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THE SIGNIFICANCE OF MODIFIED PIRO SCORING WITH NLR BIOMARKER ON ENHANCING MORTALITY PREDICTION OF PATIENTS WITH VENTILATORS-ASSOCIATED PNEUMONIA IN INTENSIVE CARE UNIT

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ABSTRACT

Ventilator-associated pneumonia (VAP) is a pulmonary infection that occurs as a mechanical ventilator-related disease which accounts for almost 80% of hospital-acquired pneumonia with of high mortality rate, lengthens the hospital-stay rate and increases health costs. To provide a description of the likelihood of the patient's life expectancy, mortality, and prognosis of patients in ICU, a scoring system should be utilized in order to assess the severity of the disease and estimate mortality during hospital treatment. The PIRO scoring system is a comprehensive concept that provides good validity and derivation in predicting mortality risk in a wide range severity of the disease so that it is very useful in the selection or categorization of patients, especially those admitted to the ICU with VAP. A conjunction or integration with a simple biomarker such as Neutrophil-to-lymphocyte ratio (NLR) provides a better performance of the tool in regards to the predictive value in VAP mortality risk estimation. Since the NLR has a strong predictive value, is simple, low-cost, and easily available compared to other biomarkers, therefore it is practical and useful for prognostic indications for VAP with conjunction with the PIRO score where medical facilities are lacking.

Keywords: Ventilator-associated pneumonia (VAP), intensive care unit, PIRO scoring system, Neutrophil-to-lymphocyte ratio (NLR), mortality.
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INTRODUCTION

Ventilator-associated pneumonia (VAP) is a pulmonary infection that occurs after 48-72 hours after endotracheal intubation and/or mechanical ventilator.[1] Conceptually, it is defined as an inflammation of the lung parenchyma caused by an infectious agent that incubates as the mechanical ventilation begins. According to the CDC (The Center of Disease Control and Prevention) National Healthcare Safety Network (NHSN) data, Ventilator-associated pneumonia is the most healthcare-associated infection occurred in the intensive care unit, and nearly 90% of the episodes occur when using mechanical ventilation for up to 5.8 per 1,000 ventilators per day.[2] The incidence rate is varied in different studies depending on definition, type of hospital or ICU, population of the study and level of exposure to antibiotics.[3] It varies between 9% - 27% in Europe and America with mortality about 20% -50% and may reach 70% in MDRO (Multi-drug resistant organisms) infection. The VAP accounts for almost 80% of hospital-acquired pneumonia and occurs in 8% to 28% of intubated patients.[4] A Systematic Review shows that VAP occurs in 10% -20% of patients with mechanical ventilation for more than 48 hours and it has been estimated to increase mortality by 30% and even double in critical patients.

The initial assessment of the disease severity is important for managing patients with VAP and those who are associated with disease prognosis. To improve the outcomes in the management of VAP, there has recently been a significant attention paid to focus on the use and implication of a simple, validated, evidence-based scoring systems and biological markers to justify hospital admission in either acute medical settings or ICU, and to classify the disease severity which will help in predicting the life expectancy, mortality rate, and prognosis.[5] The scoring systems for the critical patient in ICU have been introduced and developed since 30 years ago, but currently, no such similar disease-based scoring system is in use for VAP. Therefore, in clinical trials of VAP, the enrolled patient cohort is very heterogeneous with varied mortality risks, thus incorporation of severity scoring, risk adjustment, clinical scores or biomarkers in clinical trials of VAP may be a significant advancement.[1,5]

CLINICAL SCORES IN PREDICTING MORTALITY FOR PATIENT WITH VENTILATOR ACQUIRED PNEUMONIA IN INTENSIVE CARE UNIT

There are a few numbers of surrogate measurements for severity of disease and assessment scores frequently used to predict mortality in VAP clinical trials, such as the Predisposition, Insult, Response, and Organ dysfunction (PIRO), the Acute Physiology and Chronic Health Evaluation score (APACHE II, APACHE III, and APACHE IV) as measurements for overall severity of illness, and Sequential Organ Failure Assessment (SOFA) score as a measurement for organ dysfunction and failure.[1,5] We have conducted a comprehensive search regarding identification of disease severity, short and long-term mortality among VAP patients cohort in MEDLINE, PubMed, and Google Scholar.

The scoring system that commonly used at hospital admission is APACHE (Acute Physiological and Chronic Health Evaluation). This score was divided into a physiology score to assess the degree of the acute illness and preadmission condition to assess the chronic health status of the patient.[6] The original model was then revised and simplified into APACHE II, III and IV. The standard scoring system commonly used for patients with pneumonia in ICUs is APACHE II.[7,8,9] APACHE II is a computer-based ICU scoring system with maximum points of 71 based on 12 physiological variables i.e. patient's age, oxygen partial pressure (PaO_2), body temperature, mean arterial pressure, arterial pH, heart rate, respiratory rate, serum sodium, serum potassium, creatinine, hematocrit, white blood cell count (WCC), and Glasgow Coma Scale (GCS).[9] It is applied within 24–hours of ICU admission to describe patient's morbidity, assess the disease severity and mortality risk. Despite the common use, the APACHE II is recognized as having a number of important drawbacks, some of which relate to the simplicity and performance of the scale. The APACHE II is a complex and well-calibrated scoring system; however, it requires data that are not available in the ED for all health facilities and does not include all patient risk factors or predisposition and is applied only for critical patients with limited varying severity.[6,10]

The SOFA score was based on 4 laboratory parameters and 2 clinical parameters for their assessment, including PaO_2/FiO_2, mean arterial pressure, bilirubin, platelets, creatinine, and GCS. It is used to determine the extent of a person's organ function and rate of failure[11,12] during ICU stay. It has been shown that the SOFA scores help in predicting survival in patients with VAP-associated sepsis. A data from multicenter prospective trials on VAP (PNEUMA Trial) was confirmed that organ dysfunction measured by SOFA was an independent predictor of VAP recurrence and mortality.[1] In addition, acute refractory multiple organ dysfunction syndromes were the most frequent cause of death in the ICU (47%) in a study involving 3700 patients admitted to an adult ICU.[1]

However, the SOFA score uses only physiologic and laboratory variables but does not consider host factors such as age, ethnicity, and comorbid disease burden, which are important drivers of mortality in VAP with sepsis. It is also considered to be less practical and some assessment parameters are still not available at some health facilities i.e. PaO_2/FiO_2 and bilirubin level, so the modified Modified Sequential Organ Failure Assessment (MSOFA) is developed.[13,14] The MSOFA developed was initially applied to critical care triage in the United States. Currently, SOFA scoring is widely used due to its simplicity and good validity, but it still does not include the patient risk factors or predisposition, and can not stratify the severity of the critical patients.

In recognition of host and virulence of pathogen factors, the Predisposition Insult Response and Organ failure (PIRO) model has been proposed to reflect each of those domains. The PIRO model is a system that first proposed by the International Sepsis Definitions Conference in 2001 which quantitatively categorizes the relationship between the patient's premorbid state, type of infection, the degree of patient response and organ dysfunction. This single scoring system combines both severity and/or acuity of illness and organ dysfunction and provides disease stratification by both baseline risk of unfavorable outcome and response to therapy. This model is more useful in VAP clinical trials to predict 28-day mortality rate in VAP patients in ICU and associated with increased healthcare resource utilization in these patients.[15] PIRO has been validated not only for critical patients but also for patients with varying severity, thus provides good validity and derivation in predicting mortality risk in a wide range of patients so that it is very useful in the selection or categorization of patients, especially those admitted to the ICU.

This concept is based on predisposition (P) parameters, insult/infection (I), host response (R) and dysfunction organ (O). This idea was

designed to discriminate morbidity from infection and morbidity of the host response to infection. PIRO concept can serve as an accurate predictor of mortality in internal and external validation cohorts.

Recently, an early version of the PIRO staging model for risk stratification in severe sepsis developed with classification was used to obtain a scoring system and was validated by using 2 (two) global databases of patients with severe sepsis (840 and 10,610 patients).[16] The PIRO VAP score was then developed as a concept for stratifying the risk of death of patients with VAP in the ICU. A prospective observational cohort study was conducted by Lisboa T. et al (2008) which included 441 patients with VAP in 3 multidisciplinary ICUs.[17] The independent variables associated with ICU mortality were analyzed by multivariate logistic regression. The results revealed the presence of a significant 4-variable score for ICU mortality risk stratification in patients with VAP ($p < 0.001$), including (1) comorbidity (chronic obstructive pulmonary disease, immunocompromised state, cardiac failure, cirrhosis, or chronic renal failure, (2) bacteremia , (3) 90 mmHg systolic blood pressure, and (4) acute respiratory distress syndrome.[3,17] On the basis of the observed ICU mortality according to VAP PIRO score, the patients were stratified into three levels of risk: (1) mild, 0 to 1 point; (2) high, 2 points; and (3) very high, 3 to 4 points. In Cox regression analysis among the group at high risk and very high risk, the VAP PIRO score was related with higher risk of death with hazard ratio 2.14 (95% CI, 1.19–3.86) and 4.63 (95% CI, 2.68–7.99) respectively. When compared with the APACHE II score, the VAP PIRO score performed better and was well-discriminated for ICU mortality (ROC AUC, 0.81 [95% CI, 0.77–0.85] vs ROC AUC, 0.53 [95% CI, 0.47–0.58]; $p<0.001$). The authors concluded that the VAP PIRO score is the first approach to stratify patients corresponding to the severity of the VAP episode. It would be useful either to measure or to balance severity in randomized clinical trials since it is a simple and practical clinical tool for predicting ICU mortality.[3,17]

Another study by Howell *et al.*[18] proved that the PIRO classification approach provides better phenotypic characterization of patients with several dimensions of severity, therefore this approach can stratify patients better, predict mortality accurately in both its derivation and internal and external validation cohorts, and also determine the prognostic of critical patients in the ICU. The study was conducted at two large US tertiary care centers with three independent, observational, and prospective cohorts. A derivation cohort (n = 2,132) was used to create the PIRO score, identify independent predictors of mortality, and the prognostic performance was then investigated in independent internal (n = 4,618) and external (n = 1,004) validation cohorts. A number of covariates were analyzed with multivariate regression, and significantly revealed an association with mortality for each PIRO category: Predisposition (P) consists of sub-variables of premorbid and comorbid factors such as age, history of disease or presence of an aggravating disease (COPD, liver disease, malignancies) and nursing home resident, Infection (I) consists of the presence of pneumonia and or other sources of infection, Response (R) consists of sub-clinical and laboratory variables of host response to infection i.e. respiration rate, bands and heart rate, and Organ Dysfunction (O) consists of sub-variables of response to organ dysfunction in cardiovascular (systolic blood pressure), respiratory (presence of respiratory failure or hypoxemia), renal (BUN value), hematologic (the platelet count) and metabolic (the lactate level). The PIRO score was stratified into 5 (five) intervals; <5, 5-9, 10-14, 15-19 and ≥ 20 and the mortality rate 0 – 0.3%, 1.9 – 3.7%, 6.5 – 10.4%, 20.1 – 32% and 38.9 – 57% respectively. The model validation of PIRO score in this study showed an accurately predicted mortality in both validation sets with respective areas under the receiver operating characteristics curve of 0.86 and 0.83, with a clear stepwise, increased in mortality with an increasing PIRO score, but the overall mortality was low.[10,18]

A prospective observational ED study of 240 patients presenting evidence of shock, hypoxemia, or other organ failure was conducted by Macdonald et al (2014). In this study, the PIRO score was compared with the Sequential Organ Failure Assessment (SOFA) to predict mortality in ED patients with features suggesting severe sepsis or septic shock in the ED. The study revealed area under curve ROC (AUCR) for mortality was 0.86 (95% confidence interval [CI] = 0.80 – 0.92) for PIRO, and 0.78 (95% CI = 0.71 – 0.87) for SOFA scores. Furthermore, the mortality increased with an increasing PIRO scores: PIRO < 5, 0%; PIRO 5 to 9, 5%; PIRO 10 to 14, 5%; PIRO 15 to 19, 37%; and PIRO ≥ 20, 80% ($p < 0.001$).[10] This data suggested that PIRO scores performed better than SOFA scores, and PIRO model may have better sensitivity for 30-day mortality prediction.

The advance of disease-specific (pneumonia) severity scoring and risk modification tools in clinical trials of VAP would signify an advancement in this clinical trial. A number of independent predictors of outcome of pneumonia must be considered in this pneumonia risk stratification, including

severity of disease and illness, the presence of organ dysfunction, underlying diseases and comorbidities, and specific causative pathogens. Therefore, the PIRO score for VAP is a suitable concept for the consideration.

BIOMARKERS – THEIR ROLE IN PREDICTION OF DISEASE SEVERITY AND MORTALITY IN PATIENT WITH VENTILATOR ACQUIRED PNEUMONIA IN INTENSIVE CARE UNIT

Biologic markers are defined as molecular markers, cellular, or biochemical which are measured objectively in human tissues or fluids and play a vigorous role in supporting physiological processes, indicating pathogenic processes or pharmacological responses to a therapeutic intervention, establishing the diagnosis and assessing severity and prognosis.

Important biomarkers that commonly used for monitoring in ICU-related infections are leukocyte count, CRP, and Procalcitonin.[19-21] C-Reactive Protein (CRP) is an acute-phase protein produced by the liver, whereas Procalcitonin (PCT) is the pre-hormone of calcitonin secreted by Parafollicular C-cells of the thyroid gland and markedly elevated in systemic infection and sepsis.

The role of PCT and CRP biomarkers in predicting the survival and mortality in patients with VAP has been assessed in several studies.[19-21] An observational cohort study was conducted in 71 patients with VAP by Seligman et al (2011). The accuracy of CRP, PCT, and SOFA was compared in predicting the VAP mortality. The result demonstrated an association of high PCT value with mortality as well as SOFA score. Another study by Afifi et al (2015) in 50 patients with VAP has also found that the PCT kinetics can be used to assess prognosis in VAP because it can discriminate between survivor and non-survivor significantly during the course of the VAP with $p < 0.001$. The CRP is useful as a diagnostic but not as a prognosis biomarker in VAP.

However, the studies also failed to stratify the severity of disease, did not count the presence of underlying diseases and comorbidities, were very limited in specificity and sensitivity, remain expensive in some countries and are not systematically used at hospitals, placing them in practical and are out of reach from poor patients. Those two biomarkers also do not always perform satisfactorily highlighting the need to identify better biomarkers for a significant improvement of the predictive value.[21,22]

The Neutrophil-to-lymphocyte ratio (NLR) is a simple biomarker and often used in predicting mortality in ICU patients. It is an easily available biomarker that can be calculated based on a complete blood count. This ratio proves its usefulness in mortality stratification in the incidence of heart disease, myocardial infarction as a prognostic factor in some cancers, or as a predictor and marker of inflammation or pathological infection, postoperative and in the evaluation of systemic inflammatory responses.[22-24]

Several studies have assessed the potential of NLR to help to predict the prognosis of patients with CAP and/or VAP.[22,25] A study cohort consisted of 395 patients diagnosed with community-acquired pneumonia (CAP) was conducted by Jager et al (2010). The study showed an area under the curve (AUC) of 0.701 in predicting mortality in CAP, and it was better than the AUC for the neutrophil count, WBC count, lymphocyte count and CRP level (0.681, 0.672, 0.630 and 0.565, respectively).[26] A retrospective study by Yang et al (2012) in a consecutive series of 318 adult patients which examined the prediction of NLR towards in-hospital mortality of adults with CAP showed an index predicted in-hospital mortality with a sensitivity of 82.61% and specificity of 72.20% (area under ROC curve, 0.799).[22]

A prospective trial was conducted by Liu et al (2016) on consecutive 333 adult patients with sepsis due to some conditions including CAP, HAP and VAP admitted to the ICU. In this prospective observational study, they evaluated the potential association of NLR on ICU admission with the clinical prognosis and disease severity. They found that NLR had a modest power for predicting 28-day mortality as suggested by the area under the curve (AUC) of 0.695 ± 0.036. Multivariate linear regression also pointed out that increased NLR levels were associated with unfavorable outcome independently of the effect of possible confounders.[27]

It is clear that the NLR is a simple and promising marker for assessing the severity of CAP and/or VAP and identifying adult patients at elevated risk of in-hospital mortality. However, in general biomarkers alone are clearly less suited in the prediction of prognosis and severity of disease, and the use of a biomarker alone for severity assessment remains premature.[17]

INTEGRATION OF CLINICAL SCORES PIRO AND BIOMARKERS NLR IN PREDICTING MORTALITY OF VENTILATOR-ASSOCIATED PNEUMONIA

The significance of clinical scoring and biological markers in predicting mortality of VAP when used alone has been examined in this review. But when they were used in conjunction or integrated, its

predictive accuracy would enhance and provide good validity in predicting the mortality risk in a wide range of patient especially VAP patients in ICUs.

The PIRO scoring system was comprehensive and performed better than the other available scoring system for predicting VAP mortality. However, the assessment variables are not entirely available for all health facilities. The modification or integration of PIRO with a simple and useful biomarker is a key to this problem. One possibility is the neutrophil-lymphocyte count ratio (NLR), an easily determined index already widely used to evaluate systemic inflammatory responses.[22]

There are some studies conducted on this integration, especially in patients with CAP, but very limited data are available concerning the integration of PIRO score with biomarker NLR in VAP. Current data available is only a prospective, multi-center, observational study designed by Granja et al (2013) to evaluate the epidemiology of community and healthcare-associated sepsis in patients who were admitted in ICUs.[28] In this study, they identified specific variables related with each of the four components of PIRO, including biomarkers CRP integration and a dynamic view of the patient daily clinical course. This study was the first to introduce and integrate the CRP biomarkers to the PIRO staging system and showed a very good discriminatory ability (AUC 0.85, CI95%: 0.82–0.88) with $p < 0.001$.[28]

This study showed that the integration of the clinical score PIRO with biomarker CRP has increased the ability of the tools and enhanced its predictive accuracy concerning mortality in predicting the mortality risk of the patients with sepsis in ICU. Further validation of these biomarkers and more advanced biomarker discoveries or other integration with clinical scores are required in prospective trials to explain their application in clinical practice.

CONCLUSION

The conclusion of this review based on the available data suggests that the PIRO scoring system performed better, was well-discriminated and had better sensitivity for 30-day mortality prediction in VAP patients than other available clinical scores. In the setting of limited financial and laboratory resources, the modification of PIRO score in conjunction with a simple and useful NLR biomarker seems to be a reasonable approach for the evaluation of these patients. Based on the inflammatory response of each patient that has been assessed with PIRO score, the biomarker may improve the mortality prediction of the prognosis.

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