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Prediction model to discriminate leptospirosis from hantavirus

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SUMMARY

OBJECTIVE: The aim of this study was to build a prediction model to discriminate precociously hantavirus infection from leptospirosis, identifying the conditions and risk factors associated with these diseases.

METHODS: A logistic regression model in which the response variable was the presence of hantavirus or leptospirosis was adjusted.

RESULTS: As a result, the method selected the following variables that influenced the prediction formula: sociodemographic variables, clinical manifestations, and exposure to environmental risks. All variables considered in the model presented statistical significance with a $p<0.05$ value. The accuracy of the model to differentiate hantavirus from leptospirosis was 88.7%.

CONCLUSIONS: Concluding that the development of statistical tools with high potential to predict the disease, and thus differentiate them precociously, can reduce hospital costs, speed up the patient's care, reduce morbidity and mortality, and assist health professionals and public managers in decision-making.

KEYWORDS: Leptospirosis. Hantaviruses. Differential diagnosis. Public health.

INTRODUCTION

Hantavirus infection and leptospirosis are diseases relevant to public health and have high lethality coefficients. The incidence of hantavirus in Brazil is, on average, 118 cases/year[1], while leptospirosis presents 3,926 cases, with an average of 1.02 cases/100,000 inhabitants/year[2].

Both are infectious diseases that can present remarkably similar clinical conditions, making differential diagnosis exceedingly difficult in clinical practice. Hantavirus and leptospirosis are transmitted by rodents and are most often reported based exclusively on clinical suspicion since specific diagnostic tests are not available in many locations[3].

The main risk factors of both diseases are floods in the rainy period and inappropriate working and housing environmental conditions, among which occupation of inadequate buildings, disordered urban growth, and agricultural activities stand out[4].

Diseases related to inadequate environmental conditions and water transmission have been on the agenda of international meetings, and the sustainable development goal is to ensure a healthy life and promote well-being for all, aiming to end various epidemics and waterborne diseases[5].

According to Russell et al.[6], the rapid increase in the occurrence of emerging and reemerging zoonoses has led to the development of robust strategies, which enables a more accurate assessment of the situation's gravity, allowing for faster decision-making. Moreover, it was also stated that the early development of these prediction models and their immediate use can control and minimize the impact of these diseases.

Given these possibilities, this study aims to build a prediction model to discriminate precociously hantavirus infection from leptospirosis, identifying the conditions and risk factors associated with these diseases.

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METHODS

An epidemiological study, with observational, analytical, and cross-sectional nature with a quantitative approach, was carried out from 2001 to 2016.

This research used secondary data from the public domain and exempted from the appreciation of the CEP/CONEP system.

This study consisted of 2,254 confirmed cases of each hantavirus and leptospirosis, thus completing a total of 4,508 balanced observations. Explanatory sociodemographic variables of epidemiological, clinical, care, and laboratory background were used. The database used was composed of non-nominal information from the notification forms for hantavirus and leptospirosis of the Notifiable Diseases Information System (SINAN) and was provided by the Ministry of Health of Brazil through the Electronic Information Service System to the Citizen (e-SIC).

The descriptive statistics of the study variables were obtained through absolute (N) and relative (%) frequencies.

Logistic regression was used to classify hantavirus and leptospirosis cases based on their explanatory variable values. The probability to differentiate one disease from the other, given covariant x_i, was calculated using the following formula:

$$P(Y=1|x_i) = \frac{\exp(\beta_0 + \beta_1 x_{i1} + \cdots + \beta_k x_{ik})}{1 + \exp(\beta_0 + \beta_1 x_{i1} + \cdots + \beta_k x_{ik})}$$

where $x_i = (x_{i1}, x_{i2}, \ldots, x_{ik})$ are the explanatory variables for i^{th} observation, β_0 is the intercept, and β_j ($j = 1, \ldots, k$) is the corresponding coefficient for the explanatory variable j^{th}[7].

To assess the predictive capacity of the model, the database was divided into two sets, namely, training and testing. The training database was formed through a random selection of 70% of the observations of the original database and was made up of 1,577 cases of hantavirus and leptospirosis with a total of 3,154 cases. In contrast, the test database consisted of the remaining observations (30%) with 677 cases of hantavirus and leptospirosis with a total of 1,354 cases.

The model parameters were estimated using the training set, and the test set was used to validate it. The prediction capacity was evaluated estimating the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of the 2×2 confusion matrix, formed by the observed information (columns) and the information predicted by the model (lines).

All statistical analyses were conducted using R version 3.3.0 software.

RESULTS

Sociodemographic conditions

Among the results to be described, only the gender variable was not selected by the prediction model constructed to differentiate hantavirus infection from leptospirosis. Thus, four sociodemographic variables were selected, namely, age, ethnicity, region, and education.

The individuals that fell ill due to hantavirus and leptospirosis were mostly males (79.1 and 78.9%), aged between 20 and 49 years (70.9 and 59.1%), and whites (68.7 and 45.1%), respectively.

Leptospirosis cases occurred mainly in urban areas, 81.4% (1,283) against 14.2% (224) in rural areas, while those with hantavirus were equally distributed among urban 47.7% (752) and rural areas 47.1% (743).

Regarding education, only 1.4% of individuals had complete higher education and more than a quarter (28.9%) had an ignored level of education. Those with incomplete elementary education, plus illiterates, corresponded to approximately 30 times the number of those with complete higher education, corresponding to 44.5%.

Clinical manifestations

Some signs and symptoms capable of helping in the clinical differentiation between hantavirus and leptospirosis were found in the prediction model; the following characteristics presented the greatest effect on the formula: fever, myalgia, headache, vomiting, dyspnea, and abdominal, renal, hemorrhagic, and neurological manifestations.

Fever was the most frequent symptom, occurring in 86.4 and 90.2% of hantavirus and leptospirosis cases, respectively. Followed by myalgia, fever was also frequently observed in both hantavirus (70.1%) and leptospirosis (82.6%).

Another frequent symptom in both diseases was headache, present in approximately three quarters of individuals with 74.4% in hantavirus and 77.7% in leptospirosis cases.

Vomiting was found in more than half of the cases in both diseases, being present in 60.5% of hantavirus cases and 58.1% of leptospirosis cases.

Dyspnea was reported in more than half of hantavirus cases (54.9%) and approximately a quarter (23.4%) of leptospirosis cases, while abdominal manifestations were observed in approximately one-third of the patients, both in hantavirus (35.9%) and leptospirosis (31.6%) cases.

Regarding renal manifestation, analyses showed that its occurrence was one and a half times higher in leptospirosis (21.7%) than in hantavirus (14.3%) cases.

Hemorrhagic manifestations occurred at the same frequency in hantavirus and leptospirosis (10%) cases. However, almost half (47.7%) of the cases of hantavirus disease ignored this information.

Neurological manifestations were less frequent, appearing only in 7.2% of individuals with hantavirus and 4.1% of leptospirosis cases.

Exposure to environmental risks

Regarding the probable site of infection, it shows that hantavirus was presented at work (55.5%), against 24.2% at home and 4.9% at leisure places, while leptospirosis predominated at home (38.7%), 24.3% at work and 6.8% at leisure places. These results showed that hantavirus disease presented a work-related risk twice higher than leptospirosis, while this presented an infection risk at home one and a half times higher in relation to hantavirus disease.

The presence of rodent signs was identified in 42.7% of hantavirus cases and 45.7% of leptospirosis cases. Direct contact with rodents was identified as a lower risk factor than the presence of rodent signs, considering that only 7.1% of leptospirosis cases were exposed to this risk and 29.2% of hantavirus cases.

Leisure in fresh water was a risk factor almost twice as frequent for leptospirosis infection (31.5%) than for hantavirus (17.0%).

Statistical model

In the construction of the predictive model to discriminate between hantavirus and leptospirosis, 16 variables that influenced the prediction formula were identified. Four were sociodemographic variables, eight were related to clinical manifestations, and four were variables related to environmental risk exposition. All variables considered in the model showed statistical significance with a $p<0.05$ value (Table 1).

The confusion matrix (Table 2) shows the absolute number of hantavirus and leptospirosis cases in the database, called observed, which are distributed in the lines. The cases selected using the statistical tool, called predicted, are distributed in the columns.

The predictive performance of the logistic regression to differentiate hantavirus from leptospirosis based on the data from the compulsory notification forms was assessed by means of accuracy, sensitivity, specificity, and positive and negative predictive values.

The test's accuracy was 88.7%, sensitivity was 89.4%, and specificity was 88%, while the positive predictive value of the test was 88.2% and the negative predictive value was 89.2% (Table 3).

DISCUSSION

It was observed in this study that hantavirus was presented in 18 states of the Brazilian Federation with a higher occurrence in the South, followed by the Southeast and Midwest regions, corroborating with the data described by Brazil[8], in which more than 90% of the registered cases were found in that regions, with 39.3%, 30.2%, and 22.3% cases, respectively. In this study, it was also shown that 69.5% of the cases were registered in only five states of those regions.

Regarding leptospirosis, its occurrence was recorded in all Brazilian states, being more frequent in São Paulo, Rio Grande do Sul, Santa Catarina, Paraná, and Acre, making up for more than half of the reported cases. According to Brazil[4], leptospirosis has an endemic distribution throughout Brazil, with occurrences reported throughout the year.

It was observed that the individuals with leptospirosis presented a similar distribution between urban and rural areas like the percentage of the Brazilian population distribution in these regions, as described by Brazilian Institute of Geography and Statistics (IBGE)[9]. This finding agrees with Longo et al.,[10] and Diaz[11], who stated that leptospirosis affects populations uniformly, both in urban and rural areas.

In this study, the increased risk of illness due to hantavirus was noticeable in people from the rural area (47.1%) when compared with the percentage of the Brazilian rural population (15.6%)[9]. According to Pinto Junior et al.[12] and Longo et al.[10], hantavirus affects mainly rural residents, since they usually live in houses that are permeable to rodents or work under risk exposure conditions.

Male individuals predominated the cases of hantavirus (79.1%) and leptospirosis (78.9%). A survey carried out in Brazil on rural workers' health identified that these have worse health conditions and the majority are males (73.2%), whereas 26.8% are females[13].

According to Goeijenbier et al.[14], environmental and occupational factors are associated with hantavirus infection risk, since the presence of rodents or even their excretions close to homes significantly increased the risk of infection. Walks in forests or rural recreational activity, handling of firewood, house cleaning, and occupational exposure were also identified risk factors. These findings corroborate with those of this study, which found that both exposure to rodents and their excreta, as well as work-related illness, are statistically significant to sicken due to hantavirus and leptospirosis.

The results found in this study, referring to exposure to environmental risks such as leisure activity in fresh water, rodent signs, or even having had direct contact with rodents, as well as illness at work, agree with the study by Gressler et al.[15].

Table 1. Estimated coefficients in the logistic regression and respective descriptors.

	Estimate	Standard error	Odds ratio	Z	p	95%CI (odds ratio scale)	
						Lower bound	Upper bound
(Intercept)	2.604	1.183	13.518	2.202	0.028	1.331	137.300
Sociodemographics							
Black race	0.288	0.289	1.333	0.997	0.319	0.757	2.348
Yellow race	-0.085	0.682	0.918	-0.125	0.900	0.241	3.495
Mixed race	0.792	0.167	2.208	4.752	<0001	1.593	3.061
Indigenous race	-2.626	1.249	0.072	-2.102	0.036	0.006	0.837
Ignored race	1.383	0.240	3.985	5.752	<0.001	2.488	6.384
Age							
5–9 years	-0.397	0.822	0.672	-0.483	0.629	0.134	3.368
10–14 years	-0.276	0.661	0.759	-0.417	0.676	0.208	2.772
15–19 years	-0.653	0.593	0.520	-1.101	0.271	0.163	1.665
20–24 years	-0.821	0.579	0.440	-1.419	0.156	0.141	1.368
25–29 years	-0.979	0.575	0.376	-1.703	0.089	0.122	1.159
30–34 years	-1.093	0.578	0.335	-1.893	0.058	0.108	1.039
35–39 years	-1.584	0.582	0.205	-2.724	0.006	0.066	0.641
40–44 years	-1.205	0.577	0.300	-2.087	0.037	0.097	0.929
45–49 years	-0.695	0.585	0.499	-1.188	0.235	0.159	1.571
50–54 years	-0.653	0.590	0.521	-1.105	0.269	0.164	1.656
55–59 years	-0.850	0.629	0.427	-1.352	0.177	0.125	1.466
60–64 years	-0.822	0.637	0.440	-1.290	0.197	0.126	1.532
65 years or above	-0.225	0.628	0.799	-0.358	0.721	0.233	2.736
Regions							
Rural area	-1.719	0.161	0.179	-10.685	<0.001	0.131	0.246
Peri-urban area	-1.625	0.482	0.197	-3.373	<0.001	0.077	0.506
Ignored area	-0.769	0.350	0.464	-2.195	0.028	0.233	0.921
Educational qualification							
1st to 4th incomplete elementary school grade (EF)	-1.690	0.971	0.185	-1.741	0.082	0.028	1.237
4th complete EF grade	-3.013	0.965	0.049	-3.122	0.002	0.007	0.326
5th to 8th incomplete EF grade	-2.634	0.954	0.072	-2.762	0.006	0.011	0.466
Complete EF	-2.863	0.965	0.057	-2.967	0.003	0.009	0.378
Incomplete high school	-2.296	0.987	0.101	-2.325	0.020	0.015	0.697
Complete high school	-1.351	0.981	0.259	-1.377	0.168	0.038	1.771
Incomplete higher education	-2.871	1.355	0.057	-2.119	0.034	0.004	0.806
Complete higher education	-1.788	1.082	0.167	-1.653	0.098	0.020	1.394
Ignored	-2.346	0.951	0.096	-2.466	0.014	0.015	0.618
Not applicable	-1.103	1.415	0.332	-0.780	0.436	0.021	5.313

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Table 1. Continuation.

	Estimate	Standard error	Odds ratio	Z	p	95%CI (odds ratio scale)	
						Lower bound	Upper bound
Clinical manifestations							
Vomiting absent	0.134	0.148	1.144	0.911	0.362	0.857	1.527
Vomiting ignored	-0.933	0.444	0.393	-2.104	0.035	0.165	0.938
Renal manifestation absent	-1.172	0.195	0.310	-6.009	<0.001	0.211	0.454
Renal manifestation ignored	-0.392	0.349	0.676	-1.122	0.262	0.341	1.340
Dyspnea absent	1.804	0.155	6.073	11.659	<0.001	4.484	8.224
Dyspnea ignored	2.856	0.391	17.391	7.307	<0.001	8.084	37.410
Hemorrhagic manifestations absent	1.752	0.217	5.764	8.086	<0.001	3.770	8.812
Hemorrhagic manifestations ignored	-3.443	0.284	0.032	-12.107	<0.001	0.018	0.056
Fever absent	-0.519	0.220	0.595	-2.360	0.018	0.387	0.916
Fever ignored	0.159	0.526	1.172	0.301	0.763	0.418	3.287
Neurological manifestations absent	0.537	0.292	1.711	1.839	0.066	0.965	3.033
Neurological manifestations ignored	1.849	0.427	6.355	4.328	<0.001	2.751	14.682
Myalgia absent	-1.169	0.178	0.311	-6.583	<0.001	0.219	0.440
Myalgia ignored	-0.395	0.431	0.673	-0.919	0.358	0.290	1.566
Abdominal manifestations absent	0.700	0.149	2.014	4.696	<0.001	1.504	2.697
Abdominal manifestations ignored	1.228	0.398	3.414	3.084	0.002	1.564	7.450
Exposure to environmental risks							
Work	-1.858	0.169	0.156	-11.022	<0.001	0.112	0.217
Leisure	-0.506	0.328	0.603	-1.541	0.123	0.317	1.147
Other	0.912	0.444	2.488	2.054	0.040	1.042	5.940
Exposure ignored	-0.148	0.202	0.862	-0.735	0.462	0.581	1.280
Leisure in fresh water absent	-1.256	0.168	0.285	-7.485	<0.001	0.205	0.396
Leisure in fresh water ignored	-1.531	0.407	0.216	-3.767	<0.001	0.097	0.480
Rodent signs absent	-0.422	0.144	0.655	-2.934	0.003	0.494	0.869
Rodent signs ignored	-1.856	0.282	0.156	-6.573	<0.001	0.090	0.272
Direct contact with rodent absent	0.995	0.177	2.706	5.617	<0.001	1.912	3.829
Direct contact with rodent ignored	4.041	0.260	56.886	15.517	<0.001	34.145	94.774

Source: Research Data, 2018.; Note; TIPO level “lepto” coded as class 1.

Table 2. Confusion matrix.

		Predicted	
		Hanta	Lepto
Observed	Hanta	605	72
	Lepto	81	596

Source: Research data; 2018.

Table 3. Predictive performance of logistic regression.

	Value
Accuracy	0.887
Sensitivity	0.894
Specificity	0.880
Predictive positive value	0.882
Predictive negative value	0.892

Source: Research data; 2018.

These authors consider leptospirosis an occupational disease, as its occurrence is associated with some work activities.

Corroborating with this study, Goeijenbier et al.[14] and Clement et al.[16] identified that the most frequently observed signs and symptoms in hantavirus were abdominal pain, nausea, vomiting, headache, fever, myalgia, and dyspnea, which can progress to severe acute respiratory failure. Hantavirus can also manifest itself as hemorrhagic fever with renal syndrome, which is recognized by fever, renal failure, and hemorrhage, an almost complete overlap of the classic leptospirosis symptoms.

In patients with leptospirosis, symptoms can vary widely, from asymptomatic patients or even with mild disease, to the most severe manifestation, known as Weil's disease, with the classic triad of jaundice, kidney failure, and hemorrhagic manifestations that is rapidly progressive and has a high lethality rate[14].

In a study by Loubet et al.[17], sociodemographic, clinical, and epidemiological variables were thus used to build the prediction model and like the results of this research, and some clinical signs and symptoms that stood out in the prediction formula, such as intense fatigue and gastrointestinal manifestations, but mainly high fever and anorexia, were identified.

Hong et al.[18] built a prediction model from a clinical database to assess the probability of developing advanced colorectal cancer. In this study, the variables that presented an effect on the prediction formula were age, gender, smoking time, alcohol consumption frequency, and aspirin use.

A similarity between the study by Hong et al.[18] and the present one regarding the nature of the variables identified was observed, as both contain sociodemographic variables and exposure to risk factors.

According to Rouquayrol and Almeida Filho[19], even by achieving the recommended quality, no 100% sensitive or specific test exists, with the possibility of always finding false-positive and false-negative results in diagnostic tests.

In addition, it is relevant to highlight that, according to the Pan American Health Organization[20], the validity of a diagnostic test is composed of some parameters, among them, sensitivity, specificity, and, most importantly, accuracy. As observed in this study, the prediction model developed showed a high accuracy of 88.7% to discriminate between hantavirus and leptospirosis.

CONCLUSIONS

The predictive discrimination of hantavirus and leptospirosis based on sociodemographic, clinical, and epidemiological indicators, obtained through the forms of compulsory notification, become possible to target treatment more precociously and thus speeding up assistance to the sick person, in addition to supporting health managers in the design and implementation of public policies related to health promotion as, healthy housing, basic sanitation, sustainable development, work environments, vector control, among others.

These policies can reduce the population's exposure to the main risk factors and thus minimize the impact of these diseases, considered serious and of high lethality, on public health.

AUTHORS' CONTRIBUITIONS

MRGR: Conceptualization, Formal analysis, Investigation, Methodology, Project Administration, Resources, Visualization, Writing – original draft. **NFGA:** Formal analysis, Investigation, Supervision, Visualization, Writing – review & editing. **SBR:** Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing.

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