ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 09, Issue, 03, pp.26474-26479, March, 2019

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

SURVIVAL ANALYSIS IN PATIENTS HOSPITALIZED WITH INFLUENZA (H1N1)

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ARTICLE INFO

Article History:

Received 22nd December, 2018
Received in revised form
29th January, 2019
Accepted 22nd February, 2019
Published online 31st March, 2019

Key Words:

Survival Analysis,
Hospitalization,
Influenza A virus H1N1 Subtype.

ABSTRACT

This is a descriptive, epidemiological, epidemiological study of the ecological type of a time series, with a quantitative approach, aiming to identify the relationship between social and demographic characteristics in the survival of patients hospitalized for influenza in Paraíba. The research was performed by the method of survival analysis and counted with 2,846 records collected from January to June 2016. Of these patients, 192 (6.7%) died. It was found that the influenza death rate of hospitalized individuals is higher in patients over 50 years of age, hospitalized by clinical specialty, and who incur greater expenses with hospitalization.

Citation: Ericka Holmes Amorim, Isis Milane Batista de Lima, Rozileide Martins Simões Candeia, Larissa Targino Soares de Lucena et al. "Survival analysis in patients hospitalized with influenza (H1N1)", *International Journal of Development Research*, 09, (03), 26474-26479.

INTRODUCTION

Influenza or influenza A (H1N1) is considered the inf ection which caused more diseases / deaths today. In the year 2009, the population Mexican has encountered this new type of flu. I dentificado in Mexico for the first time, the *influenza A virus,* bovine, has expanded rapidly throughout the change. It is characterized as an acute respiratory system disease, with a high global transmission and distribution capacity. In that month, the World Health Organization (WHO) declared a pandemic of the new influenza and asked health authorities to monitor cases of influenza and pneumonia (BELLEI, MELCHIOR, 2011). Epidemiological surveillance of *influenza A* in Brazil started in the year 2000, from sentinel health units and presents as objectives: identification of respiratory viruses to improve the seasonal *influenza* vaccine; characterization of virulence and pathogenicity; guaranteed minimum viral circulation throughout the country; early identification of a new viral subtype (VASCONCELOS; FARIAS, 2017). Influenza virus transmission between humans occurs through the respiratory tract, through secretions such as aerosols, droplets or through direct mucosal contact (ZAMBON, 2014). Each year, influenza becomes a significant cause of illness and human deaths producing important imp act on health, is therefore a continuing threat to public health (JERIGAN, COX, 2013). Despite similar symptoms with other viruses that affect the respiratory tract, sudden fever, for example - lasts about three days accompanied by muscle pain and prostration - s d are also characteristic to influenza virus infection. Epidemics are unpredictable and affect a considerable number of people. The setting of an epidemic will depend d inter alia, the prevention and control measures. Such epidemics are commonly evidenced by the increase in hospitalizations for bronchopneumonia, associated with secondary bacterial infections and with excess deaths, especially in the elderly and people suffering from chronic heart failure and pulmonary disease (BRASIL, 2014). According to Uyeki (2014), the clinical manifestations of the disease appear after the incubation period between one and three days. Most people with symptomatic influenza infection may have uncomplicated disease, with sudden onset of fever, cough, headache, sore throat, runny nose, nasal congestion, and muscle aches that resolve within three to five days, although coughing and fatigue may persist for longer. Children with influenza may have diarrhea and abdominal pain, combined with respiratory

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symptoms. Gastrointestinal problems were observed in adult subjects with Influenza virus infection duringthe 2009 pandemic, however the symptoms / symptoms may vary according to age and clinical conditions. The age range has great Influe INSTANCE on the individual risk of influenza, with greater focus on young people and more significant lethality in person s elderly in subjects who have medical conditions, or comorbidities, which can put them at risk for complications of influenza (WHO, 2012). Accurately quantifying the deaths caused by the virus Influenza is a difficult task because the disease is not always registered as the primary or contributing cause due to the lack of laboratory diagnosis. Therefore, the under-registration of the number of cases, since the causal nexus with influenza is not always realized due to lack of clinical suspicion / lack of laboratory diagnosis in the presence of severe respiratory disease. In this sense, mortality and mortality coefficients for influenza are affected by errors in the numerator in obtaining the mortality indicator and the denominator for the calculation of lethality (COSTA, 2015). According to the Ministry of Health (2014), in Brazil, occurrences of outbreak or deaths and cases of human influenza produced by new viral subtype are compulsory notification, and seasonal influenza is not included in this registry.

Epidemic episodes of influenza are recorded worldwide and if, on the one hand, the disease is a reason for apprehension in populations due to the occurrence of pandemics, on the other hand, in the endemic seasonal occurrence, it is considered a common disease. The population is familiar with influenza almost permanently. However, when it occurs in an epidemic way, the fear of the disease increases, due to the registered increase in virulence and pathogeni city, with consequent increases in morbidity / lethality (LIMA, 2015). Considering the importance of knowing the influenza, number of cases and the populations that most affects in the State of Paraíba - Brazil, it was decided to carry out a survey of the number of deaths due to influenza in the first period of 2016. Logo t and study aims to: Identify the relationship between social and demographic characteristics in the survival of patients hospitalized for influenza in the State of Paraíba.

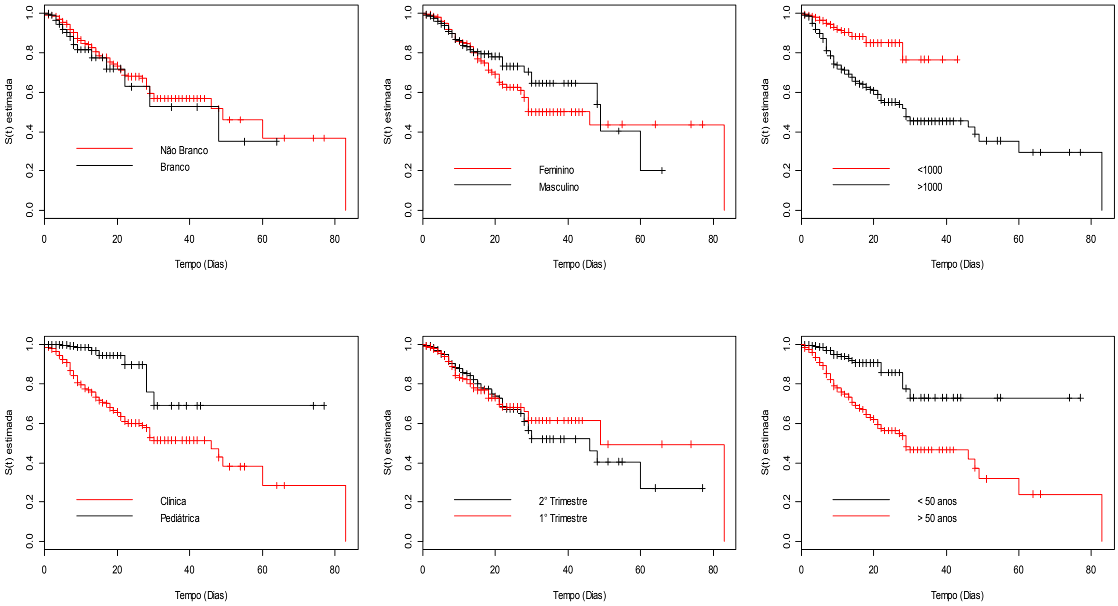
METHOD

Three minutes is a descriptive, observational epidemiological ecological time series type, with quantitative ordagem ab, about survival analysis of patients hospitalized with the influenza diagnostic. We studied 2.846 records collected from January to June 2016, referring to the state of Paraíba - PB. Survival analysis, also called survival analysis, is used when the variable of interest is time, interpreted as time until the occurrence of an event or as the risk of occurrence of an event per unit of time (Carvalho et al, 2011). According to Carvalho et. al (2011) the survival model is a regression model composed of a response variable, explanatory variables, the link function and the error structure. In survival analysis the response variable can be expressed in three ways: the probability of survival, ie the probability of not occurring the event of interest within the time interval; the incidence rate or risk function, the instantaneous rate of occurrence of the event of interest in time subject to its non-occurrence prior to; and the cumulative incidence, emphasizing that this concept differs from the concept of risk, although they are numerically equal when the incidence is low. The data were collected from the platform of the Department of the Unified Health System (DATASUS), through Tabwin. Being data of public domain and for that reason does not present necessity ofapproval by the Committee of Ethics and Research, according to the resolution 466/2012 of the National Council of Health. Therefore, all the ethical and legal aspects of a scientific research were fulfilled. Thus, the following variables were included: time (length of stay in days until death or exit from the individual), censorship (leaving the individual for causes other than "death"), race (white and nonwhite), age (<50; >50), amount spent on hospitalization (<R$ 1.000,00; > R$ 1.000,00), sex (male or female), specialty(clinical or pediatric), service period (1 trimestr and/ Q22016). It should be noted that all variables were dichotomized for the study. The analysis of the data was done through the statistical program R, version 3.2.4. Descriptive analysis of the data including simple frequencies and percentages was initially performed. Then began the survival analysis using non - parametric Kaplan-Meier method, and then tested methods are parametric and Cox log-normal.

RESULTS AND DISCUSSION

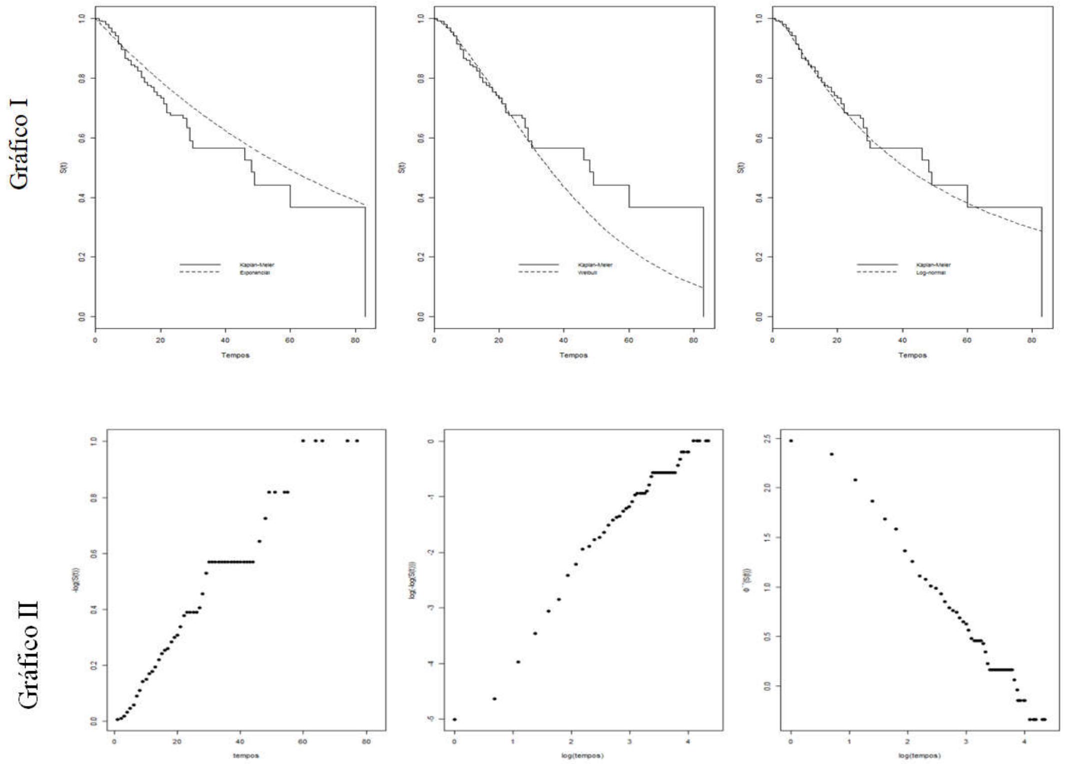
The sample consisted of 2,846 records of patients diagnosed with H1N1, admitted to public hospitals in the State of Paraíba, in J anuary period J une 2016. The hospital stay varied between 0 1 and 83 days. Of these patients, 192 (6.7%) died at the hospital. Age ranged from 0 to 99 years, with a mean of 31.48 years and 32.05 standard deviation, of which 1870 (65.7%) were younger than 50 years and 976 (34.3%) were older than 50 years. As to race, 331 (11.6%) white, and 2515 (88.4%) non-white were obtained. Furthermore, 1476 (51.8%) were males, and 1370 (48.2%) were females. The specialties of the visits were classified as pediatric with 1513 (53.2%) cases and clinical with 1333 (46.8%). The number of visits during the 0 6 months of the study varied, with 1215 (42.7%) the number of visits in the 1st Quarter (January to March), and 1631 (57.3%) in the 2nd Quarter (April to June).

Using the non-parametric Kaplan-Meier model: Kaplan-Meier nonparametric statistics were performed starting survival analysis. The stratified test revealed that in 46 days, approximately 52.5% of the individuals had an improvement in the condition, evolving to a high by cure, during this approximate estimate of mean time. The calculation for the mean hospitalization time was also performed, and the time of 48 days was found. It is observed, therefore, that the mean and median times are very close, indicating a possible symmetry in the distribution of the presented data. Furthermore, the survival estimates rm ranges between 01 and 83 days in the hospital rmanência piece; in this case, on the first day of hospitalization, the patients chances are still alive was 99.3%, while in 60 days reduces the chances IRAM to 26.8% and in 83 days there was no chance of survival in the case studied. The stratified Kaplan-Meier tests were then performed, considering the following variables: race / color, age, amount spent on hospitalization, sex, specialty and month (period of hospitalization) (Figure 01). For this, it was observed that white individuals died faster than non-whites; regarding gender it was shown that the female sample dies u r more apidamente the younger age, whereas with advancing age, males had a steeper decline in the survival Texa. The patients who demanded higher expenses with hospitalization were also those who were more likely to die; the clinical specialty is more related to thedeaths that died; n 2nd trimester the risk of death was considered to begreater, given that there was a



Source: DATASUS - TabWin, 2016.

Figure 0 1. Kaplan-Meier stratified for race, sex, amount spent, specialty of care, length of hospitalization and age, Paraíba, 2016



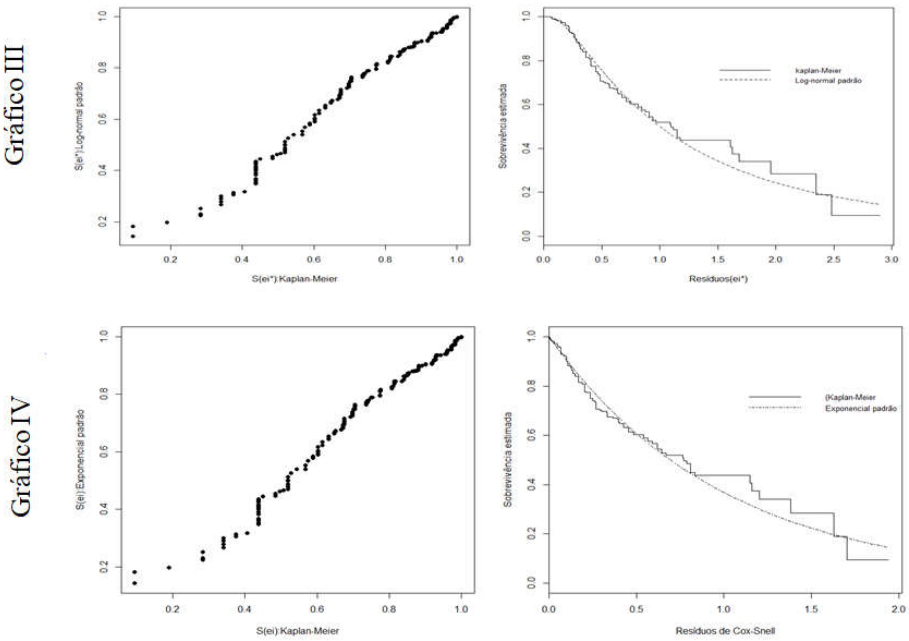
Source: DATASUS - TabWin, 2016.

Figure 2. Survival estimated by Kaplan-Meier (Graph I) and linearity distribution (Graph II) versus Exponential, Weibull and Log-normal models, Paraíba, 2016

Table 01. Non-parametric tests for comparison of survival curves for individuals hospitalized with H1N1, Paraíba, 2016

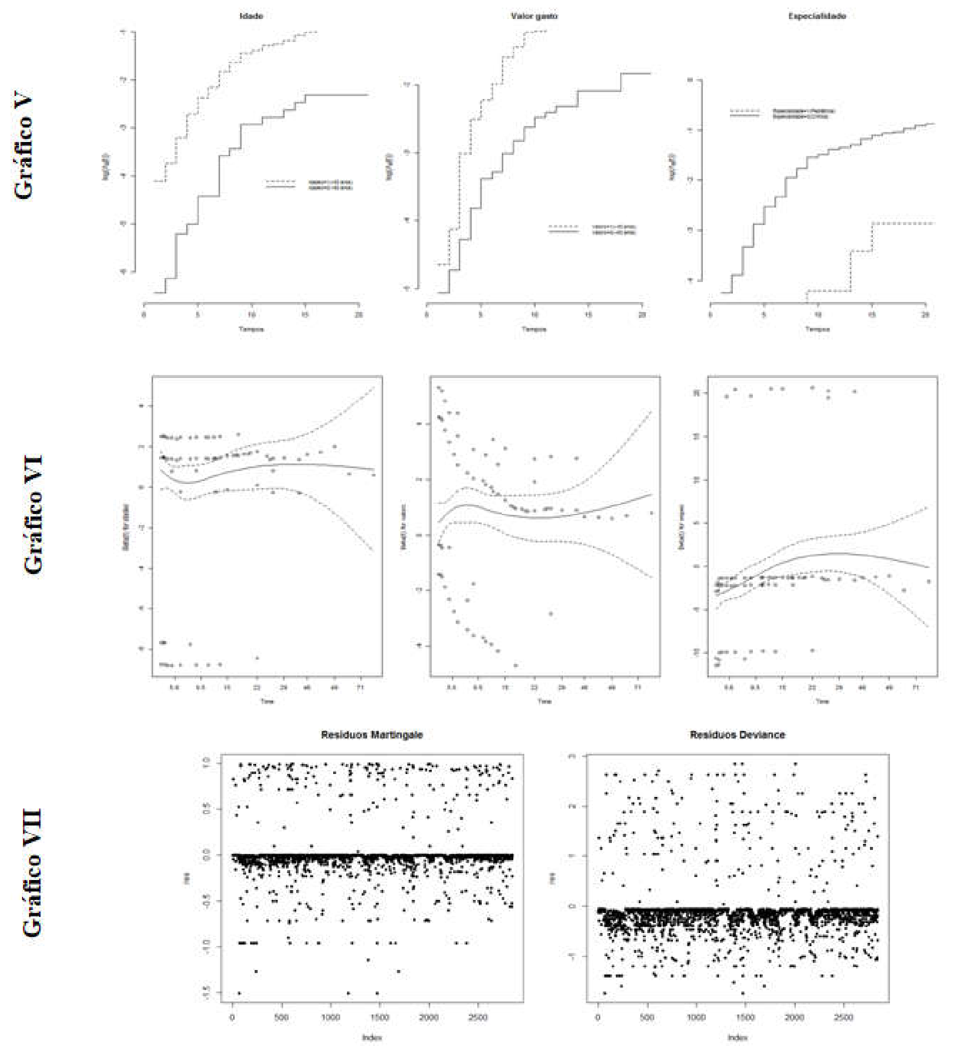
Variables	Log- rank (p-value)	Breastplate (p-value)	Decision
Race / color	0.157	0.13	I reject
Age	0.039	0.015	I reject
Value	9.21e-15	2.33e-15	I reject
Sex	0.903	0.765	I do not reject
Specialty	0.014	0.0011	I reject
Month	0.622	0.47	I do not reject

Source: Research data, 2016.



Source: DATASUS - TabWin , 2016.

Figure 03. Survival of the residues estimated by the Kaplan-Meier method and by the standard Log-normal model (Figure III) and Survival of the Cox-Snell residues estimated by the Kaplan-Meier method and the standard Exponential model (Graph IV), Paraíba, 2016



Source: Research data, 2016.

Figure 04. Assumptions of proportional failure rates (Graph V), Schoenfeld standard residuals associated with covariates (Graph VI), *Martingal* and *deviance residuals* versus linear predictor of the adjusted final Cox model (Graph VII), Paraíba, Brazil, 2016

Table 02. Results of the final log-normal regression model for influenza data, Paraíba, 2016

Term	Estimate	Default error	Statistics Z	p-value
Intercept	4.194	0.2160	19.42	5.60e-84
Breed	0.473	0.2143	2.21	2.73e-02
Age	0.504	0.1763	2.86	4.26e-03
Value	0.511	0.1462	3.50	4.74e-04
Specialty	1,267	0.2699	4.69	2.69e-06
Log (scale)	0.311	0.0537	5.79	6.92e-09

Source: DATASUS - TabWin, 2016.

Table 03. Estimates obtained for the initial Cox model, Paraíba, 2016

Covariável	Coefficients Dear	Default error	P-value	RTF	IC (95%) RTF
Age	0.5884	0.5552	0.0106	1.8011	(1.14717; 2.8278)
Value	0.7867	0.4553	4.55e-06	2.1962	(1.56892; 3.0742)
Specialty	-1.7291	5.6355	1.36e-05	0.1774	(0.08143; 0.3867)

Source: Research data, 2016.

marked increase for this period, with individuals over 50 years of age with a higher chance of developing death than the younger ones. In order to test the possible differences between the strata, the Log- Rank and Peto hypothesis tests were performed, as presented their p-values in table 01. The variables: age, race, value and specialty rejected the null hypothesis that there is no difference between the strata. Therefore, for these variables, there is difference between the analyzed groups. To proceed with statistical modeling and use the parametric models, only the variables that passed the above test were included. However, since the number of co - variables is small (total of 0 6) and which can be import prior to the conclusion of the study, it was decided to include all the variables in the settings of the parametric models and semi - parametric. F pray performed adjustments of parametric models for Exponential distributions: Weibull and Log-normal. When performing the estimates of survival were observed differences between these three distributions and the Kaplan-Meier method. The median times are Kaplan-Meier are closer to the Log-nomal distribution with median times of 46 and 41, respectively. In order to select the method to be used to fit the model, the graphs I and II, shown in figure 0 2, were performed. In the Graph I method, the distributions estimates were compared with the values for Kapla n-Meier and in Chart II, the linearity in each distribution was observed. The graphs (Figure 02) show that possibly presented log-normal distribution is the most suitable for the model, given that their points are closer to the straight line. For that, the likelihood ratio test (TRV) was carried out to ratify the result. The hypothesis test performed as results showed the p-value of 1.11e-16 for the Exponential distribution; 1.15e-05 for the Weibull distribution and finally 0.5455 for the Log-normal distribution. Thus, the Exponential and Weibull distributions obtained p-values lower than the significance level set at 0.05, giving sufficient statistical evidence to reject the h_0 that the model is suitable. On the other hand, the log-normal model was the only one that passed the test and will be used for the modeling of survival analysis.

Using the non-parametric log-normal model: When starting the adjustment of the Log-normal model, all the variables present in the study were included, since even if they were rejected in the Kaplan-Meier model, since there are few variables, we chose to use them in this modeling. Based on the hypothesis test statistic, the variables "month" (p-value = 8.85e-01) and "sex" (p-value = 1.41e-01) had their p-values higher than the level of significance set at 0.10 for this test, needing, therefore, to be in withdrawals from the model. The adjusted model presented the statistics described in table 02.

In order to confirm the fit of the model, the two graphs (III and IV), shown in figure 03, were performed. For figure III, it should be considered, according to Colosimo and Giolo (2006) normal is well adjusted for the data, the distribution of the residues on the logarithmic scale should be quite close to the normal pattern. As the residues are censored, the Kaplan-Meier estimator should be used to estimate the survival function of the residues, which have both negative and positive values. So it was applied s and exponential ransformation in waste, this is,to produce waste from a known distribution, the standard log-normal. Equivalently, Cox-Snell residues should also follow the standard exponential distribution so that the log-normal model is considered adequate. Thus, it is observed that these are well adjusted (Graph IV).

Using the semi-parametric model from Cox: For the adjustment of the Cox model, the model was known as *backward*. In this way the initial model counted on all the variables of the study, in view of having few , which may be significant with the model: "time, censorship, race, age, value , sex, specialty and month". For the first model to be adjusted, it was necessary to withdraw the variable "month", since it presented the highest p-value among the others (0.4663). After the removal of this variable, a second model originated, in which it was necessary to exclude the variable "sex", since it obtained a high p-value (0.40544). And, in a third model adjustment, the variable "race" was withdrawn, with p-value also high (0.1788). After the exclusion of the three variables, the model was adjusted (Table 03).

The Interpretation the result ed of reason failure rates conclu iu that:

- The influenza death rate of hospitalized individuals over 50 is 1.8 times that of individuals under 50 years of age. With 95% confidence, this estimate varies between 1.15 and 2.83;
- The death rate per influenza of hospitalized individuals, who had spent amounts greater than 1,000.00 and 2.2 times the rate of individuals who demand hospitalization expenses of less than 1,000.00. With 95% confidence, this estimate ranges from 1.57 to 3.07.
- The influenza death rate of individuals hospitalized for pediatric specialty is approximately ½ (half) of individuals hospitalized for clinical practice. With 95% confidence, this estimate ranges from 0.08 to 0.34.

In order to confirm the results, a graphical test was performed involving the logarithm of the cumulative failure rate function for the covariates race, age, value and specialty. For these, it is observed that the curves do not cross, and therefore there is no violation of the assumption of proportional failure rates (Graph V). In this it is possible to visualize that there is an approximately constant difference between the curves for each one of the variables. Although the curves are not perfectly parallel over time, there are no marked deviations (Figure 04). *Schoenfeld's* standardized residue chart was also used to identify possible strong trends for any of the variables present in the adjusted model (Figure VI). The residue analysis shows that there was no violation of the assumption of proportional failure rates (Figure 04). Therefore, the graphic method of *martingal* and *deviance* residues was also carried out. In both, we observed the random distribution of residues in the neighborhood of zero, thus providing indications favorable to the adequacy of the previously adjusted model (Figure VII) (Figure 04).

Conclusion

From the development of this study it was possible to identify the social and demographic characteristics that interfere in the survival of hospitalized patients with influenza in Paraíba. However, survival analysis is also a decision model and can be used by several other regions, with the purpose of acting with a focus on the risk group and avoiding the death of the patient, contributing to the promotion of health policies for this group population. It is worth mentioning that this study is a pioneer in the application of the detailed survival analysis for hospitalized individuals due to influenza virus infection, thus constituting one of the limitations found by the researchers, the confrontation of information that would challenge the findings. Thus, it is recommended that greater focus be given to the care of patients hospitalized with influenza for clinical specialty, older than 50 years and who demand higher hospital expenses with hospitalization, since they are more likely to die.

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