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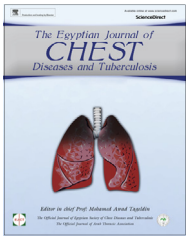

ORIGINAL ARTICLE

Diagnostic accuracy of inflammatory biomarkers in bronchoalveolar lavage from patients with ventilator-associated pneumonia

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KEYWORDS

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Soluble urokinase plasminogen activator receptor;
Macrophage migration inhibitory factor

Abstract *Background:* Ventilator associated pneumonia (VAP) is a common complication in intensive care patients. The clinical diagnosis is difficult and a definite microbiological diagnosis based on quantitative culture of bronchoalveolar lavage (BAL) fluid is mandatory. Many biological markers have been studied in an effort to improve the rapidity and performance of current diagnostic procedures in VAP. So, this study was done with the objective to determine the discriminative power of single or combining multiple biomarkers in bronchoalveolar lavage including soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), soluble urokinase plasminogen activator receptor (suPAR), and macrophage migration inhibitory factor (MIF) for the diagnosis of bacterial VAP among patients who were receiving mechanical ventilation.

Patients and methods: This study was conducted in the intensive care units of Chest, Internal Medicine and Anesthesia Departments, Zagazig University Hospitals, Egypt, between January and December 2012, 66 adult patients were included who were receiving mechanical ventilation

Abbreviations: VAP, ventilator-associated pneumonia; CI, confidence interval; CPIS, clinical pulmonary infection score; ROC, receiver operating characteristic; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; suPAR, soluble urokinase plasminogen activator receptor; MIF, macrophage migration inhibitory factor.

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and eligible for BAL for suspected VAP. The microbiology was assessed with quantitative cultures of BAL obtained within the first 6 h after the development of a new pulmonary infiltrate on chest radiography. All patients were divided into: Group 1, "definite VAP" with positive quantitative culture results, Group 2, "indeterminate VAP" with negative BAL culture and received new antibiotics at least 24 h prior to BAL, and Group 3, "definite absence of VAP," with negative BAL culture and not receiving antibiotics at the time of BAL.

Measurements: Procalcitonin was measured using an ultrasensitive chemiluminometric assay. CRP was measured using an enzyme immunoassay. Measurements of sTREM-1, suPAR, and MIF were performed using a Luminex multiplex assay. Two composite markers were constructed; one including a linear combination of the three best performing markers and another including all six markers and the area under the receiver operating characteristic curve (AUC) was used to compare their performance and those of the individual markers.

Results: Of the total 66 enrolled patients receiving mechanical ventilation and undergoing BAL for suspected pneumonia, 20 patients (30.3%) met definite microbiologic criteria for group 1, 28 patients (42.4%) with indeterminate VAP in group 2, and 18 patients (27.2%) with definite absent VAP in group 3. The mean concentrations of all studied biomarkers were not statistically significant when their levels in BAL samples from patients with definite VAP were compared with either from definite absence of VAP or from indeterminate VAP (all $p > 0.05$). The AUCs for discrimination between infection of bacterial origin and no infection were 0.83 (95% CI 0.79–0.88) for CRP, 0.77 (95% CI 0.69–0.79) for PCT, 0.72 (95% CI 0.67–0.77) for neutrophils, 0.60 (95% CI 0.83–0.69) for MIF, 0.68 (95% CI 0.56–0.67) for sTREM-1 and 0.51 (95% CI 0.48–0.59) for suPAR, 0.86 (0.79–0.89|) for the composite three-marker test (CRP, PCT, and neutrophils), and 0.90 (0.83–0.96) for the composite six-marker test. The six-marker test performed significantly better than all of the single markers ($P < 0.05$ for the three-marker test and CRP and $P < 0.001$ for the five remaining markers).

Conclusions: Single measurements of sTREM-1, suPAR or MIF concentrations in the BAL fluid of mechanically-ventilated patients with new or progressive infiltrates do not enhance identification of VAP. However, combining results from several inflammatory markers may significantly improve the ability to differentiate bacterial from nonbacterial infections. Further studies are needed to fully determine the diagnostic accuracy of these and other biomarkers.

Introduction

Ventilator-associated pneumonia (VAP) is a serious complication of mechanical ventilation which increases the patient's stay in the ICU and overall length of hospital stay. VAP is defined as inflammation of the lung parenchyma attributed to bacterial infection and occurring 48 h after endotracheal intubation and mechanical ventilation and is considered the most common cause of new infiltrates among patients requiring mechanical ventilation [1]. However, VAP is difficult to diagnose in the critically ill patient because of the presence of underlying cardiopulmonary disorders, the non-specific radiological and clinical signs, and the rapid invasion of the normally sterile lower respiratory tract by microorganisms in all patients with an endotracheal tube, requiring that colonization be differentiated from true infection [2].

Delayed diagnosis and subsequent delay in initiating appropriate therapy may be associated with worse outcomes in patients with VAP; On the other hand, an incorrect diagnosis may lead to unnecessary long-term use of broad-spectrum antibiotics that is linked to the emergence and selection of resistant bacteria. VAP is clinically suspected when a patient has radiological new or progressive pulmonary infiltrates with fever, leukocytosis or leukopenia, and purulent tracheobronchial secretions [3]. However, there are a number of noninfectious causes of fever and pulmonary infiltrates making the above criteria of limited diagnostic value. Several other criteria have been proposed for improving the clinical criteria for VAP, including bronchoscopic lower airway sampling with quantitative cultures, which is the preferred method for diagnosis of VAP, but microbiological cultures often take 48–72 h to yield results, and cultures can be influenced by new antibiotic therapy [4].

Recent studies have outlined a number of biomarkers including soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), soluble urokinase-type plasminogen activator receptor (suPAR), macrophage migration inhibitory factor (MIF), procalcitonin (PCT), copeptin, C-reactive protein (CRP), interleukin-1-beta, granulocyte colony-stimulating factor, surfactant protein D, receptor of advanced glycation end-products, midregional pro-atrial natriuretic peptide, and endotoxin or elastin fibers, which have been tested recently for use in determining the diagnosis of patients with suspected or confirmed VAP [5].

sTREM-1 is a transmembrane glycoprotein expressed on neutrophils, macrophages and monocytes that amplifies the inflammatory response. Its expression by the effector cells is upregulated in tissues infected by different strains of bacteria [6]. Soluble urokinase plasminogen activator receptor (suPAR) has recently been recognized as a potential biologic marker of disease. Numerous observational studies prove that levels of suPAR in different body fluids are increased with various