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Statistical method to determine the need for hospitalization of COVID-19 patients

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The growth rate of COVID-19 is causing worldwide concern. The development of indirect methods used to determine hospitalizations only for necessary cases is of fundamental importance to prevent overcrowding in the health system. The general objective of this article is to propose a statistical method, based on logistic regression, capable of indicating whether a patient who tests positive for COVID-19 should be directed to home isolation or be admitted to a hospital, based on blood tests and age. The data was collected from 5,645 blood tests of patients in March and April 2020. Based on the use of the independent variables 'C-reactive protein,' 'neutrophils,' and 'monocytes,' as well as the age of the patient affected by COVID-19, it is possible to predict with a reasonable degree of accuracy whether, upon arriving at the hospital and testing positive, the individual should be recommended to isolate at home or be admitted to a healthcare facility.

Keywords: COVID-19; logistic regression; protocol.

Elaboração de uma metodologia baseada em estatística para encaminhamento dos casos da COVID-19

A taxa de crescimento da COVID-19 é preocupante em todo o mundo. O desenvolvimento de métodos indiretos para direcionar as internações hospitalares somente para os casos necessários é de fundamental importância para impedir superlotação do sistema de saúde. O objetivo geral deste artigo é propor uma metodologia estatística, baseada na regressão logística, capaz de indicar se um paciente que testou positivo para COVID-19 deve ser direcionado ao isolamento domiciliar ou ficar internado no hospital com base em exames básicos de sangue e na idade. Os dados partiram de 5.645 testes de sangue de pacientes no período de março e abril de 2020. Com a utilização das variáveis independentes proteína C-reativa, neutrophils, monocytes e idade do paciente acometido pela COVID-19, pode-se prever com razoável grau de precisão se, ao chegar ao hospital e testar positivo, o indivíduo deve ser recomendado a ficar recolhido em sua residência ou se deve ser internado numa unidade de saúde.

Palavras-chave: COVID-19; regressão logística; protocolo.

Elaboración de una metodología basada en estadísticas para la derivación a tratamiento de casos de COVID-19

La tasa de crecimiento de la COVID-19 es preocupante en todo el mundo. El desarrollo de métodos indirectos para orientar las internaciones hospitalarias solo en los casos necesarios es de fundamental importancia para prevenir el hacinamiento en el sistema de salud. El objetivo general de este artículo es proponer una metodología estadística, basada en regresión logística, capaz de indicar si un paciente que dio positivo para COVID-19 debe permanecer en aislamiento domiciliario o internado en un hospital según los análisis de sangre y la edad. Los datos se tomaron de 5.645 análisis de sangre de pacientes en el período de marzo a abril de 2020. Utilizando las variables independientes proteína C reactiva, neutrófilos, monocitos y edad del paciente afectado por COVID-19, se puede determinar, con un grado razonable de precisión, si al llegar al hospital y tener resultado positivo, se debe recomendar que el individuo permanezca en su residencia o sea internado en una unidad de salud.

Palabras clave: COVID-19; regresión logística; protocolo.

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1. INTRODUCTION

The global pandemic caused by the Severe Acute Respiratory Syndrome – Corona Virus 2 (SARS-CoV-2) started in Brazil when the Ministry of Health confirmed the first case in the national territory, on February 25, 2020, in a 61-year-old Brazilian who vacationed in the Lombardy region of Italy during a time when the epidemic was already widespread in Europe and Asia, as well as other countries around the world (Rodriguez et al., 2020).

To contain the spread of the epidemic, several countries have adopted policies of social isolation, shutting down commercial activities and reducing air passenger traffic (Grilli, Marsili, & Sanguinetti, 2020). There are concerns regarding the availability of, not only the intensive care units (ICUs) needed for the treatment of serious infections, but also the tests used for detection, since several cases were not diagnosed due to the absence of specific tests (Rodriguez et al., 2020).

The overcrowding situation of public health services in Brazil tends to be compounded due to the handling of cases related to COVID-19 (Weinberg, 2003). The early detection of cases during the incubation period, that is, before the appearance of the first symptoms, has not been possible since it is based on complete contact tracing and tests of the asymptomatic individual (Pellis et al., 2020), which is why the development of indirect methods for detecting the disease is of substantial importance for containing the epidemic. Likewise, there are several statistical and computational studies aimed at predicting the tendency of virus contamination and the effectiveness of social isolation measures adopted by countries in order to stop the spread of the disease. (Hong & Li, 2020; Hossain, 2020; Picchiotti, Salvioli, Zanardini, & Missale, 2020; Sarkodie & Owusu, 2020; Zhang, Jiang, Yuan, & Tao, 2020).

In several studies carried out in China, increased levels of C-reactive protein have been verified in critically ill patients with COVID-19 (Bai et al., 2020; Gao et al., 2020; Wan et al., 2020; Wang, Yang, Li, Wen, & Zhang, 2020), including with regard to referring the best coverage to those who are ill when they find themselves in this situation.

The problem which the research faces consists in formulating a method capable of anticipating the referral of patients who have tested positive – for treatment at home or in the hospital – based on the results of the basic blood tests and the age of the individual. This, certainly, makes it possible to anticipate the choice and direction of hospital beds, in order to achieve greater efficiency in health services.

2. THEORETICAL REFERENCE

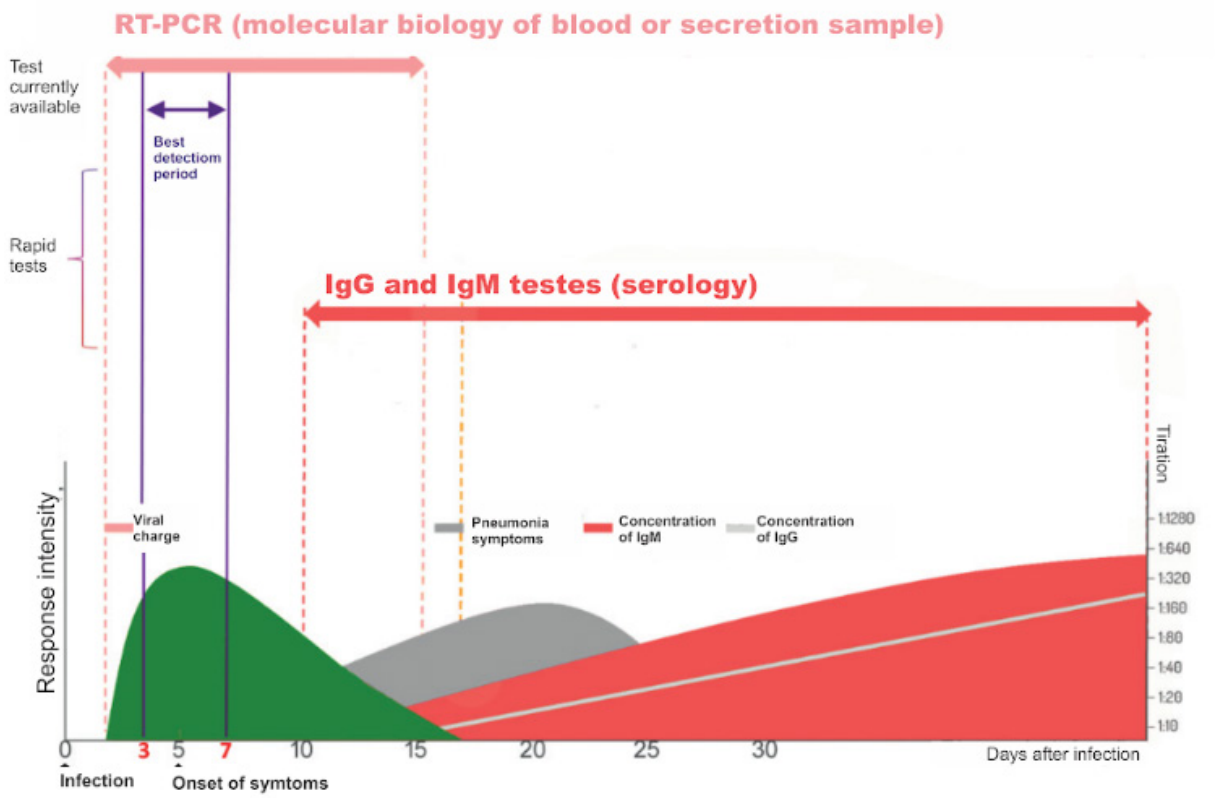
On April 28, 2020, there were more than 3 million cases of COVID-19 globally, with around 210 thousand deaths and 5.6 million people infected, with over 68,188 cases detected in Brazil and 4,674 deaths (Johns Hopkins, 2020). Due to the worsening of the health crisis, on January 30, 2020, the World Health Organization (WHO) in Geneva, Switzerland declared a public health emergency of international importance (Opas, 2020).

In Singapore, several decisions restricted people from mainland China and regions of northern Italy, Iran, and South Korea from entering. Likewise, Hong Kong and Brazil imposed a quarantine for their local populations (Peckham, 2020). Along the same lines, Rwanda installed hand washing

stations in transport centers. In Senegal, chatbots offer reliable information and quick diagnostics via social networks, while in Nigeria call centers with volunteer teams and an information campaign with celebrities have been set up (Dalglish, 2020), all to contain the virus and preserve the capacity of the already precarious public service in these countries.

The mechanisms of prognosis and immunological status of patients with COVID-19 are still unclear, which is why the countries are afflicted by the health crisis. As shown in Figure 1, the usual tests available for the detection of COVID-19 take a relatively long time for the results to return or they require that the incubation period has passed before being performed.

FIGURE 1 SUMMARY OF THE STEPS USED TO PERFORM COVID-19 TESTS.



Source: Health Ministry (Ministério da Saúde, 2020).

Relative to indicators extracted from blood tests, in a group of 5 patients from the same family admitted to The Fifth People's Hospital of Anyang, in China, increased levels of C-reactive protein (CRP) were found in those who presented symptoms (Bai et al., 2020; Gao et al., 2020; Wan et al., 2020; Wang et al., 2020). In another study done by Gao et al. (2020), in 43 adult patients with COVID-19, the most severe cases showed a significantly higher level of CRP (39.37 ± 27.68 mg/L) than those who had milder symptoms (18.76 ± 22.20 mg/L). Likewise, it was found that 135 patients in the northeast of Chongqing, China, had high levels of CRP, especially in the most severe cases (WAN et al., 2020).

By analyzing the studies evidenced, it can be seen, therefore, that there is a direct relationship between the level of CRP and the severity of the symptoms of the disease.

Thus, the search for faster and cheaper indirect means for detecting the disease is extremely important to optimize the use of the health infrastructure, especially when there is an overload in the system thanks to the expansion of cases throughout the national territory, increasing the overcrowding of ICUs.

3. METHODOLOGY

The present research is characterized as that of an applied nature, since it focuses on real problems of society, organizations, groups or actors of the population, for the purpose of making diagnoses, identifying problems and presenting solutions to social demands (Thiollent & Oliveira, 2009).

The data for conducting the research came from the laboratory tests of 5,645 patients at Hospital Albert Einstein in São Paulo, from the collected blood samples and the tests performed for the detection of COVID-19 until March 27, 2020. The hospital reported that, until March 23, 2020, it had 477 confirmed cases and 30 deaths due to the disease. According to information from the institution itself, the results are already in standardized form with zero mean and unit standard deviation. The binary logistic regression model was used, establishing an equation that allows referring patients who tested positive to their residences or to be admitted to a hospital with a satisfactory level of correct responses.

Therefore, SPSS 20 software (Statistical Package for the Social Sciences) was used for processing basic data and obtaining statistical results. Initially, the research model considered the age of the patients – originally called patient age quantile and represented by means of percentiles – as independent variables, and the levels of CRP in the blood, while the dependent was the recommendation of whether to admit the patient or not, represented by the variable referred to here as the referral indicator (RI). By definition, the value of 0 was used to represent the recommendation to stay at home, while number 1 was the indication for referral to be admitted to the hospital.

Following this, the independent variables of patient age quantile, neutrophils and monocytes were also tested as an alternative way of making the referral, seeking to find more precise, economical and equally reliable ways of applying the procedure.

To assess the efficiency of the predictive power of the logistic model employed, the Hosmer-Lemeshow, Cox and Snell and Nagelkerk tests were used and the measure given by "-2 Log Likelihood", all with the purpose of assessing the degree of adherence to the real data (Hair, Babin, Money, & Samouel, 2005). To build the model, we used the database called Datasetcovideinsten, made available by Hospital Albert Einstein on the website Kaggle.com,[1] comprised of 5,642 patient laboratory test records. Only those who tested positive for COVID-19 were selected: a total of 557. For the elaboration of the logistic function, it was necessary to dispose of the records that contained blood test results (hemogram) of the patients, which totaled 70.

Based on the indicators extracted from the hemograms performed, it was sought to select the relevant ones to estimate the dependent variable RI, with a value of 0 for home and 1 for hospital.

[1] Retrieved from https://www.kaggle.com/allen-institute-for-ai/CORD-19-research-challenge/discussion/139347

For this, the one-way ANOVA mean difference test for variables was used with normal distribution and the Mann-Whitney U non-parametric test of the distribution difference for the others. Those considered significant at the 5% level were patient age quantile, mean platelet volume, lymphocytes, eosinophils, monocytes, neutrophils, CRP, creatinine and sodium.

Next, the stepwise binary logistic regression model was applied with all the variables listed above, which disregarded those not significant, some having presented high collinearity. The procedure indicated the patient age quantile and CRP variables as significant. Calibrations were also made at the cutoff points of the logistic function in order to adjust the probabilities considered, in order to make the model more adjusted to reality.

Similarly, the possibility of creating another more accurate model was also tested, in which more variables would be incorporated, with the CRP being replaced by others. For this purpose, the Pearson and Spearman correlation between CRP and the other variables was studied, observing those with greater significance. Next, the stepwise linear regression between these variables and CRP was performed, where patient age quantile, neutrophils and monocytes were shown to be the best predictors. It was decided, then, to build another equation to forecast RI, using the three mentioned variables to estimate the same dependent variable. Box 1 shows the conceptualization of each independent variable used in the equation in the specialized literature. By the concepts presented from the independent variables, there is a relationship between these and infections, as caused by COVID-19.

BOX 1 INDEPENDENT VARIABLES

Variables	Concepts
C-reactive protein	Produced in the liver in response to inflammatory cytokines (Brasil et al., 2007), which has been studied since the 1970s to diagnose inflammatory conditions and infections (Baumann & Gauldie, 1994).
Patient age quantile	Age of patients in classes with a range of 5 years.
Neutrophils	Cells originating from bone marrow with relatively short life and the main function of defending the body against foreign agents, by the migration to the tissues in which they exert phagocytic and bactericidal functions. However, the intensity of the inflammatory response caused by its action can cause irreversible tissue damage (Freire & Queluz, 1995).
Monocytes	Monocytes are part of the immune system, are formed in the bone marrow and, later, transformed into macrophages in connective tissues, with increased phagocytic and antimicrobial power (Abbas, 2015).

Source: Elaborated by the authors.

As the results will later show, the second logistic function presents slightly better results, which is why it can be assumed that both models serve to refer patients affected by COVID-19 for home isolation or hospitalization.

4. RESULTS AND DISCUSSION

As previously mentioned, the stepwise binary logistic regression model was applied with the patient age quantile, mean platelet volume, lymphocytes, eosinophils, monocytes, neutrophils, CRP, creatinine and sodium variables. The stepwise procedure disregarded the non-significant variables and selected patient age quantile and CRP as the most appropriate to predict patient referral. In fact, the level of significance of the chosen independent variables is less than 0.05, as shown in Table 1, indicating that both are relevant for estimating RI.

TABLE 1 VARIABLES CHOSEN FOR THE RI FORECASTING MODEL

							95% C.I.for Exp(B)	
	B	S.E.	Wald	df	Sig.	Exp (B)	Lower	Upper
C-reactive protein	1,812	,650	7,767	1	,005	6,125	1,712	21,911
Patient age quantile	,177	,076	5,423	1	,020	1,193	1,028	1,384
Constant	-2,110	1,075	3,849	1	,050	,121		

Source: Elaborated by the authors.

The Exp(B) coefficients shown in the previous table allow us to conclude that CRP has a strong impact on the chance the patient has of being referred to the hospital, since the increase of 1 unit in his or her level, keeping the age constant, increases the chance of hospitalization by 6.125 times (or 512.5%), while the increase of 1 year in age, leaving the level of CRP constant, increases the chance of hospitalization by 19.3%. These results corroborate the tests performed in China, where there was an increase in CRP in critically ill patients affected by COVID-19 (Bai et al., 2020; Gao et al., 2020; Wan et al., 2020; Wang et al., 2020).

According to Table 2, the Hosmer and Lemeshow test resulted in a chi-square statistic of 21.213 with 8 degrees of freedom with a significance level of 0.007, thus greater than 0.05. Thus, the null hypothesis that the predicted classifications are the same as the adjusted ones is not rejected, which endorses the adherence of the model to the data.

TABLE 2 HOSMER AND LEMESHOW TEST

Chi-Square	Degrees of freedom	Descriptive level
21.213	8	.007

Source: Elaborated by the authors.

The Nagelkerke R^2 test is a variation adapted from Cox and Snell to provide results between 0 and 1. Both are analogous to the R^2 obtained by linear regression. Thus, Table 3 shows that the proposed model is able to explain around 37.3% of the registered variations of the dependent variable as a function of the independent variables.

TABLE 3 COX AND SNELL AND NAGELKERKE R^2 TEST

-2 Log likelihood	Cox and Snell R Square	Nagelkerke R Square
72.838	0.278	0.373

Source: Elaborated by the authors.

Table 4, below, shows the general probability of correctness of the model, in the order of 81.4%, as well as the probabilities for each type of forecast – home or hospital. This means that the logistic function using the patient age quantile and CRP independent variables is able to predict with a reasonable degree of accuracy which cases of COVID-19 should be admitted to the hospital or isolated at home. In the case of not using independent variables for forecasting purposes, the proportion of correct responses would only be 57.1% of the cases. Therefore, the inclusion of the chosen variables significantly increased the predictive power of the logistic function.

As can be seen in Table 4, the model was correct in 70% of cases when it indicated that the patient should be sent home and 90% of the times when it suggested home care. The correctness in indicating that the patient be hospitalized (90%) is more important according to the aspect of his or her health, since the error would indicate the individual be referred to go home when he or she should receive medical care in a hospital. On the other hand, the error in referring the individual to the hospital when he or she could be at home (30%) would cause a false alarm, but it would certainly be detected upon arrival at the healthcare facility.

There is no doubt that this false indication would generate a waste of time and a possible waste of resources that are actually already so scarce today. However, referral to home when it should be hospital (4%) seems to us to be a much more serious error, since it would deprive the patient of medical care. The model, therefore, was calibrated to minimize this last type of error, leading to the consequent maximization of correct responses when indicating hospitalization.

TABLE 4 CLASSIFICATION MATRIX

		Provided		
		Home	Hospital	Total
Observed	Home	21 (70%)	9 (30%)	30 (100%)
	Hospital	4 (10%)	36 (90%)	40 (100%)
Overall percentage of correct responses				**81.4%**

Source: Elaborated by the authors.

With the purpose of maximizing the probability of correctness when recommending referral to the hospital, the level of assertiveness was simulated for different cutoff points, as shown in the Table below:

TABLE 5 CALIBRATION TO INCREASE THE PROBABILITY OF CORRECT RESPONSES IN THE INDICATION OF HOSPITALIZATION

Cutoff point	% Correct responses "Home"	% Correct responses "Hospital"	% total correct responses	Significance at 5%	Number of observations
0.3	43.3	97.5	74.3	Yes	70
0.35	56.7	97.5	80	Yes	70
0.4	63.3	**95**	81.4	Yes	70
0.45	70	90	81.4	Yes	70
0.5	70	87.5	80	Yes	70

Source: Elaborated by the authors.

The alternative was chosen in which the probability sought (% correct hospital responses) was 95%, without being too reduced to the equivalent of the recommendation to go home (% correct home responses), which reduces to 63.3%. When calibrating this type of model to increase the probability of the event of interest, there is essentially a variation in the others, leaving the researcher to choose the combination that best meets his or her needs.

As mentioned, an alternative model was developed for the same RI dependent variable, now based on other independent variables in place of CRP and patient age quantile. This was done with the aim of having an accurate model for the purposes of applying the test. For this purpose, correlations were made between CRP and the other variables previously selected. With a stepwise linear regression between the variables with the highest degree of significance found in this matrix of correlations, it was found that neutrophils together with monocytes were the best predictors of CRP, which is why they were chosen to assemble a new model with the objective of improving the precision of the proposed equation. The resulting model is presented in Table 6.

TABLE 6 BINARY LOGISTIC MODEL FOR RI FORECAST

		B	S.E.	Wald	df	Sig.	Exp(B)
1st Step	Neutrophils	.968	.454	4.535	1	.033	2.632
	Patientagequantile	.362	.106	11.574	1	.001	1.436
	Monocytes	-1.010	.411	6.027	1	.014	.364
	Constant	-4.089	1.446	7.996	1	.005	.017

Source: Elaborated by the authors.

As can be seen, all the variables are significant at 5%. The most striking, however, is neutrophils, as a variation of 1 unit, keeping all others constant, increases the chance of the patient being hospitalized by 163.2%. The opposite occurs with the monocytes variable, in which the increase of 1 unit, leaving the others unchanged, reduces the chance of hospitalization by 64%. For this new configuration of independent variables, there was an increase of 5 observations in the number of records, since the new variables contained a smaller number of missing data. The adhesion parameters are shown below. As can be seen, it was possible to increase the probability of success when making the referral to the hospital.

TABLE 7 CLASSIFICATION MATRIX

		Provided		
		Home	Hospital	Total
Observed	Home	26 (72.2%)	10 (27.8%)	36 (100%)
	Hospital	3 (7.7%)	36 (92.3%)	39 (100%)
Overall percentage of correct responses				**82.7%**

Source: Elaborated by the authors.

A subsequent calibration made by changing its cutoff point led to an increase in the probability of a correct referral for hospitalization (% correct hospital responses) to 97.4%, with the consequent reduction in the probability of referral to home (% correct home responses), as shown in Table 8.

TABLE 8 CALIBRATION TO INCREASE THE PROBABILITY OF CORRECT RESPONSES IN THE INDICATION OF HOSPITALIZATION

Cutoff point	% Correct responses "Home"	% Correct responses "Hospital"	% total correct responses	Significance at 5%	Number of observations
0.25	61.8	97.4	80	Yes	75
0.3	66.7	**97.4**	82.7	Yes	75
0.35	69.4	92.3	81.3	Yes	75
0.4	72.2	92.3	82.7	Yes	75
0.45	72.2	87.2	80	Yes	75
0.5	72.2	82.1	77.3	Yes	75

Source: Elaborated by the authors.

Through the results obtained using the age of the individual together with some basic results of the hemogram, it is possible to predict which procedure to adopt for each patient before carrying out the specific tests of COVID-19 or during the waiting phase of the longer tests.

The values of these variables are obtained directly by performing a simple hemogram with a value often lower and with a faster result when compared to conventional tests (antigen, IgM and IgC) or even to the PCR performed to detect contamination of the patient by COVID-19.

Studies for the treatment of this disease are accelerated worldwide, with approximately 991 patents and 115 clinical tests that, for the most part, have yet to begin. Only two of them, however, deal with vaccines (Quintella, Mata, Ghesti & Tavares, 2020), which is why the adoption of indirect protocols to treat and refer patients appropriately – as is the case of this article – should be of value in this phase of the pandemic.

The dissemination of COVID-19 in the entire population is already causing an overload in the healthcare system, and the model proposed here, by anticipating the action of the patient referral, may contribute to the optimization of the public health service and impede patients from being directed to their residences when they should go to a hospital.

It should be considered that any quantitative models have their natural limitations, as they seek to represent the real world by mathematical equations, with no way to consider all the variables verified in loco. In addition, the present model was developed on the basis of a relatively small number of cases and has not yet been tested on a database other than that used for its construction. Therefore, it must pass further classification tests and possible recalibrations of parameters, in order to be applied more safely. However, its preliminary assessment allows us to have a positive expectation for its usefulness in the current Brazilian situation.

Evidently, this construction does not diminish the need to analyze the clinical condition of patients affected by COVID-19. However, the model presented can be used as a preliminary protocol for decision making in this moment of uncertainty, especially in situations involving less assisted populations, for which tests are scarce. This is particularly true in small municipalities whose resources are insufficient to obtain the more comprehensive tests. Even with a limited level of reliability in relation to specific tests, it is possible that this model, with simple and accessible application, could constitute a preliminary protocol for testing patients. Likewise, future studies with the inclusion of other variables are suggested, in addition to those provided for in the work, to make the model more robust in its predictive ability, including the use of other techniques of a quantitative nature.

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