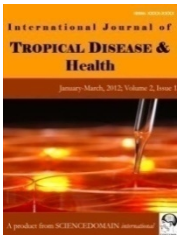

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Evaluation of the Effectiveness of Oseltamivir for the Treatment of 2009 Pandemic Influenza A (H1N1)

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Research Article

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ABSTRACT

Aims: Evaluate retrospectively the effectiveness of treatment with oseltamivir in a Brazilian subpopulation infected during the 2009 pandemic influenza A(H1N1) and compare drug activity based on the presence or absence of other disease risk factors and also the time from onset of symptoms to initiation of treatment.
Study Design: Observational and retrospective.
Place and Duration of Study: Federal University of Paraná and Parana State Secretary of Health, between April 2009 and December 2010.
Methodology: 1,917 patients were included (842 men, 1,075 women; age range 0-90 years) with positive diagnosis for the 2009 influenza virus A (H1N1) characterized by RT-PCR, whose notification forms were available at the time of data collection and that contained information of the use or not of oseltamivir. The patients were categorized by age, gender, symptoms, presence or absence of co morbidities, outcomes (cure or death) and treated or untreated with oseltamivir. The odds ratio (OR) was estimated using a multivariate logistic regression analysis. Kaplan-Meier method was used to determine if differences existed between the survival of untreated patients and oseltamivir treated patients.
Results: Out of 1,917 patients, 1,644 had cleared the infection and 273 patients died. Age, education level, cardiopathies, nephropathies, immunodepression, smoking, diabetes, systemic arterial hypertension, obesity, diarrhea, dyspnea, hemoptysis and pneumonia were considered risk factors. The use of oseltamivir provided about 32.3

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times more likely to clear the infection compared with untreated patients. Moreover, the effectiveness of oseltamivir is reduced by approximately 7-fold in smoking patients. For each day that passed to initiate treatment after the onset of symptoms, the risk of death increased by 32.3%.
Conclusion: The findings suggest that treatment with oseltamivir was effective in producing favorable patient outcomes in those who contracted the 2009 influenza A (H1N1) strain.

Keywords: Influenza A virus; H1N1 subtype; oseltamivir; prognosis; risk factors; treatment effectiveness.

1. INTRODUCTION

Oseltamivir was the first choice of pharmacological agent during the influenza A (H1N1) pandemic that occurred in Brazil in 2009. As oseltamivir had not been previously used in pandemic events, its effectiveness in these conditions was previously unknown.

The study of therapeutic interventions can be performed by two forms of clinical research: studies of efficacy or effectiveness. Efficacy studies consist of randomized controlled trials that evaluate a treatment under ideal conditions. The results of these studies reveal whether the treatment is effective when used under established conditions but are not reproducible when the treatment is applied to the general population. Studies of effectiveness, in turn, attempt to evaluate such results within the reality of clinical practice. These studies are related to the performance of a treatment in real conditions because the population participating in the study is heterogeneous and the therapeutic intervention is administered in a typical clinical setting (Nash et al., 2005; Coutinho et al., 2003). The effectiveness of a treatment depends not only on its pharmaceutical quality but also on its effects within individual patients. Oseltamivir, commercially known as Tamiflu®, is a second generation antiviral and belongs to the class of neuraminidase inhibitors (NAI) (Oxford, 2007; Neumann and Kawaoka, 2011). Due to its structural similarity with the sialic acid residues found on the cell surface, oseltamivir interferes with NA viral enzyme function, thereby preventing the release of new viral progeny from infected cells and consequent dissemination throughout the host organism (Baz et al., 2009; Agrawal et al., 2010).

The administration of oseltamivir is intended to prevent disease progression in infected individuals by reducing viral load and shortening the duration of the transmission period. Due to its high bioavailability, oseltamivir can be administered orally. Oseltamivir should be given twice daily for five days, with dosages adjusted according patient's age and weight (Baz et al., 2009; Agrawal et al., 2010).

Previous efficacy studies demonstrated a statistically significant survival advantage in patients diagnosed with influenza A (H1N1) and treated with oseltamivir compared to an untreated group. Beyond increasing survival, oseltamivir also reduced the magnitude and duration of viral replication, thereby decreasing the severity and duration of symptoms, reducing complications and hospitalization rates of adults and shortening the transmissibility period (Hanshaoworakul et al., 2009). These effects are observed especially when comparing patients who were treated early with the drug to those who did not receive treatment (García et al., 2010). Moreover, these studies indicated that treatment with the

antiviral drug is more effective when administered within 48 hours of symptom onset to interrupt the initial phase of viral replication. However, other evidence indicates that treatment can be accomplished even 48 hours after symptom onset, particularly in patients with severe disease (Tanaka et al., 2009; Donaldson et al., 2009).

Given the scarcity of studies that have evaluated the effectiveness of oseltamivir, the aim of this study was to retrospectively evaluate the effectiveness of treatment with this antiviral agent in a Brazilian subpopulation infected during the pandemic of 2009 and compare drug activity among various subgroups of this population based on the presence or absence of other disease risk factors and the time from onset of symptoms to initiation of treatment. These results complement those from existing efficacy studies to enhance the rational and correct use of this product, thereby preventing the emergence of resistant viral strains.

2. METHODOLOGY

2.1 Study Population

The study design was observational and retrospective, conducted from March to December 2010 through document analysis. The study subjects were patients from the state of Parana in Brazil who presented positive diagnoses for acute infection by the influenza virus A (H1N1) subtype during the 2009 pandemic (from April to December 2009). The data about these patients were obtained from the medical records and forms of disease notification. Data source was the National Information System of Diseases Notification (SINAN) of the Brazilian Ministry of Health, and included all patients with laboratorial confirmation of disease.

We only included patients whose notification forms were available at the time of data collection, contained a positive diagnosis for the 2009 influenza virus A (H1N1) based on results from Reverse Transcriptase - Polymerase Chain Reaction (RT-PCR) analysis and that contained information on the use or lack of use of oseltamivir. To minimize the biases of the study, patients who had laboratory-confirmed cases but were not treated because their cases did not comply with clinical treatment protocol (absent signs and symptoms of worsening disease and no risk factors) were excluded. Therefore, to obtain two comparison groups, we only included untreated patients who had characteristics similar to those of the treated patients. The final database was compiled into an electronic file and checked for inconsistencies.

2.1 Data Collection and Data Analysis

The patients were categorized by age, gender, symptoms and the presence or absence of co morbidities. We considered two clinical outcomes: cure or death. Cases of death in each group were used to determine patient factors that could have influenced this outcome. We tried to identify what circumstances predisposed or protected patients from death. To this end, we constructed a logistic regression model using the backward stepwise likelihood ratio method, and patient outcomes were used as the dependent variable. All variables were initially tested by univariate analysis with $p<0.05$ considered statistically significant. The selected variables were used to determine independent predictors of mortality by the 2009 influenza A (H1N1) virus as determined using multivariate analyses. The odds ratio (OR) was estimated using a multivariate logistic regression analysis and included the strength and

the interactions through likelihood ratio tests with a confidence interval (CI) of 95% and $p<0.05$, which was considered to be significant.

The patients were further divided by disease outcomes (cure or death), whether they had been treated with oseltamivir and whether they had exposure to risk factors (comorbidities, age and smoking). Patients were organized by the aforementioned characteristics using a 2x2x2 table. The results were obtained by comparing the OR of treated patients compared with untreated patients among the exposed group (with risk factors) to the OR of treated patients compared with untreated patients among the unexposed group (without risk factors). In these cases, the OR for the infection clearing within each group was obtained by assessing whether patients had been exposed to the identified risk factors. We performed a homogeneity test using the Breslow-Day method ($p<0.05$) to determine whether these differences were significant.

Furthermore, the Kaplan-Meier method was used to determine if differences existed between the survival of untreated patients and oseltamivir treated patients. These results were obtained from the survival curves using the time elapsed between the onset of symptoms and the date of death.

The average time to the start of treatment was compared to the disease outcomes correlated with the effectiveness of treatment. The comparison of the proportions between the groups was performed using the z-test. S.P.S.S. 17.0 for Windows was used for statistical analysis.

3. RESULTS

In total, 1,917 patients had notification forms that met the inclusion criteria and were selected for this study. Of these patients, 1,075(56.1%) were female, 1,644(85.7%) had cleared the infection and 273(14.3%) patients had died. The mean age of participants was 23.9(0-90) years. The average age of cured patients was 21.7(±15.6) years, and the average age of patients who died was 37.7(±15.8) years.

The patients were also evaluated for the presence of underlying pre-existing diseases and risk factors. Among the reported comorbidities were heart disease, lung and kidney diseases, immunosuppression, diabetes, hypertension and obesity. Smoking was considered a risk factor.

Regarding treatment, 1,827(95.3%) patients received oseltamivir, and 201(11.0%) of those patients subsequently died. In contrast, 90(4.7%) patients were not treated with oseltamivir, and 72(80.0%) of those patients subsequently died. The characteristics of the groups of treated and untreated patients are shown in Table 1.

Variables related to sociodemographic characteristics, comorbidities and pre-existing symptoms and treatment were tested by univariate analysis. The results allowed the exclusion of variables such as gender ($p=0.291$) and race ($p=0.164$), indicating that patients of both genders and all ethnic categories were equally predisposed to death. Variables initially selected for inclusion in the multivariate analysis were: age ($p<0.001$), education level ($p=0.001$), cardiopathies ($p<0.001$), pneumopathies ($p=0.021$), immunosuppression ($p<0.001$), nephropathies ($p=0.004$), smoking ($p=0.001$), diabetes ($p<0.001$), hypertension ($p<0.001$), obesity ($p<0.001$), diarrhea ($p=0.002$), dyspnea ($p<0.001$), hemoptysis ($p<0.001$), pneumonia ($p<0.001$), use of oseltamivir ($p<0.001$), time to start treatment after the onset of symptoms ($p<0.001$) and number of comorbidities prior to infection ($p<0.001$).

Table 1. Characteristics of patients in each group according to whether or not they were treated with oseltamivir

		Untreated (N=90)			Treated (N=1,917)		
		Count	Row N (%)	Column N (%)	Count	Row N (%)	Column N (%)
Age (Mean)		36.3			23.4		
Gender	Male	45	5.3	50.0	797	94.7	43.6
	Female	45	4.2	50.0	1,030	95.8	56.4
Comorbidities	With	45	3.4	50.0	1,295	96.6	70.9
	Without	45	7.8	50.0	532	92.2	29.1

Multivariate analysis was performed to obtain the OR of the predisposition or resistance to death. The results are shown in Table 2.

Age and level of education were categorized into three subcategories based on the percentage of deaths and the similar characteristics between individuals.

For the evaluation of the age groups, we compared patients ≤ 19 years of age to patients of other age groups because this population had the lowest proportion of deaths according to age, how illustrated in Fig. 1. The results indicated that the OR for death increased as an individual patient's age increased.

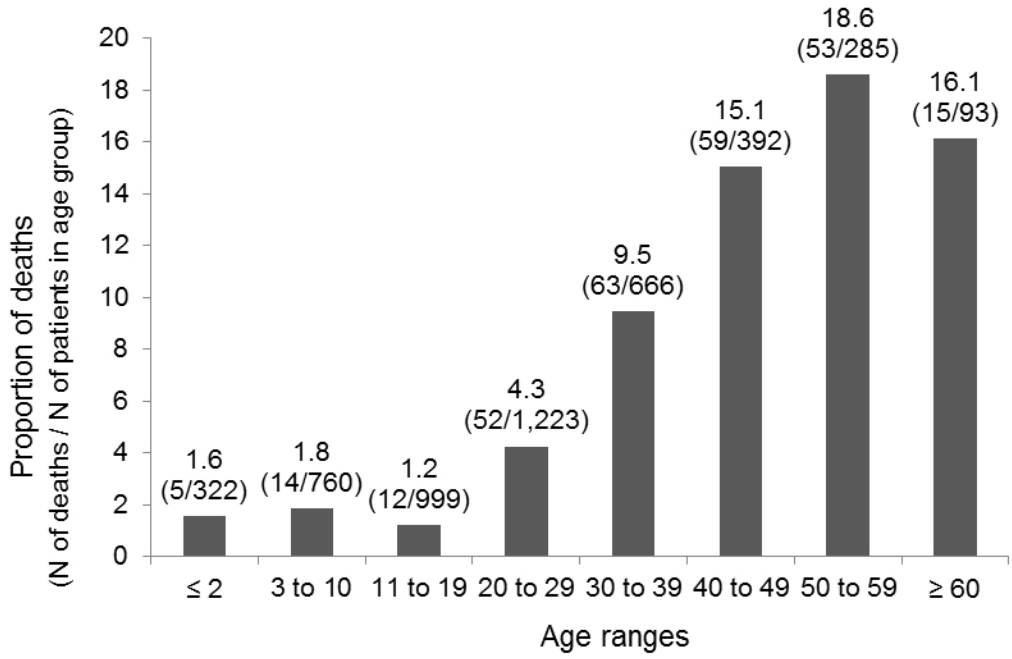

Fig. 1. Proportion of deaths by age ranges in patients who contracted the 2009 influenza virus A (H1N1) in Paraná, Brazil

Another sociodemographic characteristic that was correlated with patient outcomes was education level. To assess the impact of this variable on the risk of death, we considered

patients over 25 years of age. These patients were divided into the following three categories: illiterate or primary education, high school or academic degree. We compared patients to the group of patients with higher education levels because this group had lower rates of death, noted as percentage values (%) in Table 2.

Table 2. Variables evaluated in the multivariate logistic regression model

Variable	N†	Deaths	%	B‡	S.E. §	*P*	OR	95%CI
Age group								
≤ 19 years*	879	31	3.5	---		0.000	1.000	---
20 to 49 years	850	174	20.5	1.967	0.294	0.000	7.148	(4.014 – 12.727)
≥ 50 years	188	68	36.2	2.444	0.350	0.000	11.521	(5.804 – 22.869)
Education Level								
Illiterate and primary level	104	32	30.8	2.070	0.664	0.002	7.927	(2.157 – 29.135)
High school	309	73	23.6	1.702	0.624	0.006	5.486	(1.615 – 18.630)
Academic degree*	161	7	4.3	---		0.011	1.000	---
Baseline diseases and risk factors								
Cardiopathies	79	28	35.4	1.316	0.265	0.000	3.728	(2.216 - 6.272)
Pneumopathies	198	29	14.6	-0.060	0.239	0.802	0.942	(0.589 - 1.506)
Nephropathies	25	8	32	1.242	0.451	0.006	3.463	(1.430 - 8.388)
Immunodepression	58	18	31	1.184	0.308	0.000	3.266	(1.785 - 5.976)
Smoking	117	27	23.1	0.774	0.245	0.002	2.168	(1.341 - 3.506)
Diabetes	69	30	43.5	1.595	0.276	0.000	4.930	(2.871 - 8.466)
SAH¶	70	21	30	1.060	0.291	0.000	2.887	(1.631 - 5.109)
Obesity	31	16	51.6	1.350	0.446	0.002	3.859	(1.611 - 9.246)
Number of comorbidities				0,312	0.101	0.002	1.367	(1.122 - 1.664)
Signs and symptoms								
Diarrhea	215	40	18.6	0.625	0.255	0.014	1.868	(1.134 - 3.079)
Dyspnea	1058	247	23.3	1.917	0.249	0.000	6.801	(4.177 - 11.075)
Hemoptysis	10	7	70	2.070	0.852	0.015	7.926	(1.492 - 42.096)
Pneumonia	9	6	66.7	2.162	0.830	0.009	8.687	(1.709 - 44.162)
Treatments								
Treated with oseltamivir	1827	201	11	-3.460	0.370	0.000	0.031	(0.015 - 0.065)
Time to initiation of treatment (days)				0,280	0.032	0.000	1.323	(1.241 - 1.409)

Not treated with oseltamivir: N = 90, deaths = 72(80%); OR (IC 95%) = 32.26(15.38 – 66.67); OR, odds ratio; CI, confidence interval.

**Reference class, †Evaluated patient, ‡Regression coefficient, §Standard error, ¶Systemic arterial hypertension.*

Because the presence of risk factors increased the susceptibility to death by infection, we compared the effectiveness of oseltamivir in the presence or absence of these factors. This analysis aimed to assess whether the drug's effectiveness can be compromised by exposure to some risk factors. Thus, we obtained the results shown in table 3, in which the OR values indicate the chance of cure in treated vs. untreated patients, according to the presence or absence of risk factors.

Table 3. Comparison of the effectiveness of oseltamivir through the Breslow-Day test

Groups	Oseltamivir	Outcomes (N†)		Total (N†)	OR (95%CI)	Breslow-Day (*p*)
		Cure	Death			
With comorbidities	Treated	448	84	532	34.67	0.688
	Untreated	6	39	45	(14.23–84.46)	
Without comorbidities	Treated	1178	117	1295	27.69	
	Untreated	12	33	45	(13.92–55.06)	
Smokers	Treated	88	24	112	5.50	0.031*
	Untreated	2	3	5	(0.87–34.81)	
Non-smokers	Treated	1538	177	1715	37.47	
	Untreated	16	69	85	(21.28–65.97)	
Hypertensive	Treated	48	17	65	11.29	0.330
	Untreated	1	4	5	(1.18–108.24)	
Non-hypertensive	Treated	1578	184	1762	34.30	
	Untreated	17	68	85	(19.73–59.64)	
Male	Treated	711	86	797	22.7	0.147
	Untreated	12	33	45	(11.4–45.5)	
Female	Treated	915	115	1030	52.6	
	Untreated	6	39	45	(21.3–125.0)	
Age < 30 years	Treated	1207	65	1272	30.3	0.672
	Untreated	11	18	29	(13.7–66.7)	
Age 30 to 39 years	Treated	183	46	229	22.7	
	Untreated	3	17	20	(6.33–83.3)	
Age > 39 years	Treated	236	90	326	24.4	0.930
	Untreated	4	37	41	(8.40–71.43)	

OR, odds ratio; CI, confidence interval.
**Significant value (p<0.05), †Evaluated patients.*

As indicated by the OR values, treatment with oseltamivir was effective in all groups. However, the effectiveness in smokers was significantly reduced (Breslow-Day p<0.05).

To verify drug effectiveness in these groups, treatment conditions were made equal, and the effectiveness of the drug treatment in the group of patients with the above risk factors who cleared the infection was compared to that of a control group (also patients treated with the drug but without the above risk factors) who also overcame the disease.

The results of this analysis showed that the drug effectiveness in all cases was higher in patients who did not have risk factors for heart disease, kidney disease, immunosuppression, diabetes or obesity. These results indicated that these risk factors may interfere with oseltamivir treatment. However, it was not possible to perform the Breslow-Day test to confirm whether these decreases in the effectiveness of treatment were significant.

In addition to providing increased chances for survival in all subgroups of evaluated patients, oseltamivir also increased the survival time of infected patients, as illustrated by the survival curve in Fig. 2. The survival time was obtained by determining the interval between the date of symptom onset and date of death in treated and untreated patients who cleared the infection (n=273). The cleared infection was determined by a clinical evaluation that confirmed the disappearance of signs and symptoms of infection.

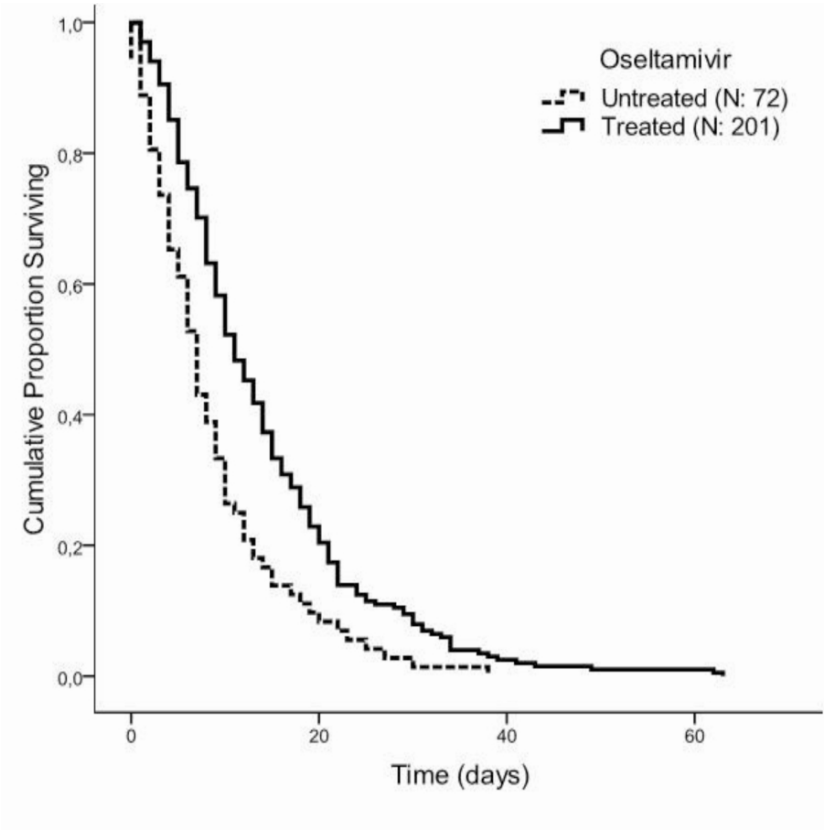

Fig. 2. Kaplan-Meier survival analysis

Patients who received oseltamivir demonstrated an increase in survival time compared to untreated patients. The average time-to-death after infection by influenza A (H1N1) for patients who did not receive medication was 8.6 days. As for the patients who were treated, this period increased to 13.8 days, demonstrating the ability of oseltamivir to significantly increase mean survival time following infection by approximately 5.5 days (Log Rank/Mantel-Cox, Breslow/Wilcoxon widespread and Tarone-Ware $p<0.05$). This increased survival time may enable physicians to explore other treatment options aimed at curing the patient.

3.1 Evaluation of the Relationship between the Time of Symptom Onset and the Initiation of Treatment

An evaluation of the time from symptom onset to the initiation of treatment revealed that the average time to initiate treatment was 2.1 days (±2.0) in cured patients and 5.4 days (±5.1) in patients who died, indicating a difference of approximately 3.3 days between the two groups.

A Pearson correlation test revealed that this variable is correlated with disease outcomes with a $p < 0.05$. Patients who received treatment within three days of symptom onset had significantly higher cure rates than patients who were treated after this time interval. These results were obtained with a z-test for the comparison of cure rates and death in different time intervals for treatment initiation.

Fig. 3 shows a graphic comparison of the time-to-treatment initiation between the group of patients who cleared the infection and the group that progressed to death and identifies the maximum time interval from symptom onset in which oseltamivir treatment made a difference in survival time. This time interval was determined by comparing the cure and death groups in the box plot and by evaluating when the whisker extends 1.5-fold of the interquartile range above the 75th percentiles.

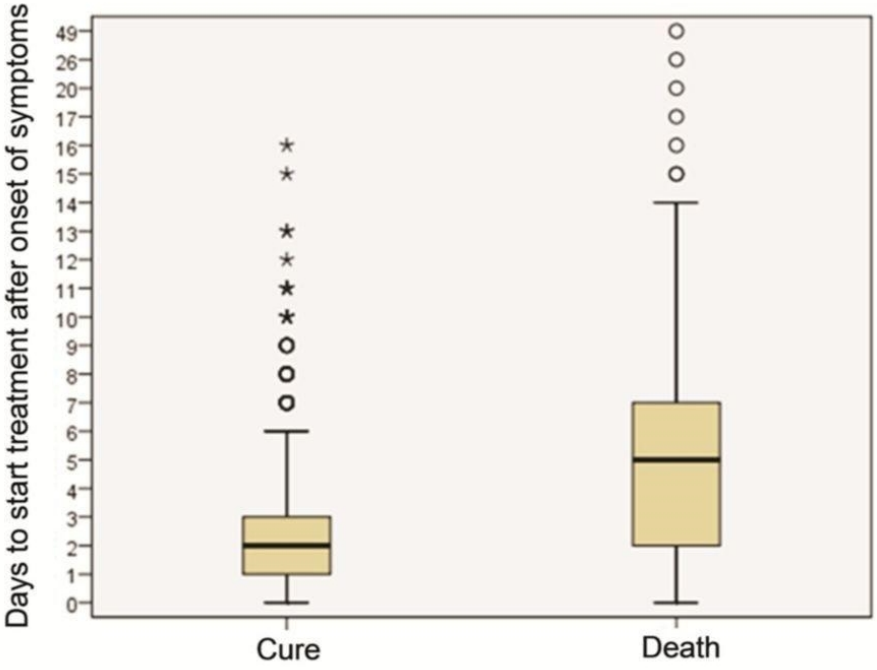

Fig. 3. Comparison between the time to the start of treatment in patient cure or death
The horizontal line represents the median, and the box represents the interquartile range (50% of the data mean). Vertical straight lines (whiskers) extend 1.5-times the interquartile range above and below the 75th and 25th percentiles. Patients with atypical results outliers) appear above this line, as represented by circles and asterisks.

Results suggest that the effectiveness of oseltamivir is higher if the treatment is started within 3 days of symptom onset and that the treatment is still effective if the patient is treated

within 6 days after the onset symptoms. After this time, patient outcomes will depend more on the prior health of the individual than the drug itself, which then operates only as an adjuvant. Most patients for whom the time-to-treatment initiation exceeded 6 days after the onset of symptoms progressed to death. Therefore, we observed that early treatment with oseltamivir directly affects its effectiveness, as measured by patient outcomes.

3.2 Quality Analysis by Logistic Regression

The adjustment quality of the regression model indicated an adequate capacity to characterize the factors that influenced the disease outcomes using retrospective data. The model was constructed in 13 steps with a variance estimate, a minimum and maximum of 29.3% and 52.4%, respectively, as evidenced by the R2 Cox & Snell and Nagelkerke pseudo R2 tests. The values of the Hosmer and Lemeshow tests showed no statistically significant differences between the observed and predicted ratings for all variables remaining in the final model, and the overall accuracy rate was 90.4%.

4. DISCUSSION

The highest proportion of female patients and the mean age of patients were similar to epidemiological data from other recent studies (Zarychanski et al., 2010; Campbell et al., 2010).

The results of the logistic regression analysis revealed that age was a risk factor for death as the OR increased for the occurrence of this outcome. Results indicated that by increasing education levels, the OR for death decreases, as patients that were illiterate or had completed only primary school had a 7.9-fold greater chance of death than those with higher education levels (complete or incomplete). Educational level was already associated with higher risk of hospitalization due to influenza A (H1N1) 2009 infection (Launes et al., 2012). Patient education level had a direct relationship with the socioeconomic level of the individual. Patients from disadvantaged social classes are more prone to contracting infections because they depend on public transportation, may potentially live in areas with greater population density and may not have access to financial resources for preventive and therapeutic measures.

Regarding comorbidities, we found that the presence of pneumopathy was not significantly associated with death and, therefore, is not considered as a risk factor in this population. This fact can be explained by the characteristics of lung diseases in this group of patients who are mostly children. As was previously reported, patients younger than 19 years of age had a lower risk of death compared to patients of other age groups. Thus, the impact of this comorbidity was balanced by age in these patients.

However, all other co morbidities had significant OR values that indicated an increased risk of death. Underlying medical conditions (cardiac and renal conditions, diabetes, asthma, and other) and delayed consultation were associated with hospitalization by other study (Glica et al., 2011). Among the co morbidities, those with the greatest effects on the odds of death were diabetes, obesity (without reference to degree) and heart disease. Similar results have been observed in other studies (Mikić et al., 2011; Louie et al., 2009; Lee et al., 2010; Santa-Olalla Peralta et al., 2010). The risk of a severe outcome was also associated with the presence of one or more underlying medical conditions, age of 20 years or more and a delay in hospital admission by Campbell et al. (2010). Among the signs and symptoms of disease

that increased the risk of death were dyspnea, hemoptysis and pneumonia. The last two symptoms clearly indicate patients who have more severe lung involvement.

Regarding treatment, we observed that the use of oseltamivir undoubtedly protected patients against death. Moreover, the results indicated that for each day that passed after the onset of symptoms, the risk of death increased by 32.3%. Early treatment has been associated with reduced mortality (Mikić et al., 2011; Louie et al., 2009) and a longer interval from onset of symptoms to treatment with antiviral therapy was already associated with necessitating admission to the ICU (Zarychanski et al., 2010).

Treated, non-smoking patients were 37.47 times more likely to be cured than untreated non-smokers. These results show that despite being effective for both smokers and nonsmokers, the effectiveness of oseltamivir is reduced by approximately 7-fold in smoking patients.

Oseltamivir was equally effective in all patients with diarrhea, dyspnea, hemoptysis and pneumonia and in all patients without these symptoms, indicating that the antiviral drug is effective even in clinically severe cases. No significant differences regarding the effectiveness of oseltamivir treatment were observed between the various age groups ($p>0.05$) or between the genders ($p>0.05$).

The fatality rate observed in this study was higher than the observed by Campbell et al. (2010) described as 4.9%. In patient groups who had risk factors for heart disease, kidney disease, immunosuppression, diabetes and obesity, the comparison between treated and untreated patients could not be performed because all untreated patients in these groups died. This fact alone demonstrates the need for therapeutic intervention to improve the chances for curing individual patients.

Treatment with neuraminidase inhibitors, such as oseltamivir, has been associated with increased survival, reducing the duration and severity of symptoms and reducing the incidence of secondary complications (Treanor et al., 2000; García et al., 2010; Hanshaoworakul et al., 2009).

In addition to the importance of treatment to decrease the probability of death, as observed by the results of logistic regression analysis, minimizing the time from symptom onset to treatment is extremely important to ensure the greatest effectiveness of oseltamivir. It was observed that patients who started treatment within 3 days of symptom onset had approximately 20 to 55 times more likely to live and be cured of the infection than patients who did not start treatment within this period. From the fourth to fifth day following symptom onset, the difference in survival observed between the groups was still approximately 5 to 10 times higher. After this period, the cases of cures and death become equivalent; thus, oseltamivir has a low efficacy in determining outcomes at this late stage of the disease.

The risk of a severe outcome was elevated among those who had an underlying medical condition and adults (age ≥ 20 years). Despite these associations, the cause and outcomes of pandemic H1N1 influenza may involve many complex and interrelated factors, all of which require further research and analysis.

5. CONCLUSION

Our findings suggest that the treatment with oseltamivir was effective in determining favorable patient outcomes in those who contracted the 2009 influenza A (H1N1) strain. Of

the patients who died, treated individuals showed an increase in the mean survival time of 5.5 days compared to untreated patients. In the case of an acute illness, this result is significant. Among the risk factors for death, the effectiveness of treatment was significantly reduced only in patients who smoked. Moreover, the results significantly extend the period of treatment initiation from 48 hours to baseline (suggested in the literature) to 72 hours (3 days) after the onset of symptoms.

5.1 Limitations

The limitations of this study include underreporting, the inaccuracy of data collected from medical records and the collection of temporal information in days, preventing the calculation of time from symptom onset to initiation of treatment in hours.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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