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Ventilator-associated pneumonia prediction model based on ultrasound and biomarkers compared to bronchoalveolar lavage

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Introduction

Ventilator-associated pneumonia (VAP) is a problem that generates an increase in morbidity and mortality and is one of the main causes of nosocomial infection in the ICU. Therefore, early diagnosis is essential to reduce adverse effects. Currently, bronchoalveolar lavage (BAL) is the gold standard for its diagnosis and involves human resources trained in the use of the bronchoscope and specialized materials, which are not available in most hospital units, so it would be pertinent to have a diagnostic prediction tool that can best supplant its use.

Background

During the year 2023, a prevalence of 60% of Ventilation Associated Pneumonia (VAP) was recorded in our Intensive Care Unit, compared to the global rate that ranges between 10% and 20%.[1] Likewise, an overall VAP rate of 20.5 per 1000 ventilation days was calculated. Currently in North America the incidence rate ranges between 1 and 2.5 cases/1,000 ventilation days.[2] In our country, with the data provided by the Mexican Social Security Institute, the VAP rate is placed at 14.8 per 1000 days of ventilation.[3]

Generally, biomarkers such as CRP and PCT represent proteins whose presence should be correlated not only with the severity of the disease but also as a useful diagnostic tool.[4] However, the diagnostic prediction of VAP remains uncertain and more clinical trials are needed to determine the usefulness of any biomarker in clinical practice.[5,6] A multicenter study investigated the kinetics of serum biomarkers including CRP and PCT in patients undergoing VMI from day 1 to day 27 of VMI or the day of clinical diagnosis of VAP. It was found that CRP was a good predictor of VAP with an area under the curve of 0.71 suggesting a cut-off point greater than 9.6 mg/dL. While the CRP slope (average CRP increase of 1 mg/dL/day) is 62% more likely to have VAP compared to a patient without CRP increase during the first 6 days of IMV. However, it has several limitations such as the lack of randomization and that it is an observational study design that entails several unmeasured confounding factors that may have caused bias in the results. Therefore, its interpretation must be taken with care.[5,7,8]

Different scales have been developed to help diagnose VAP, such as the Clinical Pulmonary Infection Score (CPIS), which includes the following variables: temperature, leukocyte count, tracheal secretion, culture of tracheal aspirate, oxygenation (Pao_2/Fio_2) and lung radiography. Concluding that a score greater than 6 predicts the presence of VAP with a sensitivity of 73.8% and a specificity of 66.4% and an OR of 5.56, however, it did not show superiority to BAL with the disadvantage of not characterizing the pathogen.[9,10] Another study that was found was focused on facilitating the clinical diagnosis of VAP in the ICU; a new scoring system based on the level of PCT and pulmonary USG was proposed in a retrospective study to improve the diagnostic probability of VAP: the Chest Echography and Procalcitonin Pulmonary Infection Score (CEPPIS), unlike CPIS, this scale replaced the leukocyte count variables with PTC >0.5 ng/ml and the chest x-ray with positive USG when visualizing infiltrations. In their study they concluded that the combination of USG and PCT was a good predictor of VAP with an OR of 6.738 compared to using them individually. Although this combination has an AUC of 0.619, the interpretation must be taken with caution to perform any intervention.[11]

The combination of lung ultrasound with ETA gram stain has been evaluated for the diagnostic approach of VAP, reporting that subpleural consolidation and dynamic air bronchogram had a positive predictive value of 86% with an LR+ of 2.8. And when two dynamic air bronchograms were found they produced a positive predictive value of 94% with an LR+ of 7.1. The AUC for lung ultrasound with more than 3 points (2 areas with subpleural consolidations, 1 area with dynamic air bronchogram and/or purulent ETA) combined with gram stain was 0.83 with a specificity of 77% and a sensitivity of 78% Therefore, it was considered a good study as opposed to only performing lung ultrasound with an AUC of 0.74.[12]

The gold standard diagnosis for VAP is BAL with 10^4 colony-forming units per milliliter (CFU ml−1) with a sensitivity of 71.1% and a specificity of 79.6%.[13-15]

Goals

Obtain a VAP prediction model based on pulmonary USG and biomarkers such as procalcitonin and CRP compared with BAL.

Material and methods

The study design was a prospective cohort between July 1 to December 31, 2023. The study was carried out in the adult intensive care unit service of the Fray Antonio Alcalde Civil Hospital. The calculation of the sample size was not carried out because the total number of adult patients who were admitted to the ICU in VMI with medical and surgical pathologies was taken during the period, the study design was based on establishing the period of fieldwork. Patients were selected by meeting the definition of VAE and VAP confirmed by BAL.

All patients over 16 years of age are admitted to the Intensive Care Unit (ICU) with invasive mechanical ventilation (IMV). Upon admission, vital signs and laboratory results were recorded, including leukocyte count and baseline biomarkers such as PCT and CRP. Ventilatory parameters in the ICU, such as PEEP and FIO_2, will also be noted. Subsequently, an arterial blood gas analysis was performed to evaluate pH, Pco_2, Po_2 and the Pao_2/Fio_2 ratio. Finally, a lung ultrasound was performed, longitudinally scanning six areas for each hemithorax (anterior, lateral and posterior regions, using the anterior and posterior axillary lines as reference points). Each region will be divided into upper and lower halves, using the three intercostal spaces as reference points, and the findings will be classified according to the International Consensus of the "Point of Care Lung-Ultrasound" (Standard a = 0 points, Standard b7 = 1 point, Pattern b3 or tear or static air bronchogram = 2 points, dynamic air bronchogram or hepatization = 3 points).

When ventilator-associated pneumonia (VAP) was suspected, ventilatory parameters, vital signs, arterial blood gases, PCT, CRP, and leukocyte count were taken at that time. In addition, a lung ultrasound was performed. Subsequently, bronchoscopy with bronchoalveolar lavage (BAL) was performed with sample collection for culture and colony-forming unit (CFU) counting. Pregnant patients, with a history of broad-spectrum antibiotics greater than 24 hours, acute myocardial infarction less than 2 weeks, or lung abscess upon admission to the ICU were not included in the study.

Analysis of the results

A database was created using the Microsoft Office Excel program and the collected data will subsequently be organized and analyzed in SPSS V21.0. Which will be used to perform a descriptive analysis using measures of mean, standard deviation and median. For quantitative variables, measures of central tendency such as the mean and dispersion such as the standard deviation will be used. Categorical variables will be analyzed using Pearson's Chi-square test and when this is not possible, Fisher's exact test will be applied. For quantitative variables, Student's T will be used and for non-parametric variables, Mann-Whitney U, depending on whether the distribution is not It is parametric, to determine the significance that each independent variable has on the dependent variable, considering values of $p \leq 0.05$ statistically significant.

The VAP rate per 1000 ventilator days will be calculated by dividing the number of cases by the total ventilator days per 1000.

To analyze the results, the Chi-Square test was used for the contingency tables of the change in 3-point lung ultrasound score (LUS), change of 2 cmH_20 of positive end-expiratory pressure (PEEP), Change with partial pressure of oxygen and inspiratory fraction of oxygen (PaO_2 / Fio_2) with a decrease of 20 mmHg, serum levels of procalcitonin greater than 0.5 ng/ml, serum levels of CRP greater than 10 mg/dl and serum levels of leukocytosis greater than 12 thousands/microliter

Results

During the year 2023, a prevalence of Ventilation Associated Pneumonia (VAP) of 60% was obtained. The total days of Invasive Mechanical Ventilation (IMV) were 877 days. VMI's 1000-day NAV rate is 20.5. 29 patients were recruited for the study. Most patients had surgical pathology 65% of which the majority was polytrauma 34.5% (Table 1).

Table 1 Population characteristics

Characteristics	N* = 29
Age (years)	40.96 ± 17.32**
Male Sex (%)	69
Weight (Kg)	71.20 ± 11.82**
BMI (kg/m2)	25.71 ± 4.02**
Admission diagnoses (%)	
Severe TBI	34.5
Abdominal piercing	10.3
Atypical pneumonia	10.3
Bronchiectasis	3.4
Epileptic status	3.4
Self-injury attempt	3.4
Longitudinal extension transverse myelitis	3.4
Polytrauma	3.4
Burn 10% SCT	3.4
Burn 22% SCT	3.4
Burn 25% SCT	3.4
ARDS	3.4
ARDS + HIV	3.4
Moderate TBI	3.4
C4 spinal cord trauma	3.4
Mediastinal tumor	3.4
APACHE II (points)	12.93 ± 5.52**
SOFA (points)	8.34 ± 3.21**

* Number of patients (N)

** Values of plus-minus and mean ± SD (Standard deviation). Kg is Kilograms, BMI is body mass index, m2 is square meter, TBI is traumatic brain injury, SCT is total body surface area, ARDS is acute respiratory distress syndrome, HIV is human immunodeficiency virus, C4 means 4th cervical vertebra, APACHE refers to Acute Physiology and Chronic Health Evaluation and SOFA stands for Sepsis Related Organ Failure Assessment.

The variable studied with the greatest sensitivity for predicting VAP was serum levels of C-reactive protein (CRP) greater than 10 mg/dl with a value of 83.33%, with a positive predictive value of 73.65%, with an area under the curve of 0.71 (Table 2). On the other hand, the variable with the highest specificity (81.81%) is the change associated with the increase in PEEP greater than 2 cmH20, but with poor performance for its use as a value for screening (sensitivity 50%).

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Table 2 Results of the variables of the predictive model to predict Ventilation Associated Pneumonia

Variables	Value (p)	Area down the curve (IC 95)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Delta LUS points *	0.178	0.65 (0.45-0-85)	66.66	45.45	60.39	40.49
Delta PEEP cmH20 **	0.41	0.59 (0.37-0.804)	50	81.81	38.61	62.14
Delta Pao2/Fio2 mmHg ***	0.68	0.45 (0.22-0.68)	55.55	63.63	47.42	53.42
PCT >0.5 ng/ml ****	0.41	0.59 (0.37-0.80)	72.2	27.27	73.65	27.35
CRP >10 mg/dl *****	0.05	0.71 (0.52-0.90)	83.33	72.72	54.15	46.48
Leukocytes >12 thousand/microl	0.36	0.6 (0.38-0.81)	66.66	41.17	62.79	38.14

* Lung ultrasound (LUS)

**Positive end-expiratory pressure (PEEP)

*** Arterial oxygen pressure / Inspiratory oxygen fraction (Pao_2/Fio_2)

****Procalcitonin (PCT)

*****C-reactive protein (CRP)

Previously, the important variables were evaluated individually. However, when combining two or more variables for the VAP predictive model, a decrease in sensitivity (from 50% to 16.66%) and positive predictive value (from 41.48% to 15.86%) is evident, accompanied by an increase in specificity (from 72.72% to 90.90%) and negative predictive value (from 59.34% to 85.08%), as shown in Table 3.

Table 3 Results when combining two or more variables such as Pao_2/Fio_2*, Leukocytosis, CRP** and PCT***

Variables	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
2 Variables	50	72.72	41.48	59.34
3 Variables	22.22	81.81	21.85	79.12
4 Variables	16.66	90.9	15.86	85.08

* Blood oxygen pressure (Pao_2/Fio_2)

** C-reactive protein (CRP)

*** Procalcitonin (PCT)

When combining two variables (Pao_2/Fio_2, leukocytosis) it had a sensitivity of 50% and specificity of 72.72%, but when adding more variables (biomarkers) to the predictive model, a decrease in sensitivity was evident (16.66%).

Discussion

Despite the rapid progress that has been made in the development of new diagnostic tools and methods for VAP, it remains one of the most important hospital-acquired infections, resulting in increased mortality, especially in critically ill patients.

Patients who are admitted to the Adult Intensive Care Unit and, either at the time of admission to the hospital or during their stay, have suspected ventilator-associated pneumonia. In this context, various factors linked to the underlying pathology can influence and modify the values of serum biomarkers and images obtained by lung ultrasonography. This research study was characterized by a lack of significant correlation between intermittent variables, evidenced by a sample size of 29 patients. Therefore, the creation of a predictive model for VAP is impractical under these conditions. A complex and standardized approach to the diagnosis of VAP, including not only clinical scores but also microbiological tools and serum biomarker kinetics, is recommended to adequately identify and evaluate patients with VAP.

The most important objectives in the management of VAP are its rapid identification for early administration and appropriate duration of empiric antibiotic therapy, followed by a reduction in intensity once microbiological culture results are available, to reduce both excessive use of antibiotics and emerging antibiotic resistance.

In contrast to our study, a sufficient correlation was not observed between the variables, so it was not possible to develop a logistic regression model derived from the low correlation between the variables studied, a phenomenon that can probably be explained by the low recruitment. Therefore, it was decided to carry out an analysis of the variables to determine their sensitivity and specificity, making it evident that the variables studied are associated with ventilation-associated pneumonia in some way, but there are multiple intervening variables that also modify them (trauma, surgery, burn), so the population would have to be segmented for more strict analysis, before being able to define the role of each of the variables in predicting pneumonia, in addition to possibly assigning different cut-off points according to each of the populations under study.

Conclusion

A sufficient correlation was not observed between the variables, a phenomenon that can be explained by low recruitment. Therefore, it was decided to carry out an analysis of the variables to know their sensitivity and specificity, finding multiple intervening variables that also modify them (trauma, surgery, burn), so the sample will have to be increased to be able to segment the population to carry out a more strict analysis, in addition to possibly assigning different cut-off points according to each of the populations under study.

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