragility	1549,709	1552,32	0,835

Source: Prepared by the authors.

In Table 3 one can see that all models adjusted with the presence of frailty performed better when compared to the conventional Cox model, reinforcing the idea that the heterogeneity of individuals must be taken into account.

It is also observed that the semi-parametric model with gamma fragility stood out from the others, having the lowest AIC and BIC values and the highest concordance value, being, therefore, the best fit for this data set. In the Table 4, it is possible to see the estimates of the model parameters.

Table 4. Estimates of the parameters of the Gamma Fragility model.

Covariables	**Coef**	**R.R.**	**S.E.**	$IC_{95\%}$	χ^2	**p-value**
Treatment	-0,5714	0,5647	0,2365	(0,3552;0,8978)	5,8400	0,0160
Risk	0,1932	1,2131	0,0827	(1,0315;1,4267)	5,4500	0,0200
Treat x Type 2	-1,1427	0,3190	0,3679	(0,1521;0,6687)	9,1500	0,0025
Fragility	-	-	-	-	188,64	< 0,001

Source: Prepared by the authors.

It is possible to observe that for individuals who underwent laser treatment, there was a decrease of about 43.53% in the risk of blindness. Moreover, the risk variable (risk score for one eye) represented an increase of 21.31% in the risk of blindness.

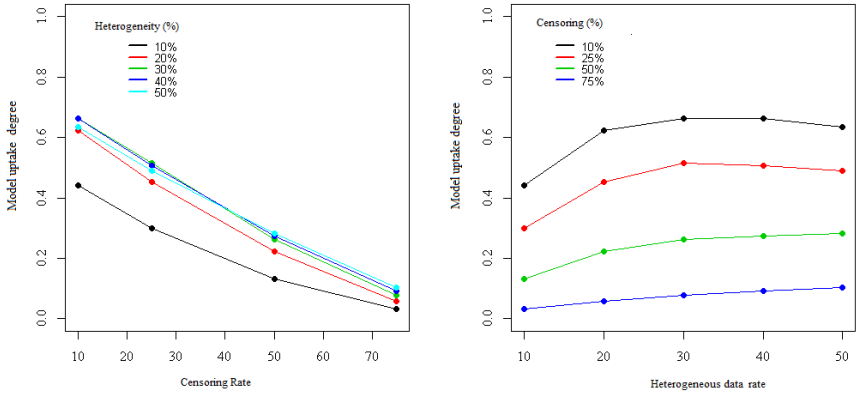
It can also be seen that for patients undergoing treatment and having type 2 diabetes, there was a decrease in the risk of blindness by up to 68.1%. Note that the random effect (fragility) was also a very significant variable for the model. We also have that the variance of this random effect was 2 (different from zero), which implies that the fragility model was applied correctly.

4.2 Simulation Study

In the simulation study, seen in figure 4, the censoring percentages of 10, 25, 50, 75% were adopted, in order to cover from models with situations of high failure rate to low failure rates (characterizing fractional cure models).

Besides, the degree of heterogeneity of the observations was relaxed employing the values adopted in the frailty parameter (10, 20, 30, 40, 50), to verify the degree of capitation of the Gamma model around the heterogeneity present in the data

Figure 4. A simulation study for different censoring rates and degree of heterogeneity in survival models with univariate fragility under Gamma distribution.



Source: Prepared by the authors.

According to Figure 4 (a) and (b), it can be seen that as the censoring rate increases, the degree of capitation of the model decreases, which indicates that a high rate of cured penalizes the degree of predictability of the model.

However, worse behavior is observed when the percentage of heterogeneity is 10%, where it is possible to observe the lowest values for the degree of the capture of the model.

It is also possible to notice in Figure 4 (b), a better behavior of the models for the censorship rates 10% and 25% concerning the others and that as the degree of heterogeneity increases, the models tend to obtain better answers regarding the capitation of the model, stabilizing to values above 30 in the heterogeneity rate.

5. Conclusions

In this research, it is clear the importance of modeling the heterogeneity present in individuals with the inclusion of the random effect in the model in survival studies, thus having a significant contribution in the estimates of the model parameters, and thus obtaining more reliable predictions to the data.

It is notorious the loss of information that one has with conventional modeling and considering that individuals have the chance to suffer the event of interest. Here the model that obtained the best results was the gamma fragility model, with the lowest values of AIC and BIC and the highest value for the degree of predictiveness, thus having better estimates than the others.

It was proven through the Log-rank and Peto tests that, for the treated eye of individuals who had type 2 diabetes, the chances of blindness were lower than for individuals who had type 1 diabetes. However, for the control eye, the result was the opposite; that is, individuals with type 2 diabetes were more likely to blind.

It was also shown that laser xenon was more effective in the treatment of retinopathy and that the right eye when treated was more likely to not blind. In contrast, when the right eye was not treated, it was more likely to blind.

The simulation study showed that high censoring rates impair the degree of predictability of the frailty model and that as there is an increase in the heterogeneity rate present in the data, there is also a contribution to the model's degree of predictability, which implies improvement parameter estimates.

The use of frailty models revealed the importance of treating the presence of a random effect in statistical modeling, considering the existence of heterogeneity among the individuals under study. These models were accurate in predicting the observed values in contrast to the conventional Cox model. Thus, it is evident in this paper the importance of considering the inherent heterogeneity of each individual under study, using this statistical tool.

Future perspectives in relation to this work is to adjust multivariate fragility models, as well as to carry out a comparative analysis between these models and univariate models. As well as, carry out a deepening with the residual analysis of these models.

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