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The diagnostic ability of procalcitonin and interleukin-6 to differentiate infectious from noninfectious systemic inflammatory response syndrome and to predict mortality☆

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ABSTRACT

Purpose: The purpose of the study was to quantify the ability of procalcitonin (PCT) and interleukin-6 (IL-6) to differentiate noninfectious systemic inflammatory response syndrome (SIRS) and sepsis and to predict hospital mortality.
Materials: We recruited consecutively adult patients with SIRS admitted to an intensive care unit. They were divided into sepsis and noninfectious SIRS based on clinical assessment with or without positive cultures. Concentrations of PCT and IL-6 were measured daily over the first 3 days.
Results: A total of 239 patients were recruited, 164 (68.6%) had sepsis, and 68 (28.5%) died in hospital. The PCT levels were higher in sepsis compared with noninfectious SIRS throughout the 3-day period ($P < .0001$). On admission, PCT concentration was diagnostic of sepsis (area under the curve of 0.63 [0.55-0.71]), and IL-6 was predictive of mortality, (area under the curve of 0.70 [0.62-0.78]). Peak IL-6 concentration improved the risk assessment of Sequential Organ Failure Assessment (SOFA) score for prediction of mortality among those who went on to die by an average of 5% and who did not die by 2%
Conclusions: Procalcitonin measured on intensive care unit admission was diagnostic of sepsis, and IL-6 was predictive of mortality. Addition of IL-6 concentration to SOFA score improved risk assessment for prediction of mortality. Future studies should include clinical indices, for example, SOFA score, for prognostic evaluation of biomarkers.

1. Introduction

Sepsis is a growing problem worldwide, with its most serious forms, severe sepsis and septic shock, responsible for the high mortality rate in the intensive care unit (ICU) [1,2]. Differentiating sepsis from noninfectious systemic inflammatory response syndrome (SIRS) is not straightforward and presents a common dilemma for the intensive care physician. Diagnostic uncertainty (to treat as sepsis or noninfectious SIRS) may delay the initiation of lifesaving standard therapies, whereas indiscriminate use of antimicrobial therapy can lead to antimicrobial resistance and superinfection with multiresistant organisms. [3] The signs and symptoms specific to sepsis may not be apparent, and microbiological cultures may be negative or take days to yield cultures with identifiable quantities [4]. The routine laboratory tests for sepsis such as leukocyte count lack diagnostic accuracy and sometimes mislead. This has led to the search for an ideal biomarker to diagnose sepsis. Many biomarkers have been studied in an attempt to identify a reliable marker able to quickly, specifically, and accurately diagnose sepsis [5]. Once sepsis has been diagnosed, prediction of survival is important for risk stratification which may determine the choice of appropriate treatment. However, accurate evaluation of critically ill patients with sepsis who are at risk of poor clinical outcomes is challenging for intensivists. The diagnostic application of biomarkers could help differentiate between sepsis and noninfectious SIRS, whereas prognostic applications could allow for early risk stratification for intensification of therapy [6].

The host response to infection includes activation of humoral elements (complement, acute-phase proteins and cytokines) and cellular elements (monocytes, macrophages, and anti-inflammatory mediators). Acute-phase proteins such as C-reactive protein (CRP) and procalcitonin (PCT) are the most widely used inflammatory biomarkers in clinical practice. Procalcitonin is a 116–amino acid peptide that has an approximate molecular weight of 14.5 kd and belongs to the calcitonin superfamily of peptides. During infection, there is increased expression of CALC-1 gene resulting in ubiquitous release of PCT from nonendocrine tissue. Serum PCT levels increase significantly in severe systemic infections and may also be elevated in some noninfectious

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SIRS conditions [7,8]. The degree of induction of PCT is associated with severity of sepsis and the presence of organ dysfunction; thus, it may also have some prognostic value [6,9,10]. However, PCT is not specific for use as a standalone diagnosis marker; and it should be interpreted in correlation with clinical evidence of sepsis. In a recent systemic review and meta-analysis of PCT for sepsis in critically ill patients, Tang et al [11] did not support the widespread use of the PCT test in critical care settings.

Interleukin-6, a proinflammatory cytokine, is an important mediator of the acute-phase reaction in response to inflammation and sepsis. Interleukin-6 is synthesized by different types of cells, mostly by monocytary cells of blood (acute stimulation) and endothelial cells (illness of longer duration). The normal IL-6 serum concentration is less than 5 pg/mL. Following inflammation, serum levels of IL-6 have been shown to rise within 1 hour; and the elevated IL-6 levels will then decrease correspondingly quickly. The plasma half-life of IL-6 is less than 6 hours. Persistently elevated IL-6 values greater than 500 pg/mL were found in patients with sepsis or multiple organ failure [12]. However, few studies have addressed the potential prognostic value of plasma concentration of IL-6 in septic patients [13,14].

This prospective study aimed to assess if PCT and IL-6 are clinically useful to differentiate between sepsis and noninfectious SIRS in critically ill patients. The prognostic performance of PCT and IL-6 was also evaluated in this population.

2. Methodology

2.1. Study design and participants

This prospective observational cohort study was conducted over 3 years (from July 2011 to June 2014) in a 12-bed ICU of a major tertiary hospital in Pahang, Malaysia. All specialties are available; however, postsurgical cardiac patients are admitted to cardiothoracic ICU and not included in this study. The study was approved by the local medical research and ethics committee and registered under the National Medical Research Register (NMRR-13-879-15223). Consecutive adult patients of older than 18 years who fulfilled the SIRS definition were recruited into the study after consent was obtained. Patients who received antimicrobial treatment for more than 24 hours before the first blood samples for biomarker analysis were taken were excluded. If a patient had more than 1 ICU admission, only the first episode was included in the study. A sample size of 153 patients with a sepsis prevalance of 55% [15] was needed to achieve the relevant anticipated area under the curve (AUC), that is, 0.7, at a significance level of 5%, power of 80%, and 20% dropout rate [16,17].

2.2. Diagnosis of SIRS and sepsis

Systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock were defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [18,19]. *Systemic inflammatory response syndrome* was defined as a patient having at least 2 of the following criteria: (1) fever greater than 38°C or hypothermia less than 36°C, (2) tachypnea (>20/min), (3) tachycardia (>90/min), or (4) leukopenia ($<4 \times 10^9$/L) or a leftward shift (>10% immature granulocytes). *Sepsis* was defined when 2 or more SIRS criteria are present along with a culture-proven or clinically identified infection. Two intensive care doctors completed a validated questionnaire (Supplement) for each patient on day 1 and day 3 to define clinical suspicion of sepsis [20]. Patients were grouped into sepsis if there was clinical suspicion of infection with or without positive culture; otherwise, they were grouped into noninfectious SIRS. They were treated based on recommendations from the current Surviving Sepsis Campaign, modified to meet the most updated evidence from the literature [21]. *Severe sepsis* was defined as sepsis with at least 1 organ failure. *Septic shock* was defined as those with cardiovascular Sequential Organ Failure Assessment (SOFA) score of 3 or 4.

2.3. Data collection and laboratory measurement

Baseline Simplified Acute Physiology II Score (SAPS II), baseline SOFA score, primary source of infection, culture results, and ICU and hospital mortalities were recorded. Clinical parameters such as body temperature, heart rate, white cell count, and clinical signs of infection were recorded on admission and daily for 3 days. Daily serum concentrations of PCT and IL-6 were measured during the first 3 days. The first blood samples were drawn within 24 hours of admission or not later than 24 hours after the first dose of antimicrobial agents administered (baseline PCT, IL-6). Subsequent samples were taken 24 and 48 hours later. The samples were centrifuged and stored at −80°C for later analysis. Procalcitonin was measured by BRAHMS Kryptor compact assay (Henningsdorf, Germany) using time-resolved amplified cryptate emission technology assay with the quantitative result in 19 minutes. Interleukin-6 was determined by using Quantikine enzyme-linked immunosorbent assay kit from R&D Systems (Minnesota, USA). The assay uses quantitative sandwich enzyme immunoassay technique and normal values corresponding to less than 9.7 pg/mL [22]. The treating ICU physicians were blinded to the PCT and IL-6 concentrations when caring for patients.

2.4. Statistical analysis

Statistical analysis was performed using PASW version 18.0 (IBM, Somers, NY) licensed to the International Islamic University Malaysia. Results are presented as mean ± SD for normally distributed variables or median (interquartile range [IQR]) for nonnormally distributed variables. Comparison of variables between the 2 groups was analyzed using the independent *t* test for normally distributed variables or the Mann-Whitney test for nonnormally distributed variables. Comparison between the 3 groups was analyzed using 1-way analysis of variance (ANOVA) after log-transformation of nonnormally distributed variables. Post hoc Fisher least significant difference (LSD) analysis was performed for all associations with $P < .05$ following the ANOVA. Categorical variables were compared with the χ^2 test. The diagnostic and predictive performance of PCT and IL-6 was assessed by the AUC of receiver operating characteristic curve of the sensitivity vs 1 − specificity. Survival was analyzed by Kaplan-Meier and Cox regression analysis. Covariates for Cox regression were to be included in the model if under univariate analysis $P < .1$. The AUC and hazard ratios (HRs) are presented with 95% confidence interval (CI). The additional value of the biomarker to a reference model was further assessed by the integrated discrimination improvement (IDI) and risk assessment plots [23,24]. The variables for the reference model for this analysis were chosen as covariates which under univariate analysis had a *P* value of less than .1.

3. Results

3.1. Demographic, clinical profile, and patient outcome

Two hundred thirty-nine consecutive patients diagnosed with SIRS were recruited, of whom 164 (69%) were diagnosed with sepsis. The demographic and outcome profiles are presented in Table 1. Patients with sepsis were more severely ill with significantly higher SAPS II and SOFA scores on admission as compared with those with noninfectious SIRS ($P < .0001$). Most patients in the sepsis group had respiratory as the primary diagnostic class, whereas most noninfectious SIRS were classified as trauma ($P < .0001$).

Among sepsis patients, there were 62 (37.8%) culture positive and 102 (62.2%) culture negative. Of this, 27 (16.5%) developed bacteremia. The most common site of infection was respiratory (34.3%).