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# The predictive role of Interleukin 6 and Procalcitonin associated with bacterial infection causing sepsis in patients with severe burn

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## ABSTRACT

**Background.** Sepsis is a major contributor to both death and illness on a worldwide scale. Bacteremia characterized by the presence of gram-negative, gram-positive, or mixed growth bacteria has been shown to be associated with a significantly increased risk of septic shock and a bad prognosis. Biomarkers are used to aid in the diagnosis of sepsis and to differentiate between bacterial causes, namely Gram-negative, Gram-positive, and mix growth bacteria.

**Objectives.** This study aimed to evaluate the role of PCT and IL-6 in predicting bacterial infection in burn patients with sepsis due to gram-negative, gram positive and mixed growth bacteria.

**Methods.** Forty-four patients with age (1.5–75 years), and nineteen healthy controls with the same age range, were involved in this study during their attendance to Specialized Burns Hospital in the Medical City, Al-Kindi Teaching Hospital in Baghdad, and Al-Nasiriyah General Hospital in Thi-Qar province. The study was conducted from 1st December 2023 to 1st April 2024 and approved by ethical committees of Institute of Genetic Engineering and Biotechnology for Postgraduate Studies/ Baghdad University. Blood samples and data were collected to evaluate the level of PCT and IL-6 associated with bacterial infection for burn patients by enzyme linked immunosorbent assay (ELISA).

**Results.** 25 (50%) showed growth for Gram-negative, 13 (26%) for Gram-positive and 12 (24%) for mix growth bacteria. Results appeared a significant increase at ($P \leq 0.01$) in each of PCT and IL-6 in burn patients to control group according to gender. Patients exhibiting a combination of bacterial growth have notably elevated levels of procalcitonin (PCT). Levels of PCT were significantly elevated in burn patients with mixed growth sepsis compared to patients with Gram-negative and Gram-positive sepsis. However, there were no significant differences in IL-6 levels between burn patients with mix growth sepsis and patients with gram-negative and gram-positive sepsis ($P > 0.05$). Measuring PCT levels may assist in selecting the appropriate empirical antibiotic treatment.

**Conclusions.** The PCT biomarker demonstrated superior performance in distinguishing between microbial sepsis caused by various kinds of pathogens. This finding has great promise for its use in clinical practice, particularly in burn units.

**Keywords:** IL-6, PCT, bacterial infection, sepsis

## INTRODUCTION

Sepsis is an intricate illness state marked by disruptions in the body's immunological, endocrine, and metabolic responses to infection, resulting in the failure of numerous organs, shock, and ultimately death. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3.0) defines sepsis as a severe condition when the body's reaction to infection becomes uncontrolled, leading to life-threatening organ failure [1]. Although modern medicine has made significant progress, the death rate among patients with sepsis remains substantial, estimated to be between 25 and 30% [2]. Hence, it is important to promptly identify and diagnose the condition, as immediate intervention and

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therapy might enhance the outlook. Several biomarkers, such as Interleukin-6 (IL-6) and procalcitonin (PCT), have been examined for the purpose of diagnosing sepsis. However, their ability to diagnose and predict outcomes is restricted [3]. Hence, it is essential to identify novel biomarkers or a combination of numerous indicators to expedite the diagnosis of sepsis and forecast clinical consequences. Sepsis arises from an intricate reaction to widespread inflammation triggered by many increased blood indicators, including immune cells and cytokines, such as White Blood Cell (WBC) and IL-6 [4].

Among the many clinical and biochemical biomarkers discussed in literature, PCT has emerged as one of the most used. This is because it has several advantages: 1) it has a relatively high level of accuracy in diagnosing both septic and nonseptic patients, even in the early stages of infection, which helps doctors decide whether to start or delay antimicrobial therapy, especially when used in a dynamic approach; 2) there is a correlation between PCT levels and the severity of sepsis; and 3) PCT levels decrease rapidly once the infection is under control [5].

Moreover, there are notable variations in PCT levels based on the causative pathogens, specifically between gram-negative, gram-positive, and mix growth bacteria. This aids in selecting the appropriate drugs for empirical use when blood culture results and sensitivity tests are unavailable.

Despite being a subject of controversy among certain authors, the measurement of blood levels of PCT has repeatedly been recommended for the purposes of diagnosing, prognosing, and managing the use of antimicrobials in burn patients. Considering the varying treatment methods for various infections, it is useful to assess the discriminative capability of PCT in order to choose the most suitable empirical therapy.

The objective of this study is to evaluate the performance of PCT in distinguishing between sepsis caused by gram-negative, gram-positive, and mix growth bacteria in a large number of burn patients.

## METHODS

This research was carried out in the immunological and Bacteriology laboratory of The Imam Hussein Teaching Hospital /Al-Nasiriyah. This research used a Case-Control design, using 100 samples of burn infection patients of varying age and sex. Additionally, a control group consisting of healthy persons was included in the investigation. from both male and female in several hospitals in Baghdad, during the time between 1st December 2023 to 1st April 2024. The age range of these individuals is between 1.5 and 75 years. Both sera and whole blood samples were obtained from each participant. The serum were specifically utilized to measure the amounts of IL-6 and PCT in all specimens.

### Control group

Two mL of blood samples were taken from (50) healthy individuals as control group who are free from any sign and symptoms for any illness.

### Measuring IL-6 and PCT by ELISA

The concentrations of IL-6 and PCT were measured using a human ELISA kit from Shanghai, China, following the manufacturer's procedure [6].

### Ethical approval

The research was done in compliance with the ethical guidelines derived from the Declaration of Helsinki. The procedure was conducted after obtaining verbal and analytical agreement from the patients prior to sample collection. The research protocol and the subject information and consent form underwent a thorough review and received approval from the Committee of the Institute for Genetic Engineering and Biotechnology for Postgraduate Studies/ University of Baghdad. Additionally, the study protocol was approved by the Ethical Committee of the Iraq Ministry of Health and Environment. To obtain this approval, written informed consent was obtained from each patient or a qualified family member.

### Statistical Analysis

The statistical analysis was conducted using SPSS software edition 26. Categorical variables were described using frequencies and percentages. Means, range, and stand range were used to represent continuous variables. A student Mann-Whitney U was used to compare the means of two groups. at P value below 0.05.

## RESULTS

**Estimation of Immunological Parameters in burn patients and healthy controls According to Gender Groups**

Table 1 show the mean of immunological parameters in burn patients and control according to gender groups which was found significant statistical difference ($P < 0.05$). The concentration of both IL6 and PCT in burn patients increased more than in healthy controls.

**Estimation of Immunological Parameters in burn patients According to Gender**

Table 2 show the estimation of immunological parameters concentration according to gender

**TABLE 1.** Differences in immunological parameters between burn patients and control according to gender groups

| Male groups | | Patients | Control | Mann-Whitney U p. value |
|---|---|---|---|---|
| | | Mean + Range | | |
| PCT | Male | 9.76 (0.20-62.2) | 0.04 (0.01-0.20) | < 0.001** |
| | Female | 11.68 (0.30-53.3) | 0.04 (0.01-0.29) | < 0.001** |
| IL-6 | Male | 29.11 (15.9-47.0) | 9.65 (8.72-13.0) | < 0.001** |
| | Female | 26.79 (14.6-45.6) | 10.5 (8.72-13.4) | < 0.001** |

Control: Male No.21, Female No 29// Patients: Male No 21, Female No. 29

**TABLE 2.** Differences in Immunological parameters between male and female groups in burn patients

| Burn patients | Male No. 21 | Female No. 29 | Mann-Whitney U p. value |
|---|---|---|---|
| | Mean + Range | | |
| PCT ng/ml | 9.76 (0.20-62.2) | 11.68 (0.30-53.3) | 0.371Non-sig |
| IL-6 ng/L | 29.11 (15.9-47.0) | 26.79 (14.6-45.6) | 0.335Non-sig |

**TABLE 3.** The relation between the type of bacterial causing sepsis and IL6, PCT and CRP

| Parameters | Type of bacteria | No. | Mean | Std. deviation | P. value |
|---|---|---|---|---|---|
| PCT titer (ng/ml) | Gram + | 13 | .92154 | .474075 | *<0.001 |
| | Gram - | 25 | 7.56000 | 13.964019 | |
| | Mix growth | 12 | 28.58083 | 16.540472 | |
| ELISA IL 6 (ng/L) | Gram + | 13 | 30.24969 | 8.949755 | *0.379 |
| | Gram - | 25 | 26.21456 | 7.412037 | |
| | Mixed | 12 | 28.31192 | 10.170495 | |

**TABLE 4.** IL 6 and PCT concentration of burn patients with and without sepsis

| Variable | With Sepsis No. 23 | Without Sepsis No. 27 | Mann-Whitney U p. value |
|---|---|---|---|
| | Mean + Range | | |
| Age | 21.7 (3.0 – 76) | 18.7 (1.5 – 68) | 0.612 |
| IL-6 | 27.8 (14.6 – 47.0) | 27.7 (15.3 – 45.6) | 0.928 |
| PCT | 22.7 (2.01 – 62.2) | 0.78 (0.2 – 1.35) | <0.001 |

group for patient detected that there is non-significant difference between male and female (P. >0.05).

**Relation between the type of bacterial causing sepsis and IL6 and PCT**

In gram-positive bacterial, the parameters of IL6 and PCT were 30.249±8.949 (max: 45.694, min: 15.72) and .921±.474 (max: 2.12, min: 0.43), respectively. In gram-negative bacterial, the parameters of IL6 and PCT were 26.214±7.412 (max: 42.877, min: 14.834) and 7.560±13.964 (max: 62.22, min: 0.2), respectively. In mixed bacterial, the parameters of IL6 and PCT were 28.311±10.170 (max: 46.996, min: 14.614) and 28.580±16.540 (max: 53.31, min: 0.3), respectively. In Serum procalcitonin (PCT) the results showed that a significant statistical difference (P<0.05), whereas a no significant in concentration of IL-6 (P >0.05) (Table 3).

**IL 6 and PCT concentration of burn patients with and without sepsis**

The study's data revealed that the serum level of procalcitonin (PCT) was significantly higher in burn patients with sepsis compared to burn patients without sepsis, with values of 22.7 ng/ml and 0.78 ng/L, respectively. On the other hand, the serum level of interleukin-6 (IL-6) showed no significant difference between the two groups, with values of 27.8 ng/L and 27.7 ng/L, respectively (Table 4).

**Identification of bacterial isolates from burn sample**

The result revealed bacterial species the most frequent was Gram-negative 28 (45%), Gram-positive (22.6 %) and Mix growth bacteria 11 (17.7%) (Figure 1).

## DISCUSSION

The present research observed a statistically significant rise, with a p-value of less than 0.05, in both procalcitonin (PCT) and interleukin-6 (IL-6) levels among burn patients compared to the control group, stratified by gender. Multiple research have been reported about the fluctuations in levels among

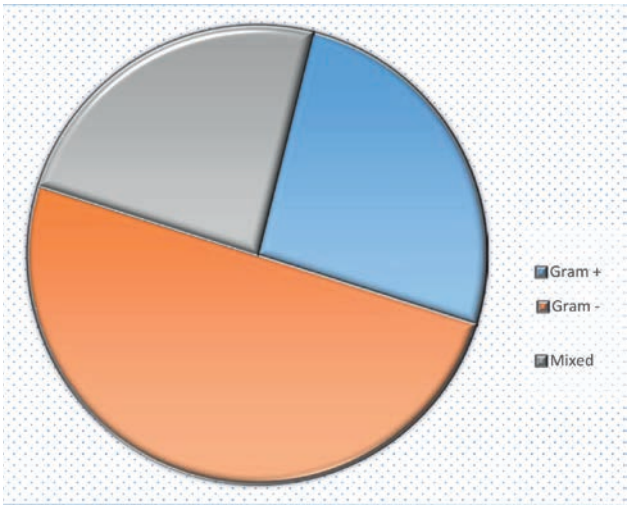


**FIGURE 1.** Bacterial isolates from burn sample

burn victims. The common finding in these previous studies and in our study is that serum levels of PCT and IL-6 are significantly increased in burn patients [4,7,8]. This indicated that higher inflammation, infection, or sepsis in severe degree of burns raised in the serum levels of PCT and IL-6 can give early warning regarding onset of sepsis. As a summary, this study has thrown up positive results regarding the utility of PCT and IL-6 in burn patients. The PCT values correctly predict of inflammation occur in majority of burn patients. Also, rise in the serum levels of PCT and IL-6 can give sufficiently early warning to severity of the degree of burns.

The results of the current study are in agreement with those of Hager et al., [9] it was found that the mean of IL 6, concentration in the male patients were no significantly different from that in the female patients at p. value <0.05. The findings of our current investigation align with the prior research conducted by Aziz et al., [8], which examined the levels of IL 6 in individuals of both genders with varying kinds and severities of burns. The research found a significant increase in interleukin levels in persons with burns. The immune system's inflammatory response is triggered by T lymphocytes and their production of interleukins, which play a crucial role in determining the intensity of the immunological response. The heightened IL-6 cellular motility is a result of the activation of immune system cells, including helper T lymphocytes, monocytes, bone marrow, and mast cells, in response to infections caused by burns. In a recent research by Gille et al., [10], it was discovered that the levels of cytokines in patients with burn injuries were considerably elevated in both males and females, indicating an increase in inflammatory processes. While in another study [8], it was found that the elevated levels of immune index in IL-6 during the early stages of age are attributed to the severity of the infection and the immune system's response to the inflammatory process, as well as the activation of T lymphocytes (Th2) that are responsible for the increase in these interleukins. These findings align with the results of our current study. This research demonstrates significant variations in the concentration of interleukins IL-6 in burn patients, ultimately leading to a conclusive outcome.

The results of the current study are in agreement with those of Yiğit et al., [11], it was found that the mean of PCT concentration in the male patients were no significantly different from that in the female patients. All patients in the current research had an increased level of PCT over the threshold of 0.5 ng/ml, indicating the presence of inflammation. In this investigation, the levels of PCT were found to be modestly increased in all patients, indicating the presence of a subtle inflammatory condition caused by burns. In contrast to IL-6, we observed no significant differences in PCT levels between the female and male groups. Significant levels of PCT may be detected within 2-4 hours following the start of an infection, reaching their highest point between 24-30 hours, and then decreasing quickly as the person recovers [10,12].

The primary discovery of this research is that IL-6 has the potential to forecast bacterial infection in people who are clinically suspected of having sepsis. The findings align with previous studies in burn victims, indicating a strong association between increased IL-6 levels and bacterial infections [13]. Currently, there is a lack of pertinent data pertaining to burn victims. We discovered a robust predictive capacity of IL-6 levels for bloodstream infections produced by gram-positive, gram-negative, and mix growth pathogens. Our recent research found that there were no significant differences in IL-6 levels between patients with gram-positive, gram-negative, and mix growth. This outcome is consistent with earlier research conducted by Gille et al., [10].

Procalcitonin is recognized as a biomarker of infection and serves as an indication of the extent or severity of the illness. This research discovered a link between the levels of serum PCT and sepsis. During the clinical suspicion of infection, individuals diagnosed as having sepsis by blood cultures had substantially elevated levels of PCT compared to those with negative blood culture findings. This finding was consistent with other research that has shown the associations between sepsis and PCT levels. It further validated the notion that measuring PCT might serve as an indicator of sepsis in patients with severe burns [14]. The concentrations of PCT are affected by the organism that causes the infection, which may be related to the activation of various Toll-like receptors by different pathogens [15,16]. We discovered a robust predictive capacity of PCT concentration for bloodstream infections

produced by gram-positive, gram-negative, and mix growth pathogens. Our recent research found that there were non-significant differences in PCT concentration between patients with gram-positive, gram-negative, and mix growth. This outcome is consistent with earlier research conducted by [5]. another study disagreement with our current study conducted by Cabral et al., [10] They found no significant difference in PCT concentration between patients with gram-positive, gram-negative, and mix growth.

In a study conducted in 2018, Thomas-Rüddel et al conducted a secondary analysis of a dataset that was obtained in advance. The dataset included a substantial sample size of 4858 patients with sepsis from 40 different hospitals. Their findings closely resembled those of the current investigation, demonstrating significantly elevated levels of PCT concentrations in patients with gram-negative bacteremia compared to those with sepsis caused by gram-positive bacteria [17].

There are many constraints in the current investigation. owing to the retrospective nature of the investigation, several individuals with suspected or confirmed infections were excluded owing to inadequate data. While our study covered an adequate number of patients for a single burn center, we were unable to thoroughly analyze some subgroups, such as the specific impact of gram-positive vs gram-negative infections. Additional research should be conducted in a larger cohort of patients via a prospective study to better examine the findings. In this investigation, blood sample and parameter assessment were considered to occur simultaneously during suspected clinical sepsis. Conducting further sample within a limited time frame of a few hours may provide insights into the dynamics of sepsis at the early stage, instead of relying on an average measurement throughout the whole first day.

Presently, sepsis is characterized as a kind of perilous organ malfunction that arises from an uncontrolled host reaction to infection [18]. Previous investigations have defined sepsis as a complex immunological response characterized by an initial release of large amounts of inflammatory mediators, followed by a fast decline in the functioning of immune cells and the development of an immunosuppressed state [19]. The excessive inflammation in early sepsis leads to significantly increased levels of inflammatory cytokines, which in turn cause organ destruction and malfunction, eventually resulting in mortality [20]. We not discovered a robust predictive capacity of IL-6 concentration between sepsis and without sepsis in burn patients. Our recent research found that there were no significant differences in IL-6 concentration between patients with sepsis and non-sepsis. This outcome is consistent with earlier research conducted by Mörs et al., [21]. Another study disagreement with this current study conducted by Al-Omari et al., [22] They found significant difference in IL-6 concentration between patients with sepsis and non-sepsis. This disparity may be explained in the following manner: The concentration of IL-6 varies in critically sick patients and is affected by many parameters, including age, burn size, time elapsed after burn damage, comorbidities or problems, and the white blood cell count. The elevated cytokines may be caused directly by the burn, or they might be secondary mediators or signs of systemic inflammation or other concurrent issues. Currently, differentiating between sepsis and non-sepsis is challenging.

After examining potential biomarkers for early sepsis detection in both septic and non-septic burn patients, we determined that PCT was the most dependable biomarker for diagnosing sepsis, surpassing the other biomarker tested, IL-6. This research represents the most extensive investigation to date on the use of PCT for diagnosing sepsis in burn patients, enabling a robust statistical analysis. Therefore, the timely anticipation of sepsis and appropriate care are of utmost significance in enhancing outcomes in cases of severe burns. In line with our findings, a research conducted by Yu et al., [19] indicates that measuring PCT may be beneficial in the early detection of pneumonia and sepsis, as well as in assessing therapy response and predicting prognosis in burn patients. Statistically significant variations in PCT levels were observed between septic and non-septic patients, indicating that PCT had the biggest impact size. At now, sepsis is the primary cause of death among patients with burns. In order to avoid these deaths, it is imperative to initiate prompt and appropriate antibiotic treatment, since every delay increases the likelihood of fatality. Identifying the beginning of sepsis in burn patients solely based on clinical criteria is challenging, especially when considering the specific characteristics of this patient population. This difficulty arises from the fact that extensive burns trigger a powerful systemic inflammatory response that closely resembles a septic episode. Because patient characteristics, comorbidities, burn size, surgical procedures, analytic devices, and other factors can slightly affect PCT levels, it is not possible to definitively establish a single and absolute value for its cut-off in diagnosing sepsis, although several have been suggested. Nevertheless, the majority of writers agree that PCT dynamics are the most valuable and dependable. Utilizing PCT in conjunction with other laboratory and clinical sepsis indicators will undoubtedly enhance the diagnostic efficacy [5].

Despite our intriguing discoveries, this research does have some constraints. Firstly, this research is

retrospective and conducted at a single center. It involves assessing a relatively small sample and a large number of time points using standardized processes for data collecting and recording. On the other hand, the approach used may give rise to concerns regarding sample bias due to the inclusion of a series of consecutive time points. However, as the patients from the sepsis and non-sepsis groups were collected at different times, their time points were recorded independently. Being unquestionably unique may largely decrease the risk of biased suspicion.

An advantage of the research is the use of well-defined and globally recognized criteria for clinical suspicion of sepsis, which enables a rigorous statistical analysis [5,23]. Further research should be conducted in other burn hospitals to investigate similar studies, and other biomarkers should also be evaluated. Moreover, a meticulously planned worldwide multicentric prospective research, directly comparing PCT with other biomarkers, will undeniably provide significant insights into its diagnostic capability for sepsis in burn patients.

It is crucial to emphasise the significance of determining the frequency of bacterial infections and antibiotic resistance in patients with severe burns. Two autopsy conducted on burn patients have shown that the primary reason for death, accounting for up to 65% of cases, is multi-organ failure resulting from sepsis [24]. Sepsis frequently occurs in the intensive care unit of burn centres and is influenced by various factors, including the duration of hospitalisation, advanced age, the extent and severity of burns, and the underlying causes of burns, as well as related conditions that compromise the immune system, such as (HIV) infection or autoimmune diseases. The primary objective of this research, which aimed to identify the disease-causing bacteria responsible for infections in patients admitted to burn units, was successfully accomplished in a cohort of 50 patients between December 1, 2023, and April 1, 2024. In our country, *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Acinetobacter baumannii* are the most often encountered bacterial pathogens in burn victims. These results align with previous worldwide research; however, the distribution of different bacteria varies across burn centres. A Bulgarian research conducted over three decades ago found Staphylococcus aureus as the primary causative agent in burn wound infections, in contrast to studies conducted in South-East Europe [25,26].

## CONCLUSIONS

The study's definitive results showed that burn patients with mixed growth sepsis had higher levels of PCT. However, there were no significant differences in IL-6 levels among patients with Gram-positive, Gram-negative, and mixed growth. This suggests that PCT could assist clinicians in selecting the appropriate empirical antimicrobial therapy, especially when definitive microbiological culture results and sensitivity tests are not yet available. Nevertheless, it is crucial to highlight that the integration of PCT within the therapeutic context and the prevailing flora of the institution is essential, and it can never replace the assessment and judgment of doctors. Stronger validation of the use of PCT values for distinguishing between Gram-negative and Gram-positive and mixed infections requires prospective multicentric investigations. An assessment of the ability of PCT kinetics to differentiate between microbial sepsis caused by various kinds of pathogens would be both intriguing and possibly valuable in clinical settings.

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