

## Modelo preditivo para diagnóstico da SEPSE em unidades de terapia intensiva.

### **Predictive model for SEPSIS in the intensive care unit.**

## Modelo predictivo para el diagnóstico de SEPSIS en unidades de cuidados intensivos.

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**ABSTRACT:** This study aimed to provide a probabilistic decision model for sepsis, early diagnosis. The data contained in the medical records of 100 individuals admitted to a general ICU in a public hospital in the inland of the State of Paraíba were analyzed, in the period from March to September, 2011. The studied variables were: age, gender, initial diagnosis, minimum and maximum axillary temperature, heart and breathing rate, oxygen and carbon dioxide partial pressure, lactate serum levels, potassium, sodium, total count of leukocytes, bands and segs., among others. The binary logistic regression were used to determine the prediction model, and data were analyzed by SPSS software, version 19.0. 63% of the subjects were male, with a 62.5 year average age. as explanatory variables the following were considered: minimum axillary temperature, maximum axillary temperature, carbon dioxide partial pressure, lactate, white blood cell count and number of bands. Through ROC curve we identified the ideal cut-off point for classifying the subjects with regard to the presence or absence of disease, which has contributed to formulating the decision-making rule for sepsis early diagnosis. The concordance degree were compared between blood culture result regarded as gold standard for infection diagnosis and the model submitted in the study using Kappa coefficient, obtaining a 0.93 concordance percentage, regarded as outstanding. It was demonstrated being possible to carry out sepsis early detection adopting statistical models as the submitted one, however, new studies with populations from different ICUs must be performed in order to provide a better casuistry, making the found results reproducible in different clinical situations.

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Keywords: Intensive Care Unit; Sepsis; Decision Model.

**RESUMO:** O presente estudo teve como objetivo fornecer um modelo de decisão probabilístico para o diagnóstico precoce da sepse. Foram analisados os dados contidos nos prontuários de 100 indivíduos internados em uma UTI geral de um hospital público do interior do estado da Paraíba, no período de março a setembro de 2011. As variáveis estudadas foram: idade, sexo, diagnóstico inicial, temperatura axilar mínima e máxima, frequência cardíaca e respiratória, pressão parcial de oxigênio e de gás carbônico, nível sérico de lactato, potássio, sódio, contagem total de leucócitos, bastonetes e segmentados, dentre outras. Utilizou-se a regressão logística binária para determinação do modelo de predição, sendo os dados analisados pelo software SPSS versão 19.0. Constatou-se que 63% dos participantes pertenciam ao sexo masculino, com idade média de 62,5 anos. Foram consideradas como variáveis explicativas: a temperatura axilar mínima, a temperatura axilar máxima, a pressão parcial de gás carbônico, o lactato, a contagem de leucócitos e o número de bastonetes. Através da curva ROC identificou-se o ponto de corte ideal para classificação dos indivíduos quanto à presença ou ausência da doença, o que contribuiu para confecção da regra de tomada de decisão para o diagnóstico precoce da sepse. Realizou-se a comparação do grau de concordância entre o resultado da hemocultura considerado como padrão-ouro para o diagnóstico da infecção e o modelo apresentado no estudo utilizando-se o coeficiente Kappa, sendo obtido um percentual de concordância de 0,93, considerado como excelente. Demonstrou-se ser possível a detecção precoce da sepse com a adoção de modelos estatísticos como o apresentado, entretanto, novos estudos com populações de diferentes UTIs devem ser realizados a fim de prover uma casuística melhor, tornando os resultados encontrados reproduzíveis em diferentes situações clínicas diárias.

Palavras-Chave: Unidade de Terapia Intensiva; Sepse; Modelo de Decisão.

**RESUMEN:** Este estudio tuvo como objetivo proporcionar un modelo de decisión probabilística para el diagnóstico precoz de la sepsis. Los datos se analizaron en los registros médicos de 100 individuos ingresados en una UCI general de un hospital público en el estado de Paraíba, de marzo a septiembre de 2011. Las variables estudiadas fueron: edad, sexo, diagnóstico inicial, la temperatura mínima axilar y la frecuencia cardíaca máxima y la frecuencia respiratoria, la presión parcial de oxígeno y dióxido de carbono, el lactato sérico, potasio, sodio, el recuento total de leucocitos, varillas y específica, entre otros. Se utilizó la regresión logística binaria para determinar el modelo de predicción, y los datos analizados por el software SPSS versión 19.0. Se encontró que el 63% de los participantes eran hombres, con una edad media de 62,5 años. Se consideraron como variables explicativas: la temperatura axilar mínimo, la temperatura máxima axilar, la presión parcial de dióxido de carbono, el lactato, el recuento de leucocitos y el número de varillas. A través de la curva ROC identificó el punto de corte óptimo para la clasificación de los individuos para determinar la presencia o ausencia de la enfermedad, lo que contribuyó a que la regla de toma de decisiones para el diagnóstico precoz de la sepsis. Se realizó para comparar el grado de concordancia entre el resultado del hemocultivo considerado como el patrón oro para el diagnóstico de la infección y el modelo en el estudio utilizando el coeficiente Kappa, y obtuvo un porcentaje de concordancia

de 0,93, considerado excelente. Demostrado que es posible la detección precoz de la sepsis con la adopción de modelos estadísticos tal como se presenta, sin embargo, otros estudios en poblaciones de diferentes UCI deben llevarse a cabo con el fin de proporcionar una mejor muestra, haciendo que los resultados reproducibles en diferentes situaciones clínicas diarias.

Palabras clave: Unidades de Cuidados Intensivos, Sepsis, Modelos de Decisión.

## INTRODUCTION

Intensive Care Units (ICUs) are complex treatment areas for treating subjects demanding intensive care and who might show good survival chance. Their appearance was due to the need to provide more specialized and continuous care to subjects with severe or risk diseases <sup>1</sup>.

The idea to combine severe patients to provide better care emerged with Florence Nightingale, in the Crimean War, in 1854. Therapeutic intervention improvement and the development of special units to shelter patients and highly-complex technological resources have transformed mortality rates for various pathologies. With the creation of specific areas and for intensive care over the last few decades, it has become feasible to maintain and recover patients with various types of diseases and acute instability conditions arising there from, hemodynamics, respiratory, metabolic, renal, among others <sup>2</sup>.

The follow-up of patients with infection is a challenge for the ICU multidisciplinary team. In patients admitted to hospitalization with prior symptoms, infection is considered as acquired in the community, those who develop infection with more than 48 hours after hospital admission, it is considered related to nosocomial or hospital stay. The main infectious syndromes that may require admission to and immediate therapy in ICU, are: sepsis, pneumonia, infectious endocarditis, intra-abdominal infections among others, yet the most prevalent and worst prognosis is sepsis <sup>3</sup>.

The term sepsis means putrefaction, organic matter decomposition by an offending agent (bacteria, fungi, parasites, viruses). The terms infection and sepsis are generally used independently, however the terminology ends up simplifying a complex relationship. The term infection is related to the presence of the offending agent in a location (tissue, cavity or body fluid) typically sterile and the term sepsis is related to the host's consequent manifestation, i.e., the inflammatory reaction triggered a severe infection. The distinction between the two is not easy, because all infectious process triggers a response from the host, and each subject shows some type of reaction with different magnitudes given a certain injury <sup>4</sup>.

Adopting strategies that enable the sepsis rapid diagnosis and treatment is critical, since that its occurrence is associated with significant morbidity and mortality if such a condition is not readily recognized and treated <sup>5,6</sup>.

Given this problem, some questions arise: How to evaluate the severity of subjects admitted to

the ICU in order to ensure the best care? The conduct held is bringing a satisfactory response to the patient's health? Is there any way to predict the evolution of a particular disease and reduce its harm to the patient's health?

Several prognostic scores that match different clinical and laboratory parameters such as Acute Physiology and Chronic Health Evaluation (APACHE II) and Sepsis Related Organ Failure Assessment (SOFA) are used to assess mortality risk in patients in ICU. However, these scores, despite showing a high positive predictive power as for mortality, are not adapted to the Brazilian reality, which hinders their application in daily clinical practice <sup>1</sup>.

Until 1988, these prognostic indexes were widely used in Intensive Care Units in Brazil, without, however, being validated as morphological differences existing between Brazil population and United States and Europe population, where they were developed <sup>1</sup>.

To this end, a multicenter study was carried out by applying APACHE II model to 1734 inpatients in ten hospitals in Brazil and, later on, data were analyzed by William Knaus team in Washington, demonstrating important differences in SMR (Standardized Mortality Rate) - relationship between the predicted mortality and observed mortality. And in general, the observed mortality was higher than the estimated by APACHE II model <sup>7</sup>.

In Brazil, a model of prognostic evaluation for hospitalized patients in intensive care Units was developed, the model referred to as UNICAMP II. This was the result of analyzing a database from a Brazilian university hospital and compared to other models published in the literature as APACHE II. In addition to its validity having been verified and the Brazilian reality portrayed, it may be pointed out, among its merits, the fact that risk estimate assigns a single score for all patients, regardless of the cause that led to hospitalization in the ICU <sup>8</sup>. However, UNICAMP II model assesses mortality in the intensive care unit, without making a specific correlation with Sepsis presence.

Thus, in Brazil, epidemiological studies that evaluate the mortality caused by sepsis are still nonexistent. In this way, it becomes essential for implementing a rigorous protocol of measures, based on scientific and guiding evidences, focused on early detection and prediction of mortality, seeking, to better optimize the allocation of technical and financial resources and, thus, obtaining more efficient results in sepsis treatment, by reducing morbidity and mortality and, consequently, their social impact.

Given the above, this study aimed to provide a probabilistic decision model for sepsis early diagnosis from clinical data of patients admitted to a general ICU of a public hospital in the State of Paraíba.

## METHODOLOGY

It is a longitudinal field study with quantitative approach, conducted in the Intensive Care Unit of Hospital Regional de Patos (HRP), during the period from April to October, 2011. The research was approved by the Ethics and Research Committee of Faculdades Integradas de Patos (Report Number: 106/2011).

HRP is situated in the town of Patos, in Sertão da Paraíba, 300 km from João Pessoa/PB, being a medium-sized municipality with predominantly urban population totaling 106,314 habitants<sup>9</sup>. The Intensive Care Unit of the Regional Hospital de Patos (HRP) has six beds, serving exclusively adult patients, characterized as a general ICU for patients affected by various distinct pathologies, such as victims of heart disease, accidents, respiratory diseases, metabolic disorders, among others.

Data were collected from the medical records of all patients in hospitalization in the ICU in the period from March to October 2011. This period coincided with data collection for preparing the Master thesis of the Graduate Program in Health and Decision Models of Federal University of Paraíba (UFPB) totaling 113. The sample was made up by the medical records of all patients showing all the research inclusion criteria, totaling 100 subjects.

The study included the subjects obeying to the following inclusion criteria: age less than 15 years, being admitted in the HRP ICU during data collection period, have in their medical records the data on all the variables of interest in the study, collected from a proper instrument made up by the researcher. All subjects who did not meet these criteria were excluded from the research.

For carrying out realization the study, a questionnaire prepared by the researcher was used, containing general patient's data, such as age and sex, initial diagnosis upon admitted to the ICU and clinical and biochemical variables, such as, minimum axillary temperature (MAT) and maximum axillary temperature (MXAT) recorded in the 24 hours prior to collection, heart rate (HR) and respiratory rate (RR), carbon dioxide (PCO<sub>2</sub>) and oxygen blood concentration (PO<sub>2</sub>), lactate serum levels (LSL), sodium, potassium, total leukocyte count (TL) and band count (Bands), result of blood culture, number of days for stay in the ICU (ICU Days), use of antibiotic therapy and changes in treatment during the hospitalization period. All the analyzed variables were chosen based on the literature pertinent to the theme.

Data were collected exclusively by the searcher, always by the morning, around 8 a.m. Adopting this measure is a way for reducing the possibility for biases from gauging with the collection standardization. It is also justified because the exchange of on duty professionals in the unit occurs in the morning period, making it easier to access the information on such patients admitted throughout the day before, including in the night shift.

Data contained in the patient's medical records were used for collecting the variables: age, gender, initial diagnosis upon admitted to the ICU, number of days for stay in the ICU, use of

antibiotics, sepsis clinical diagnosis days and changes in treatment during the hospitalization period, axillary temperature, heart and breathing rate. For measuring carbon dioxide ( $PCO_2$ ) and oxygen blood concentration ( $PO_2$ ), we carried out the patient's arterial blood gas analysis, using TI500 model gas meter available in the ICU. The total white blood cell and band count was based on the leukogram and the results written down in the patient's medical record.

After collection, data were tabulated in an Excel® for Windows spreadsheet program, version 2007, and analyzed using SPSS (Statistical Package of the Social Sciences) software, version 19.0. Initially, the variables were categorized as follows: zero "0" for absence of expected factor and one "1" for presence. This time, after categorizing, they were distributed according to the Table 1.

For constructing the statistical model, we used binary logistic regression. This model aims to describe the relationship between the dichotomous response variable  $y$ , as for example, disease status (the disease is present or absent) and the predictive variables  $X_1, X_2, \dots, X_j$ . In this model the response variable can take only two values, 0 or 1. In general, the value 1 is used to represent a "success" or the result in which we are more interested and 0 to represent failure<sup>10</sup>.

**Table 1** - Values of variables in the logistic model

Analyzed Variable	Value ("0")	Value ("1")
TAM	Se > 36° C	Se < 36° C
TAMX	Se < 38° C	Se > 38° C
FC	Se < 90 bpm	Se > 90 bpm
FR	Se < 20 irpm	Se > 20 irpm
LAC	Se < 2 mmol/L	Se > 2 mol/mml
Sodium	Se entre 136-145 mmol/L	Se other value
Potassium	If between 3.5-5.0 mmol/L	If < 3.5 mmol/L
$PCO_2$	If < 45 mmHg	If > 45 mmHg
$PO_2$	If between 80-100 mmHg	If other
LT	If < 12,000	If > 12,000
Bands	If < 10%	If > 10%
Segs.	If < 7,000	If > 7,000
Culture	If negative	If positive
Diagnosis of Sepsis	If negative	If positive

We considered as a dependent or response variable the result of blood culture for being this considered the gold standard for identifying sepsis and the other variables as independent. To determine which independent variables had statistical significance for determining sepsis presence or absence, Chi-square ( $\chi^2$ ) was carried out to test the association degree between variables, being considered a 5% significance level, i.e. p-value < 0.05.

We built the relative risk scale for each of the variables that showed statistical significance for the logistic model and from the risk calculation we developed the "weight" that each factor has played



in the disease's outcome. The assigned weight was used later on to determine the SCORE variable that indicates the global contribution of the variables analyzed for sepsis outcome emergence, being determined in a numerical scale from 0 to 100 to better understanding its clinical the importance <sup>11</sup>.

After determining the SCORE variable value, ROC curve was constructed to test the relationship between this variable and the gold standard and, thus, evaluate the relationship between them. From defining ROC curve coordinates we calculated the ideal cut-off point to characterize which subjects have probability for developing sepsis or not. Determining ROC curve Cut-off Point was performed from Youden index <sup>12</sup>.

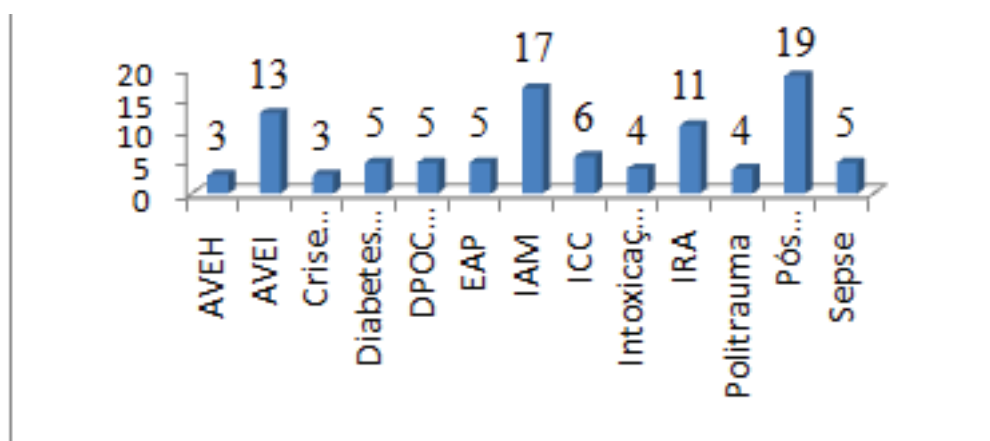
Finally, we assessed the concordance degree between the diagnoses made by the submitted decision-making model and analyzed data, using Kappa coefficient.

## RESULTS

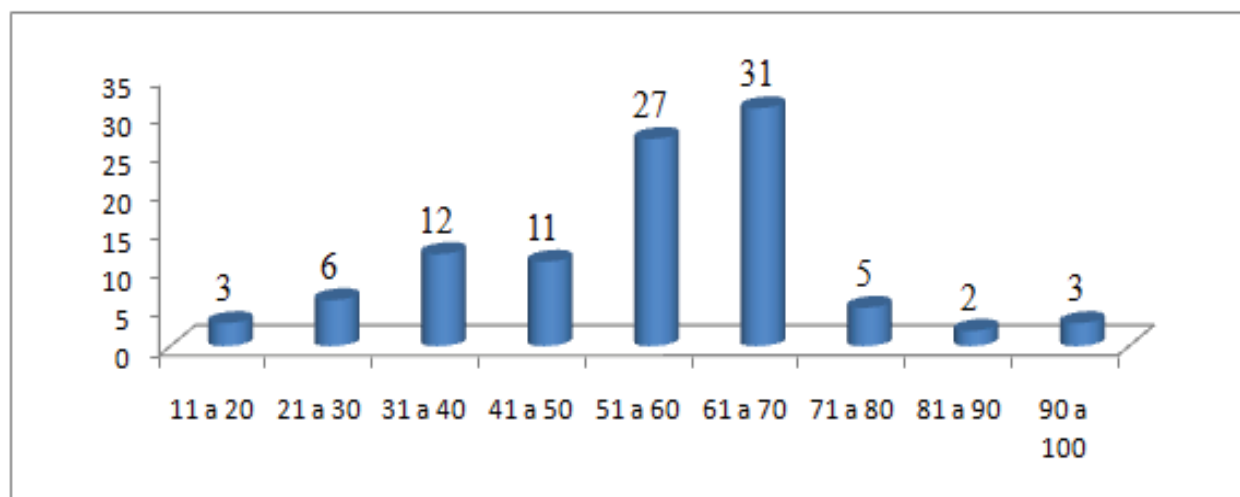
This study included the participation of 100 subjects, with 63% males and 37% women.

Chart 1 is showing the subject distribution upon the initial diagnosis (admission) in the ICU. Although some subjects showed more than one admission diagnosis, for this analysis we considered only the main diagnosis, that is, the one that justified the need for hospitalization. It is noted that the most prevalent diagnoses were: Immediate postoperative period with 19%, Acute Myocardial Infarction (AMI) with 17%, Ischemic Cerebrovascular Accident (ICA) with 13% and Acute Renal Failure (ARF) with 11% of analyzed cases.

**Chart 1** – Initial diagnosis of subjects admitted to the ICU. Patos-PB, 2011



Data concerning the age of subjects in the research are represented in Chart 2. The age of subjects ranged from 15 to 93 years, with 62.5 year on average and  $\pm 9.23$  standard deviation. It is noted that the age groups that show higher number of admitted patients were between 61 to 70 years with 31% and between 51 to 60 years with 27% of total.

**Chart 2** – Distribution of subject age in the study. Patos-PB, 2011.

With regard to sepsis diagnosis, from 100 subjects 18 had the syndrome's clinical diagnosis which provides us with 18% prevalence. However, among those diagnosed patients, just 14 or the equivalent to 77.8% of cases, the result of blood culture confirmed pathogenic microorganism presence. Infectious agents found in blood culture were *Klebsiella pulmonare*, *Pseudomonas s.p.* and *E. colli*, with 9, 7 and 2 cases, respectively.

Another analyzed variable was the number of hospitalization for the patients in the ICU. Data demonstrate that there was a variation between 1 to 56 days, with an average of 6.8 days and  $\pm 9.4$  standard deviation, while 73% of subjects remained hospitalized for up to 5 days, 14% between 6 to 10 days and only 13% remained more than 10 days in the unit.

Due to their severe condition the patients in the ICU are usually subjected to various invasive or non-invasive therapeutic modalities, among them, is using antibiotics. Using this therapeutic modality since the hospitalization period commandment was observed in our research and one can note that 81% of subjects in the unit used of some type of antibiotic and 19% did not use.

In daily clinical practice it is common for the healthcare professional to reevaluate the proposed treatment for their patients in order to determine whether the therapeutic response is appropriate or not. In this sense, our study analyzed the occurrence of alterations to the treatment given to subjects assisted by the ICU. It was found that there was no change in 88% of the subjects in the given therapeutic conduct and in 12% this change was detected.

As for the statistical procedure developed to provide a probabilistic decision model for sepsis early diagnosis, this study was based on binary logistic regression, being the Chi-square test initially applied to identify association between the studied variables, adopting 5% significance level.

Among the factors analyzed and displayed in Table 1, those with p-value  $< 0.05$  and, therefore



are statistically significant, were the following variables: minimum axillary temperature, maximum axillary temperature, lactate, potassium, carbon dioxide partial pressure, total white blood cell count, number of bands and segs. P-value for the respiratory rate variable was 0.052, discreetly greater than the initially determined significance level; however, because of its clinical importance in pathology diagnosis, it was maintained in the logistic regression analysis.

The variable type of microorganism, days of stay in the ICU and treatment changes were excluded for not attending the immediate clinical diagnosis (admission), since their values will only be known *a posteriori*, to the subject's admission in the ICU, and its maintenance in the logistic model may be considered as a confounding factor. Later on, the value for the correlation between sepsis clinical diagnosis and culture result was evaluated through Kappa coefficient and will be demonstrated.

This time, RL binary Model, had as a response variable the gold standard for sepsis diagnosis that, according to the submitted literature, is the blood culture result and as explanatory variables the minimum axillary temperature, maximum, axillary temperature, respiratory rate, lactate, serum potassium level, PCO<sub>2</sub>, the number of total leukocytes, number of bands and segs.

However, after inserting all the explanatory variables, we carried out adjustment of logistic model, in which we removed an independent variable once a time and we observed the displayed response quality. Finally, the variables minimum and maximum Axillary Temperature, Lactate, PCO<sub>2</sub>, number of Leukocytes and Bands remained as significant, as can be seen in Table 1.

**Table 1** – P-value for study variables. Patos-PB, 2011.

Variable	P-value
Minimum Temperature:	< 0.001
Maximum Temperature	0.016
Heart Rate	0.105
Respiratory Rate	0.052
Lactate	0.014
Sodium	0.282
Potassium	0.042
PCO <sub>2</sub>	0.005
PO <sub>2</sub>	0.080
Total Leukocytes	< 0.001
Bands	< 0.001
Segs.	< 0.001

To follow, we will describe the analysis for the adopted logistic regression model. It may be seen in table 2 that the tested model showed a set percentage *a priori*, i.e. without adding 82% for independent variables, which indicates that the model could determine with precision when the individual did not have sepsis (true negative), however, its predictive power for diagnosing the disease presence (true positive) is null.

**Table 2** - Classification of Regression Model a Priori. Patos-PB, 2011.

Sepsis	Test		
	Sepsis Diagnostic		Hit percentage
	Negative	Positive	
Negative diagnosis	82	0	100%
Positive diagnosis	18	0	0%
Hit percentage	100	0	82%

To assess the tested model predictive capacity, we used the Logistic Model Omnibus Tests statistics, which tested the hypothesis that all the logistic equation coefficients are null, the test result is described in table 3.

**Table 3** - Logistic Model Omnibus Tests. Patos-PB, 2011.

	$\chi^2$	df	Sig.
<b>Step</b>	87.007	6	<.0001
<b>Block</b>	87.007	6	<.0001
<b>Model</b>	87.007	6	<.0001

In the model's summary evaluation, demonstrated in table 4, we have the values 0.589 for Cox & Snell R Square and 0.952 for Nagelkerke. These tests are considered  $R_2$  pseudo and indicate the proportion for the variations that occur in the chance ratio log. It is also seen that the value calculated for Hosmer and Lemeshow test that evaluates accuracy degree for the logistic model which in this case was 0.999.

**Table 4** - Summary Evaluation for the Model. Patos-PB, 2011.

Step	-2 Log likelihood	Cox & Snell R Square	Hosmer-Lemeshow	Nagelkerke R Square
	7.271	.589	.999	.952

With the insertion of independent variables in the logistic model, one can measure whether a not change occurred or not in its predictive power. In table 5, it is observed that the, *a posteriori* hit percentage, i.e., with the insertion of the independent variables reached 98%. The most important thing to be detected is that previously the model could identify with 100% accuracy the true negative results; however, its predictive power for diagnosing disease presence was null. With the insertion of independent variables, model's specificity went down to 98.8%, however, its sensitivity went up to 94.4%.

**Table 5** - Model Classification after insertion of independent variables. Patos-PB, 2011.

Remark	Prediction		
	Sepsis Diagnostic		Hit percentage
	Negative	Positive	
Negative diagnosis	81	1	98.8%
Positive diagnosis	1	17	94.4%
Hit percentage	82	18	<b>98%</b>

For making the logistic model, it is necessary to determine the values for the  $\beta$  coefficients of each variable, which can be seen in table 6.

**Table 6** -  $\beta$  values for the logistic model variables. Patos-PB, 2011.

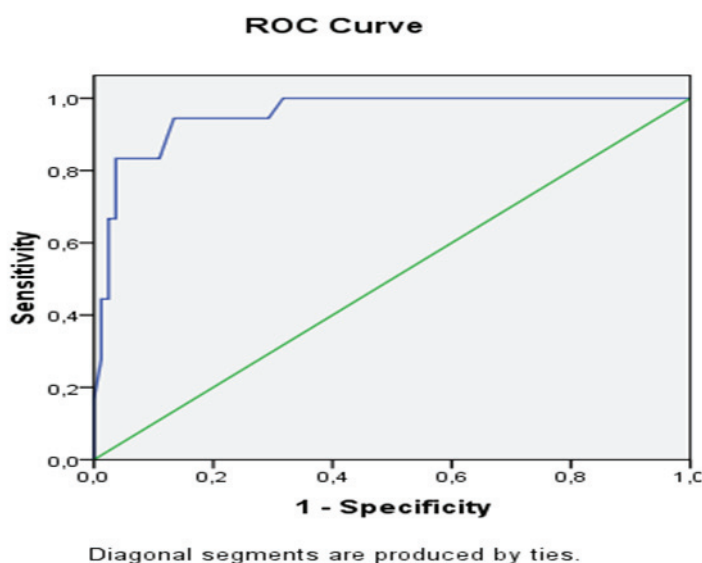
Variable	Value of $\beta$	P-value
Minimum Temperature:	35,845	< 0,001
Maximum Temperature	18,738	0,010
Lactate	18,408	< 0,001
PCO <sub>2</sub>	0,467	0,003
Total Leukocytes	16,488	< 0,001
Bands	56,592	< 0,001
Constant	-54,193	< 0,001

From the above figures, the tested model logic equation was determined by:

$$\ln\left(\frac{\pi_i}{1 - \pi_i}\right) = -54,19 + 35,85 \text{ TAM} + 18,74 \text{ TAMX} + 18,41 \text{ Lac} + 0,47 \text{ PCO}_2 + 56,6 \text{ Bast} + 16,49 \text{ LT}$$

For determining ROC curve, we compared gold standard and SCORE variable as described earlier. The chart showed an area under the curve of 0.946 (Figure 1).

**Figure 1** - ROC curve between gold standard and Score. Patos-PB, 2011

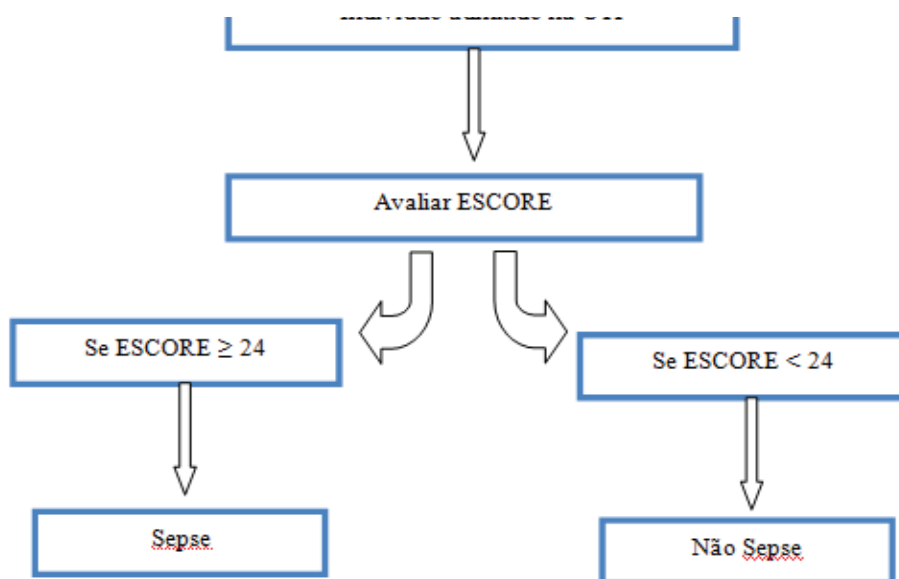


Based on the ROC curve coordinate data shown in table 7 and using the Youden Index also described earlier it was possible to determine the ideal cut-off point for diagnosing the sepsis presence or non-presence. Therefore, the value 24 was determined as an ideal cut-off point.

**Table 7** – ROC Curve coordinates

Positive if $\geq$ 1	Sensitivity	1 - Specificity
-1	1	1
3.5	1	0.598
8	1	0.463
10	1	0.378
13.5	1	0.366
18.5	1	0.354
<b>24</b>	<b>1</b>	<b>0.195</b>
27.5	0.889	0.183
29	0.889	0.134
31	0.889	0.122
33	0.889	0.098
38.5	0.833	0.098
44	0.778	0.098
49.5	0.722	0.085
55	0.722	0.073
58	0.722	0.061
62.5	0.667	0.061
65.5	0.556	0.061
69	0.5	0.037
72.5	0.444	0.037
74	0.389	0.037
76	0.389	0
78	0.333	0
80	0.278	0
84.5	0.222	0
90.5	0.056	0

Knowing the ideal cut-off point it was possible to elaborate the decision rule for sepsis diagnosis on the studied model, thus determined, as shown in Figure 2.

**Figure 2** – Decision flowchart for diagnosing Sepsis in ICU. Patos-PB, 2011

Prepared by the authors

Once the logistic model has been determined, the ideal cut-off point for classifying the subjects and the decision rule that defines the subjects as sepsis bearers, the following question remains: is this information really reliable for the syndrome diagnosis? Or we are facing another theoretical statistical model with little or no application in the clinical practice?

To address this question we compared the performance for the model herein proposed with the existing one. However, it should be noted that there is a proper model for predicting sepsis diagnosis and, in clinical practice; sepsis diagnosis is established from clinical data and performing blood culture, which is considered the gold standard to confirm or rule out the diagnosis, although not showing sensitivity greater than 85%.

However, even though blood culture is the gold standard, there are many false-negative results which make the clinic decision for the treatment even more complex, once that the non-intervention in the septic condition may lead to the patient's death. Given the above, the model herein presented can be used to support decision-making in patients with sepsis clinical and laboratory diagnosis increasing reliability and the possibility for patient's recovery.

Given the situation we decided to compare the performance of the model herein proposed with the blood culture using Sensitivity, Specificity, Positive and Negative Predictive Value, Positive and Negative Likelihood Ratio and Kappa coefficient calculation.

We can see in table 8, that we obtained 98.8% Sensitivity, 94.4% Specificity, 98.8% Positive and 94.4% Negative Predictive Value, 17.8 Positive and 0.00 Negative Likelihood Ratio; Kappa coefficient for comparing the concordance percentage between gold standard and the submitted model was 0.93; While these values when compared to the gold standard with sepsis clinical diagnosis were 95.1%; 77.8%; 95.1%; 77.8%; 4.3; 0.1 and 0.73, respectively, demonstrating that the submitted model presented trustworthy.

**Table 8** - Comparison of trustworthiness for the tested Model, Patos-PB, 2011

	<b>Tested Model / Gold Standard</b>	<b>Clinical Diagnostic / Gold Standard</b>
Sensitivity	98.8	95.1
Specialty	94.4	77.8
Positive Predictive Value	98.8	95.1
Negative Predictive Value	94.4	77.8
Positive Likelihood Ratio	17.8	4.3
Negative Likelihood Ratio	0.0	0.1
Kappa Coefficient	0.93	0.73

## DISCUSSION

Among the 100 surveyed subjects we observed male predominance with 63% of total. These findings are consistent with other studies conducted in intensive care units in Brazil that found, respectively, 54.9% and 58.2% percentage for male patients<sup>12,13</sup>. With respect to the initial diagnosis, it may be noted that study's participants had diagnosis from different areas of clinic and surgery that is due to the analyzed ICU generalist aspect. Upon evaluating a general intensive care unit, it was observed that the most frequent causes for hospitalization were systemic arterial hypertension with 15% of the diagnoses, acute myocardial infarction with 12.5%, acute and chronic renal failure with 10% and cerebrovascular accident with 7.5%<sup>14</sup>.

In this work, upon considering the age of sample members, it was found that 41% of the subjects had more than 60 years, corroborating with a study carried out in the ICU of Hospital Regional da Asa Norte (HRAN), in the Federal District, where it was found that most patients belonged to the over 60-year category (29.9%)<sup>14</sup>. This fact can be explained because, in Brazil, as well as in the developed countries, the phenomena known as the demographic transition is occurring, resulting from the decrease in the birth rate and population's increased longevity. As a result, the number of elderly patients hospitalized in the ICUs is increasing<sup>16</sup>.

Sepsis incidence of in the surveyed unit was 18%. However, this value that at first seems to be very high lies within the syndrome incidence parameters as reported worldwide. Sepsis rates reported in the literature may vary according to the characteristics of each location and the complexity of the performed procedures, and there may be situations where their impact goes from 10 to 16%, as in some countries in Europe and in the United States or even extremely high levels as around 27 to 33% in little developed nations<sup>17</sup>. The average annual incidence is 51.5 cases per 100,000 adult inhabitants

After completing the blood culture, three different microorganisms were identified in the study subjects: *Klebsiella Pneumoniae*, *Pseudomonas spp e Escherichia coli*. The main sepsis causative agents in ICU patients are *Escherichia coli* and *Pseudomonas aeruginosa* with 18.55 and 15.5% of the total of infected subjects<sup>18,19</sup>. The assessment of blood cultures performed in ICU patients of a teaching hospital in Goiania/GO demonstrated that among Gram-negative bacteria, *Pseudomonas spp* and *Klebsiella pneumoniae* were frequently reported, corroborating the results of our study<sup>18</sup>. A study developed in China found that among the most prevalent species were *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae*<sup>21</sup>.

In hospitals, mainly in the ICU where patients undergo numerous invasive procedures the longer



the permanence in this sector is, the greater is the likelihood for developing infectious processes caused by microbiological agents.

A period of stay greater than 72 hours in the ICU is associated with a 1.88 greater death risk arising from severe infections <sup>22</sup>. However, our research did not reveal direct relation between the length of stay and sepsis emergence, a fact which can be explained by the intense control for standards and routines in the studied unit, which contributes to reducing contamination risk.

One of the major problems currently faced by medicine is multidrug microbial resistance ending up by leading to increasingly powerful and costly drug use for the health services, particularly public services. The rational use of antibiotics not only reduces costs, but mainly preserves the life of infected subjects. Their indiscriminate use has led to the emergence of resistant strains that claim lives everywhere.

Studies showed that non- judicious antibiotic giving for inpatients in neonatal ICU <sup>23</sup> and elderly ICU <sup>24</sup> constitutes one of the main factors related to sepsis emergence due to multidrug-resistant organisms. The occurrence of changes in the treatment of these patients without adopting judicious measures, such as antibiogram, increases in up to 2.23 times the chance to developing sepsis.

Data from this study showed that 81% of participants made use of antibiotics during the hospitalization period, and in many cases the beginning of their medication occurred since the first hospitalization day in the unit, without, therefore, knowing blood culture results and, consequently, the antibiogram. This fact may have contributed to an increased incidence of sepsis diagnosed cases by leading to triggering microbial resistance.

The possibility to predict with accuracy the prognostics, such as mortality of patients, or quality of life of a patient is especially important because it can guide individual or group decisions. Understanding important elements that go into the development of a prognostic prediction model can help healthcare professionals to use these instruments in daily practice. To the extent that the methods to predict the individual prognostics are validated and more widely accepted. The knowledge of statistics and evidence-based medicine has brought out the necessary support for a new era of indexes that are mathematically-proven as effective.

In this study we sought to examine the influence of various clinical variables for defining sepsis early diagnosis. The obtained data show that the variables that showed statistical value for determining the predictive model for the disease were minimum and maximum axillary temperature, carbon dioxide partial pressure, lactate serum concentration, white blood cell count, and the number

of bands. However, we can ask ourselves how to clinically interpret this information?

Body temperature control process is quite complex and mediated primarily by the hypothalamus through the areas of production, conservation, and heat dissipation. The temperature remains stable thanks to the balance between heat production and loss from the body. Heat production occurs by carrying out chemical reactions necessary for the digestive process and by skeletal muscles contraction. Heat loss takes place when the ambient temperature is below the body temperature - by irradiation, when different temperature objects are not in contact or by conduction when heat exchange base is done by direct contact <sup>25</sup>.

In the patient with septic condition this body regulation mechanism is changed once that the exposure to the infectious agent and its systemic implications will lead to progressive impairment of hypothalamus response to temperature changes in the subject's internal environment and may occur at extreme high or decrease in temperature on the patient's skin. As described earlier, for SIRS diagnosis, patient's temperature should be in two distinct ranges: less than 36° C or greater than 38° C.

According to the surveyed data those subjects that showed temperature variations within the above ranges showed significant risk for the sepsis emergence, but, why this occurred? The answer to this question is very complex, but it can be explained by two distinct reasons: First, in an ICU vital signals are periodically evaluated, in the evaluated unit every 2 hours throughout the 24-hour duty. This time, discrete elevations in axillary temperature, such as the temperature record in the order of 35.9° or 38.1° C, for example, are logged and notified automatically to the medical staff that provides immediate therapeutic procedures for controlling such changes.

Second, while developing the infectious process, the body will change the basal metabolic rate as a way to combat more efficiently the suffered injury, with that, the chemical reactions of the metabolic process might be delayed or accelerated, according to the subject's energy needs which will, consequently, increase or decrease the internal temperature, and by consequence, the axillary region temperature.

The body controls blood supply automatically using heart pump. However, under systemic overload situations as in a patient affected by sepsis, the amount of blood supply to the peripheral tissues is drastically diminished. Capillary hypoperfusion disorders arising mainly from hypotension generated by peripheral vascular resistance are common, as a result there is an increase in the heart pump work load leading reflexively to raising heart beating rate <sup>26</sup>.

The respiratory process is controlled in two distinct ways: centrally by the respiratory center located on the dorsal and ventral portion of the bulb and peripherally by the carotid and aortic receptors. The central control occurs primarily due to the action of H<sup>+</sup> ions in these centers leading to elevated respiratory rate and, consequently, reducing the acid/base imbalance. Peripheral regulation already occurs in the blood oxygen concentration evaluation, in which discrete decreases at this concentration lead to elevated respiratory rate as a compensatory mechanism.

In the subject with sepsis we will have an increase in general metabolism, which will increase the oxygen demand so that chemical reactions occur, also, due to the installed metabolic imbalance, a metabolic acidosis is quickly installed, which if not corrected will take the patient to death. One of the mechanisms that the body will use to try to curb this process is increasing the RF as a way to correct the existing metabolic changes, by increasing the oxygen supply and eliminating PCO<sub>2</sub> present in the respiratory gases <sup>27</sup>.

Given the above, as a consequence from metabolic changes arising from the septic process, the body will suffer changes in lactate serum concentration and carbonic gas blood concentration, these facts are registered in our research. Furthermore, at the moment there is no consensus in the literature on the clinical significance of the individual components regarding metabolic acidosis, excluding lactate for developing sepsis, a fact that it is believed that we have managed to explain <sup>27,28</sup>. In this context, it should be noted that the deleterious hemodynamic effects of severe lactic acidosis are widely suggested by experimental data, although they are not fully confirmed by studies in humans <sup>29</sup>.

Leukocytes are the defense cells of our body and are much less numerous than the red cells in the circulating blood. They originate in the bone marrow and are divided in three classes: the granulated that make up 50% to 60% of all leukocytes and have the form of neutrophiles, eosinophiles, and basophiles (bands); lymphocytes and monocytes. Bands occur in normal blood in very small number, approximately 0.5% of the total number of leukocytes, and have as their function tissue repair in severe allergic or inflammatory processes <sup>25</sup>.

Upon occurring infectious states, such as those existing during sepsis, the body is stimulated to raise the production of white blood cells in an attempt to limit tissue injury extent, leading to the development of leukocytosis. Given the worsening in the infectious condition, a refractory inflammatory process is triggered, aiming to restore local integrity, a fact that this causes increase in the quantity of bands and their percentage may rise up to 10% or more of total white blood cells present in the blood.

In order to assess the submitted logistic model reliability, we used various statistical tests suitable for logistic regression, such as the Omnibus Tests, Cox & Snell R Square, Nagelkerke R Square and Hosmer and Lemeshow test.

Calculated Omnibus test was  $< 0.0001$ , with this result we rejected the null hypothesis, that is, we can say that introducing the independent variables is contributing to improve the model's predictive quality. This can be evidenced when we compare the model's predictive value *a priori* and *a posteriori*, in which its hit percentage changed from 82 to 98%.

Cox & Snell R Square and Nagelkerke R Square are considered pseudo R Square, being compared to R-Square of the Linear Regression. The 0.589 and 0.952 values, respectively, indicate that 58.9% of the variations occurred in the reason of possibilities log are explained by the set of independent variables (TAM,  $PCO_2$ , amongst others) and that the submitted model is capable to explain about 95,2% of the variations registered in the dependent variable, which makes it quite reliable <sup>30</sup>.

To complete the assessment on the reliability for the submitted logistic regression model, we should observe Hosmer and Lemeshow test. This test is designed to test the hypothesis that there is no significant difference between the results predicted by the model and those observed. The 0.999 calculated value leads us to accept the nullity hypothesis, which means in practice that our model can be used to estimate the probability of a particular subject to develop sepsis depending on the independent variables.

The area under ROC curve is a measure of the usual summary for performing a test, since it is estimated taking into consideration all values of sensitivity and specificity. A test totally unable to discriminate sick and non-sick subjects would have an area under the 0.5 curve. The greater is the ability of the test to discriminate the subjects according to two groups, the more the curve approaches the top of the chart, and the area under the curve will be close to 1. In this study, the area under the curve was 0.946, representing a high capacity of discrimination among subjects who developed sepsis and those who did not have it <sup>31</sup>.

By observing the information relative to the submitted model's reliability evaluating the sensitivity, specificity, PPV, VPN, Positive (RV+) and Negative (RV-) Likelihood Ratio and Kappa Coefficient value, one can see that the tested model demonstrated an outstanding overall performance when compared to the gold standard, and we may especially highlight the value of RV+ 17.8, which means to say that, at this cut-off point, the chance for a positive test to be true is 17.8 times greater than the chance to be false. Another important factor was Kappa coefficient

value upon comparing the concordance degree between the model and the gold standard that has shown to have an outstanding concordance degree. When we compared sepsis clinical diagnosis with the gold standard, we obtained satisfactory results, but, lower than the tested model.

Therefore, the analyzed data offer satisfactory conditions for concluding that the applied methodology was adequate and that the submitted model, as well as, the set cut-off point have outstanding statistical probability to predict sepsis development in patients admitted to ICU.

During research some important limitations became evident and deserve to be mentioned. When we analyze the number of sepsis clinical for the analyzed period with the previously equivalent we observe that there was a decrease in around 15%, this fact can be associated with the fact that the unit's professionals have knowledge on the study and have become more judicious in the syndrome's confirmation. Another factor to be seen is the number of subjects admitted to the ICU during the studied period. The sample included records of 100 subjects that, *a priori*, seems statistically significant, however, it is believed that more information could have improved the tested model's reliability.

However, despite the presented limitations, it is possible to build a probabilistic decision model with great predictive power for diagnosing sepsis without the need for blood culture, which in addition to its unprecedented character may contribute to reducing mortality caused by the disease, by offering high reliability coupled with low cost and quick response.

## CONCLUSION

This study aimed to provide a probabilistic decision model for sepsis early diagnosis, using as main methodological resource binary logistic regression for building the model. It was identified that the minimum and maximum axillary temperature, CO<sub>2</sub> partial pressure, lactate blood levels, number of total leukocytes and bands are clinical variables that can explain statistically the syndrome's occurrence.

From the collected data, it was possible to characterize the epidemiological profile of subjects admitted to the ICU of HRP, where we observed a predominance of males over females, higher prevalence of patients over 50-year old, and more expressive frequency of clinical pathologies over surgical pathologies, as causes for admission to the unit, which is consistent with the for the analyzed service general nature.

We noted the association of clinical information from patients in the ICU upon sepsis emergence, having the same characterized as of paramount importance for establishing the pathology's diagnosis

through the used methodology, thus demonstrating its epidemiological relevance in determining the studied syndrome, as well as the need for its recording in a standardized way in order to provide reliable data for conducting research like ours.

The results also allowed to establish an ideal cut-off point for decision making, which in turn assisted in preparing the flowchart that sorts the patients as to the occurrence or not of sepsis based on the studied variables with no need for costly exams and late response, such as blood culture.

When we compare the concordance degree as for sepsis diagnosis, between model submitted in this study and the gold standard reported by the medical literature that is the blood culture using Kappa coefficient, we obtained an outstanding concordance degree, which indicates good possibility for practical application of the model.

Although this research has achieved all the initially-proposed objectives, due to the analyzed sample being composed of a single ICU, it is recommended to carry out further studies with different populations in order to verify the findings herein mentioned, thereby contributing for reducing mortality due to sepsis worldwide.

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