A NON CONVENTIONAL USE OF SURVIVAL CURVES TO IDENTIFY FACTORS FOR GUSTATORY ALTERATIONS IN PATIENTS WITH CHRONIC OTITIS MEDIA

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- *ABSTRACT: We present an application of discrete survival-analysis and Poisson regression to identify factors that cause gustatory alterations in patients with chronic otitis media. A case study related to a prospective study to identify factors of gustatory alterations due to chorda tympani nerve involvement in patients with chronic otitis media without prior surgery was presented. The Log-rank, Tarone-Ware, and Peto-Prentice tests pointed out a significant association between survival curves of the healthy side and the affected side of the face of patients with chronic otitis media related to gustatory alterations ($p < 0.05$). Significant association was also found between survival curves of smokers and nonsmokers patients considering the healthy side of the face ($p < 0.05$). The most relevant covariates identified by Poisson regression model were the side of the face, age, gender, smoke, and cholesteatoma. The proposed method can serve as an alternative procedure to statistical test for comparison of samples of discrete variables. This approach has the advantage of being more familiar to clinical researchers.*

- *KEYWORDS: Survival analysis; Kaplan-Meier; log-rank test; Tarone-Ware test; Peto and Prentice test.*

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1 Introduction

The survival time estimates can be made through parametric models, which one assumes that data may be modelled by a particular probability distribution, or by non-parametric models. In the latter case, the Kaplan-Meier estimator is commonly used.

The product-limit estimator of Kaplan-Meier, or simply, the Kaplan-Meier estimator (Kaplan & Meier, 1958), is a estimated survival time considering that the probability that an individual will survive until a time t is independent of the probability of survival until each of the previous times. Therefore, some important concepts can be defined:

i) the probability of a death occurrence in a time interval between t_j and t_{j-1}, $j = 1, 2, \ldots, k$, given that the individual has survived beyond the immediately previous time:

$$q_j = P\big(T \in [t_{j-1}, t_j) | T \geq t_{j-1}\big)$$

ii) the probability of survival until a time t_j:

$$S(t_j) = (1 - q_1) \cdot (1 - q_2) \cdot \ldots \cdot (1 - q_j)$$

iii) and, finally, the Kaplan-Meier estimator:

$$\hat{S}(t) = \prod_{j:t_j<t} \left(\frac{n_j - d_j}{n_j} \right) = \prod_{j:t_j<t} \left(1 - \frac{d_j}{n_j} \right)$$

where n_j is the number of individuals at risk and d_j is the number of failures at time t_j.

In this paper we performed survival analysis method for discrete uncensored data. We used the number of taste strips instead of the usual time to event setting.

2 Data base and methods

This section presents a case study to illustrate the approach by using survival analysis to compare discrete data.

The case study is related to 45 patients with chronic otitis media (COM), being 25 with cholesteatoma and 20 without cholesteatomatous COM, with a mean age of 38 years. Eight cases of unilateral ageusia were found on the affected side. A prospective study was performed to identify gustatory alterations due to chorda tympani nerve involvement in patients with chronic otitis media (COM) without prior surgery, and to find out whether the presence of cholesteatoma worsened gustatory sensitivity in these patients.

The test was performed in patients with unilateral cholesteatomatous or suppurated COM not previously submitted to otological surgery. The test was based on “taste strips” with four different concentrations of salt, sweet, bitter, and sour. The analysis compares the two sides of the same patient, using the otological disease-free side as the control. The score could be between 0 (worst) and 16 (best), according to the number of taste strips which flavors have been recognized. The data were collected by interview and physical exam. The variables considered in this study were: age, gender, smoke, cholesteatoma, otorrhea, diabetes, hypertension, and side of the face. The number of taste strips recognized by the patients was outcome. Patients with cholesteatomatous or suppurated COM may present gustatory alterations, even in the absence of complaints.

3 Results and discussion

A typical result of the survival curve is shown in Figure 1 for comparison of the healthy (otological disease-free side) and affected side.

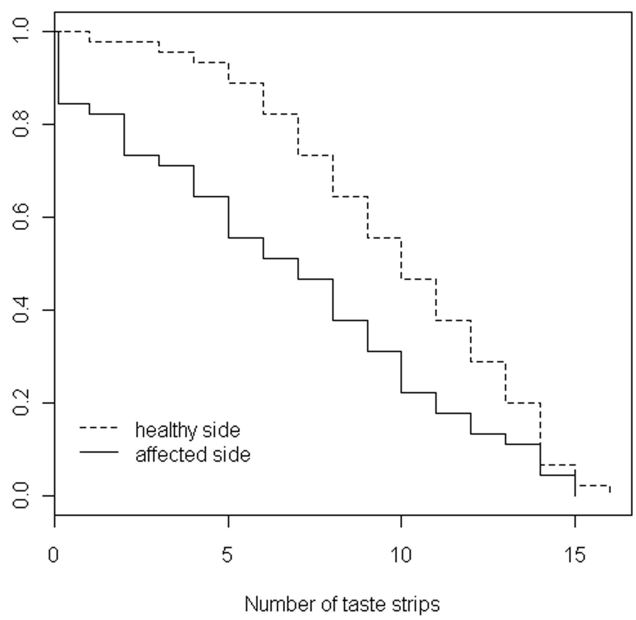

Figure 1 - Proportion of patients who recognized the flavors.

Three statistical tests were performed to assess the difference between the survival curves. The results pointed out significant association between the healthy and affected side: Log-rank test ($p = 0.00908$) (Cox, 1972; Mantel, 1966; Peto & Peto, 1972), Tarone-Ware test (Tarone & Ware, 1977) ($p = 0.00239$), and Peto and Prentice test (Peto & Peto, 1972; Prentice, 1978) ($p = 0.000943$).

Survival curves were also performed for comparison of the healthy and affected side using the remaining covariates: Gender and Smoke (Figure 2); Cholesteatoma and Otorrhea (Figure 3); and Diabetes and Hypertension (Figure 4). The survivorship functions intersect indicating that the proportional hazards assumption was violated.

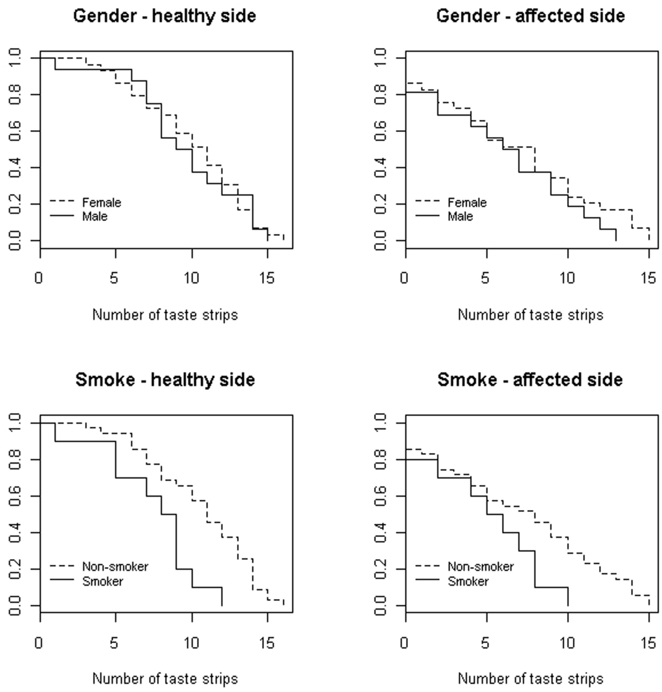

Figure 2 - Proportion of patients considering Gender and Smoke.

Table 1 shows the p-values of the statistical tests to assess difference between the survival curves regarding the covariates. The only significant association was found between the survival curves of smokers and non-smokers considering the healthy side of the face.

The factors which most influences the outcome is of great interest in epidemiologic research. Poisson Regression is a class of Generalized Linear Models (McCullagh & Nelder, 1989) often used to model count data.

Let Y_j be the number of taste strips recognized by patients with chronic otitis media and $X_1, X_2, \ldots, X_k$ a set of covariates. The Poisson regression model to this data set is

$$E(Y_j) = \lambda_j = \lambda_0\, exp(\beta_1 x_{1j} + \beta_2 x_{2j} + \ldots + \beta_k x_{kj})$$

where $\beta_1, \beta_2, \ldots, \beta_k$ are the coefficients of the independent variables and λ_0 is the

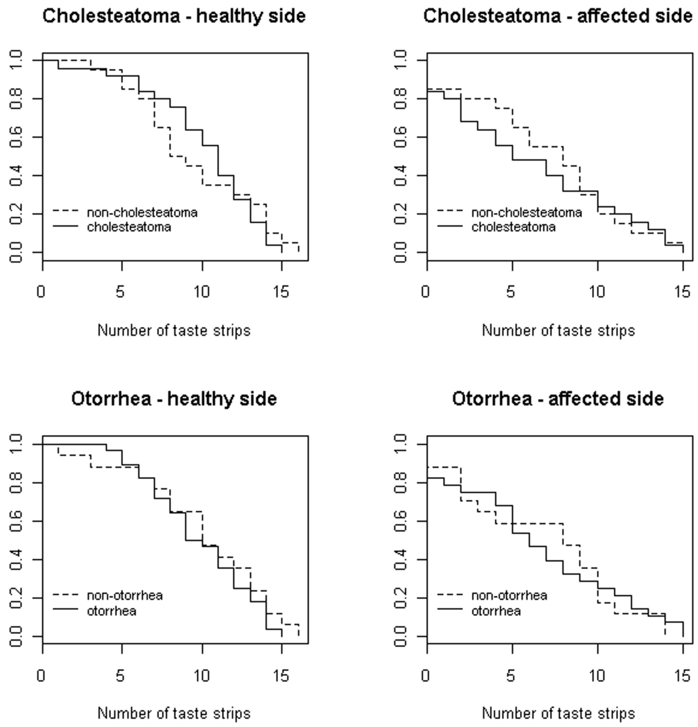

Figure 3 - Proportion of patients considering Cholesteatoma and Otorrhea.

Table 1 - Statistical tests

$Covariate(side)$	$Tarone-Ware$	$Log-rank$	$Peto-Prentice$
$Gender\ (healthy)$	0.773	0.79	0.757
$Gender\ (affected)$	0.441	0.282	0.558
$Smoke\ (healthy)$	0.005	0.003	0.008
$Smoke\ (affected)$	0.115	0.064	0.187
$Cholest.\ (healthy)$	0.676	0.962	0.467
$Cholest.\ (affected)$	0.613	0.759	0.509
$Otorrhea\ (healthy)$	0.549	0.423	0.649
$Otorrhea\ (affected)$	0.895	0.937	0.806
$Diabetes\ (healthy)$	0.343	0.364	0.377
$Diabetes\ (affected)$	0.327	0.600	0.205
$Hypert.\ (healthy)$	0.107	0.136	0.097
$Hypert.\ (affected)$	0.591	0.349	0.865

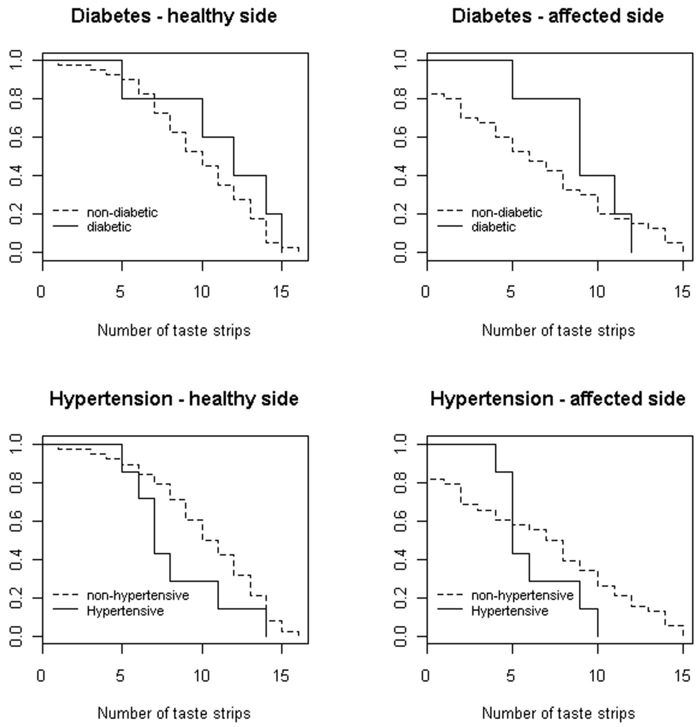

Figure 4 - Proportion of patients considering Diabetes and Hypertension.

baseline hazard rate assuming that all values of the *jth* patient is zero. Therefore the Poisson regression model may be re-written as follow

$$log_e(\lambda_j/\lambda_0) = \beta_1 x_{1j} + \beta_2 x_{2j} + \ldots + \beta_k x_{kj}$$

where $log_e(\lambda_j/\lambda_0)$ is the log rate ratio of the *jth* patient compared to an individual with baseline characteristics.

In search of the model which best fits the data, the smallest AIC (Akaike, 1974) was the used criteria to choose the model. The best model was reached through a Poisson regression model, as shown in Table 2, with the following covariates: side of the face, age, gender, smoke, and cholesteatoma. This model provided $AIC = 538.2$.

Table 2 - Poisson model

	Estimate	*Std. Error*	*z value*	$Pr(>\|z\|)$
(Intercept)	3.087648	0.132424	23.316	$< 2e-16***$
side	-0.396536	0.074669	-5.311	$1.09e-07***$
age	-0.015697	0.002726	-5.758	$8.53e-09***$
gender	-0.253850	0.083129	-3.054	$0.00226**$
smoke	-0.205866	0.102337	-2.012	$0.04426*$
cholesteatoma	-0.168641	0.077527	-2.175	$0.02961*$

Signif. codes : 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Conclusions

A further non conventional use of survival curves can be seen in Luiz et al. (2003) and Llorca & Delgado-Rodríguez (2005).

The medical problem related to the application presented in this paper was described by Felix et al. (2009).

We believe that the proposed survival curve approach can serve as an alternative procedure to statistical test for comparison of samples from quantitative and qualitative ordinal variables. In addition, this methodology may be more familiar to medical researchers.

PEREIRA, B. B; NASCIMENTO, E. M.; FELIX, F.; TOMITA, S. Uso não convencional de curvas de sobrevida para identificar os fatores de alterações gustatórias em pacientes com otite média crônica. *Rev. Bras. Biom.*, São Paulo, v.28, n.3, p.104-111, 2010.

- RESUMO: Apresentamos uma aplicação de análise de sobrevida para dados discretos e regressão de Poisson para identificar os fatores que causam alterações gustatórias em pacientes com otite média crônica. Um estudo de caso envolvendo um estudo prospectivo para identificar fatores de alteração gustatória, devido ao envolvimento do nervo corda do tímpano em pacientes com otite média crônica sem cirurgia prévia foi apresentado. Os testes de Log-rank, Tarone-Ware, e Peto-Prentice apontaram uma associação significativa entre as curvas de sobrevida do lado saudável e do lado afetado da face de pacientes com otite média crônica relacionada a alterações gustatórias ($p < 0,05$). Uma associação significativa foi também encontrada entre as curvas de sobrevida de pacientes fumantes e não fumantes, considerando o lado saudável da face ($p < 0,05$). As covariáveis mais relevantes identificadas pelo modelo de regressão de Poisson foram lado do rosto, idade, sexo, fumo, e colesteatoma. O método proposto pode servir como um procedimento estatístico alternativo para comparação de amostras de variáveis discretas. Esta abordagem tem a vantagem de ser mais familiar aos pesquisadores clínicos.

- PALAVRAS-CHAVE: Análise de sobrevida; Kaplan-Meier; teste log-rank; teste de Tarone-Ware; teste de Peto e Prentice.

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