ORIGINAL ARTICLE

# Procalcitonin, IL6 Versus Complete blood Count interpretation as diagnostic and prognostic biomarker in patient with sepsis at critical care Unit

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Abstract

*Background:* ***Unfortunately, over 5.3 million people die every year from sepsis, and septic shock is a pathological condition that affects a large percentage of intensive care unit patients. The complete blood count (CBC) includes white blood cells and red blood cell distribution width (RDW). Procalcitonin and interleukin 6 were among the biomarkers found in the circulation.***

*Aim:* ***To assess and compare the diagnostic and prognostic capability of procalcitonin versus IL-6 versus complete blood count.***

*Patients and methods:* ***Our single-center prospective cohort study was carried out on 100 patients with sepsis; 61% were males, and 39% were females, with age ranging from 25 to 85 years, with mean±SD of 56.6±16.3 years.***

*Results:* ***What this study found Patients who did not make it had significantly higher levels of interleukin-6 on days 0, 3, 6, 9, and 12 compared to those who did, suggesting a statistically significant association between vital signs and sepsis severity, procalcitonin at different time intervals and sepsis severity, white blood cells at different time intervals and mortality, and finally, interleukin-6 at different time intervals and mortality.***

*Conclusion:* ***In contrast to other diagnostic tools, procalcitonin is useful for distinguishing between deaths caused by sepsis and those caused by other causes. This makes it an ideal sepsis marker. IL-6 has the ability to serve as a biomarker for the diagnosis of sepsis and is a reliable predictor of this condition.***

*Keywords:* Sepsis; Procalcitonin; Interleukin 6; Complete blood count

## 1. Introduction

A potentially fatal medical emergency known as sepsis happens when the immune system's reaction to an infection causes systemic inflammation, which in turn damages tissues and malfunctions organs. Systemic damage caused by the immune system's response to infection is a key feature of this condition. Early recognition and intervention are critical in reducing the high mortality rate associated with this condition.[1]

Sepsis biomarkers may allow for early detection and management of sepsis by immediately initiating the treatment before the occurrence of adverse consequences. The host immune system responds to particular products from different pathogens.[2]

PCT value was found to be more efficient and more specific than other inflammatory biomarkers in cases of bacterial infection. It may be useful in predicting blood culture findings in patients who are suffering from severe sepsis.[3] Gómez et al.,[4] reached the conclusion that 3.6 ng/mL was the optimal PCT value for predicting sepsis.

IL-6 stimulates the production and secretion of acute-phase proteins by several cells, making it a critical pro-inflammatory factor during the early stages of inflammation. While IL-6 levels in healthy individuals are typically below 7 pg/mL, they spike in the blood of sepsis patients within two hours of infection beginning. A higher IL-6 level is linked to an increased risk of death, more severe organ dysfunction, and a sepsis diagnosis.[5]

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Yu et al.,[6] IL-6 was found to be a possible biomarker for sepsis diagnosis and an independent predictor of sepsis diagnosis in patients presenting to the emergency department for treatment of sepsis. The study also examined the diagnostic and prognostic utility of IL-6.

Among all the sepsis indicators being studied, CBC values may be the most helpful because they can be easily performed, are cheap, and are available in all medical facilities. This test is important for the early diagnosis of many health issues, which should then be further investigated through laboratory examination.[7]

An alteration from the normal range of CBC parameters suggested the existence of acute inflammation due to unknown causes. The CBC value, in conjunction with blood culture and other suggestive biomarkers, can offer crucial clinical data for the identification and treatment of sepsis, since there is currently no one sepsis parameter that is ideal for this purpose.[8]

The purpose of this research was to compare the diagnostic and predictive power of procalcitonin, IL6, and total blood count in sepsis patients.

## 2. Patients and methods

Patients of both sexes presented with different degrees of sepsis in ICU, Al-Azhar University Hospital, New Damietta, Damietta, Egypt according to 2021 surviving sepsis campaign were included in this single-center prospective cohort study over one year from April 2023 to April 2024.

Inclusion criteria:

Criteria such as temperature (above or below 36.5°C), respiratory rate (above 20 breaths per minute), blood pressure (above or below 32 mmHg), heart rate (above 90 beats per minute), white blood cell count (above 11,000 per cm) or white blood cell count (below 4,000 per cm), septic shock (hypotension not reversed with fluid resuscitation and associated with organ dysfunction or hypo-perfusion abnormalities), and sepsis (infection-induced organ dysfunction or hypo-perfusion abnormalities) are all criteria for this condition.

Exclusion criteria:

Patients who have undergone a transfusion within the week prior to their admission to the intensive care unit (ICU), those who are under the age of 21, those who are chronically sick or who use drugs that change the shape and size of red blood cells (RBCs), pregnant women, and patients experiencing cardiac arrest, severe bleeding, or blood loss greater than 10% of blood volume are not eligible.

Methods:

Every patient underwent a comprehensive evaluation that included taking their vital signs, reviewing their medical history, analyzing their blood gas levels, measuring interleukin-6 (IL-6) and procalcitonin (PCT), and calculating their Glasgow coma scale (GCS) score.

Within six hours of the clinical diagnosis of sepsis, all blood samples were collected for initial IL-6 and PCT values, in tubes that separate serum, whole blood was drawn. An aliquot of the serum was taken and stored at -80°C until analysis. We examined serum biomarker levels in two separate samples, both of which were frozen before analysis.

Data collection:

Patient demographics, sepsis etiology, and laboratory data were all part of the obtained dataset. After then, the patients were monitored for 28 days to see if they died. Data from the first 24 hours after admission were used to compute scores on the acute physiology and chronic health evaluation II (APACHE II) and the sepsis-related organ failure assessment (SOFA). The duration of hospital stays was also documented.

Statistical analysis:

Statistical Package for the Social Sciences (IBM SPSS) version 23 was used for data entry after data collection, revision, and coding. In cases where the quantitative data were determined to have a parametric distribution, it was displayed as mean plus standard deviation. In cases where the data did not have a parametric distribution, it was displayed as median plus inter-quartile range (IQR). Quantitative variables were also shown as percentages and numbers. When there was an expected count of less than 5 in any cell, Fisher's exact test was used instead of the Chi-square test to compare groups utilizing qualitative data. For quantitative diagnostic tests, the receiver operating characteristic (ROC) curve is a helpful tool for assessing specificity and sensitivity. A 95% confidence interval and a 5% margin of error were both accepted. Accordingly, the p-value was deemed significant ($p < 0.05$).

## 3. Results

*Table 1. Demographic data among the studied patients.*

| VARIABLES | | ALL PATIENTS (N=100) |
|---|---|---|
| AGE (YEARS) | Mean±SD | 56.6±16.3 |
| | Range | (25-85) |
| SEX (N.%) | Male | 61(61%) |
| | Female | 39(39%) |
| SMOKING STATUS (N.%) | Non-smoker | 81(81%) |
| | Smoker | 19(19%) |
| BMI (KG/M²) | Mean±SD | 25.9±2.49 |
| | Range | (21-31) |

*BMI=Body mass index.

The studied patients ranged in age between 25-85, with a mean±SD of 56.6±16.3, (61%) were males, and (39%) were females. (19%) were smokers and (81%) were non-smokers. Their BMI ranged between 21-31, with a mean±SD of 25.9±2.49, (table 1).

*Table 2. WBCs, procalcitonin and interleukin-6 at different time intervals among the studied patients.*

| VARIABLES | | WBCS | PROCALCITONIN | INTERLEUKIN -6 |
|---|---|---|---|---|
| DAY-0 | Mean±SD | 11.5±3.02 | 3.1(5.6) | 147(303) |
| | Range | (7.5-18) | (0.2-25.3) | (54-790) |
| DAY-3 | Mean±SD | 13.4±4.26 | 2.2(2.85) | 100(323) |
| | Range | (7.5-22.5) | (0.5-20.1) | (40-750) |
| DAY-6 | Mean±SD | 14.4±4.91 | 1.4(3.38) | 69(264) |
| | Range | (7.9-24.5) | (0.3-18.4) | (30-700) |
| DAY-9 | Mean±SD | 15±5.36 | 1.1(2.5) | 45(250) |
| | Range | (8-25.5) | (0.1-14.5) | (20-600) |
| DAY-12 | Mean±SD | 15.4±6.52 | 0.9(1.32) | 35(215) |
| | Range | (8-26.5) | (0.1-10.2) | (10-500) |

TLC at day-0 ranged between 7.5-18 with a mean±SD of 11.5±3.02. At day-3 ranged between 7.5-22.5 with a mean±SD of 13.4±4.26. At day-6 ranged between 7.9-24.5 with a mean±SD of 14.4±4.91. At day-9 ranged between 8-25.5 with a mean±SD of 15±5.36. At day-12 ranged between 8 -26.5 with a mean±SD of 15.4±6.52.

Procalcitonin on day-0 ranged between 0.2-25.3ng/ml with a median (IQR) of 3.1(5.6). On day-3, it ranged between 0.5-20.1ng/ml with a median (IQR) of 2.2(2.85). On day-6, it ranged between 0.3-18.4ng/ml with a median (IQR) of 1.4(3.38). On day-9, it ranged between 0.1-14.5ng/ml with a median (IQR) of 1.1(2.5). On day-12, it ranged between 0.1 -10.2ng/ml with a median (IQR) of 0.9(1.32).

Interleukin-6 on day-0 ranged between 54-790pg/ml with a median (IQR) of 147(303). On day-3, it ranged between 40-750pg/ml with a median (IQR) of 100(323). On day-6, it ranged between 30-700pg/ml with a median (IQR) of 69(264). On day-9, it ranged between 20 -600pg/ml with a median (IQR) of 45(250). On day-12, it ranged between 10-500pg/ml with a median (IQR) of 35(215), (table 2).

*Table 3. Association between WBCs at different time intervals and mortality among the studied patients.*

| VARIABLES | | SURVIVED (N=87) | DIED (N=13) | P VALUE |
|---|---|---|---|---|
| DAY-0 WBCS | Mean±SD | 11.4±2.95 | 11.8±3.54 | |
| | Range | (7.5-18) | (8.1-18) | 0.64 |
| DAY 3 WBCS | Mean±SD | 12.9±3.96 | 16.7±4.86 | |
| | Range | (7.5-19.5) | (8.5-22.5) | 0.002 |
| DAY-6 WBCS | Mean±SD | 14±4.92 | 17±4.12 | |
| | Range | (7.9-22.5) | (8.5-24.5) | 0.04 |
| DAY-9 WBCS | Mean±SD | 14.5±5.25 | 18.2±5.18 | |
| | Range | (8-23.5) | (9.5-25.5) | 0.02 |
| DAY-12 WBCS | Mean±SD | 14.9±6.4 | 18.7±6.57 | |
| | Range | (8-24.5) | (9.7-26.5) | 0.04 |

*:Student T-test, Non-significant:P>0.05, Significant:P≤0.05

A statistically significant association between WBCs at different time intervals and mortality, as WBCs at day-3, day-6, day-9, and day-12 was higher among patients who died when compared to the patients who survived (P<0.05), (table 3).

*Table 4. Association between procalcitonin at different time intervals and mortality among the studied patients.*

| VARIABLES | | SURVIVED (N=87) | DIED (N=13) | P VALUE |
|---|---|---|---|---|
| DAY-0 PCT | Median (IQR) | 2.6(3.25) | 11.3(8.6) | |
| | Range | (0.2-15.9) | (1.5-25.3) | <0.001 |
| DAY-3 PCT | Median (IQR) | 1.9(2.65) | 4.6(4.9) | |
| | Range | (0.5-20.1) | (1.9-20.1) | <0.001 |
| DAY-6 PCT | Median (IQR) | 1.1(2.9) | 5.1(4.8) | |
| | Range | (0.3-18.4) | (0.9-18.4) | <0.001 |
| DAY-9 PCT | Median (IQR) | 1(1.8) | 3.3(4.7) | |
| | Range | (0.1-9.4) | (1.1-14.5) | <0.001 |
| DAY-12 PCT | Median (IQR) | 0.8(1.3) | 4.8(3.9) | |
| | Range | (0.1-8.4) | (0.2-10.2) | <0.001 |

*:Mann-Whitney U-test, Non-significant:P>0.05, Significant:P≤0.05

A statistically significant association between procalcitonin at different time intervals and mortality, as procalcitonin at day-0, day-3, day-6, day-9, and day-12 was higher among patients who died when compared to the patients who survived (P<0.001), (table 4).

*Table 5. Association betweeninterleukin-6 at different time intervals and mortality among the studied patients.*

| VARIABLES | | SURVIVED (N=87) | DIED (N=13) | P VALUE |
|---|---|---|---|---|
| DAY-0 IL-6 | Median (IQR) | 137(61.5) | 470(60) | |
| | Range | (54-510) | (100-790) | <0.001 |
| DAY-3 IL-6 | Median (IQR) | 95(126) | 420(50) | |
| | Range | (40-470) | (250-750) | <0.001 |
| DAY-6 IL-6 | Median (IQR) | 68 (7.5) | 350(30) | |
| | Range | (30-370) | (66-700) | <0.001 |
| DAY-9 IL-6 | Median (IQR) | 45(20) | 300(20) | |
| | Range | (20-330) | (40-600) | <0.001 |
| DAY-12 IL-6 | Median (IQR) | 30(7.5) | 252(5) | |
| | Range | (10-256) | (28-500) | <0.001 |

*:Mann-Whitney U-test, Non-significant:P>0.05, Significant:P≤0.05

A statistically significant association between procalcitonin at different time intervals and mortality, as interleukin-6 at day-0, day-3, day-6, day-9, and day-12 was higher among patients who died when compared to the patients who survived (P<0.001), (table 5).

*Table 6. ROC curve analysis of procalcitonin at different time intervals in predicting septic shock.*

| VARIABLES | CUT POINT | SENSITIVITY (%) | SPECIFICITY (%) | PPV (%) | NPP (%) | AUC (%) |
|---|---|---|---|---|---|---|
| PCT DAY-0 | 4.3 | 80% | 82.86% | 66.67% | 90.62% | 0.838 |
| PCT DAY-3 | 3.6 | 83.33% | 97.14% | 92.59% | 93.15% | 0.861 |
| PCT DAY-6 | 3.1 | 90% | 95.71% | 90% | 95.71% | 0.927 |
| PCT DAY-9 | 2.6 | 90% | 91.43% | 81.82% | 95.52% | 0.908 |
| PCT DAY-12 | 1.5 | 86.67% | 87.14% | 72.29% | 93.85% | 0.892 |

ROC analysis (receiver operation curve) was conducted to determine the optimal cutoff value by procalcitonin, interleukin-6, and WBCs to discriminate patients with sepsis from patients with septic shock, (tables 6, 7, and 8).

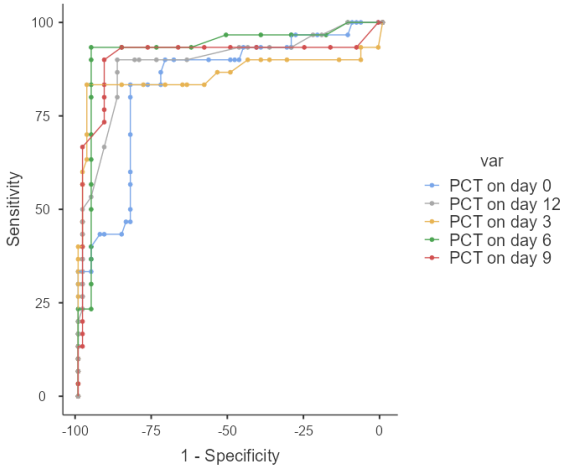


Figure 1. ROC curve analysis of procalcitonin at different time intervals in predicting septic shock.

*Table 7. ROC curve analysis of interleukin-6 at different time intervals in predicting septic shock.*

| VARIABLES | CUT POINT | SENSITIVITY (%) | SPECIFICITY (%) | PPV (%) | NPP (%) | AUC (%) |
|---|---|---|---|---|---|---|
| IL-6 DAY-0 | 280 | 80% | 81.43% | 64.86% | 90.48% | 0.769 |
| IL-6 DAY-3 | 200 | 76.67% | 91.43% | 79.31% | 90.14% | 0.789 |
| IL-6 DAY-6 | 140 | 83.33% | 90% | 78.12% | 92.65% | 0.802 |
| IL-6 DAY-9 | 95 | 83.33% | 92.86% | 83.33% | 92.86% | 0.821 |
| IL-6 DAY-12 | 45 | 86.67% | 92.86% | 83.87% | 94.2% | 0.848 |

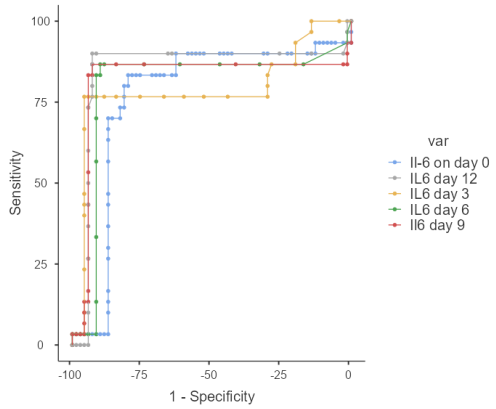


Figure 2. ROC curve analysis of interleukin-6 at different time intervals in predicting septic shock.

*Table 8. ROC curve analysis of WBCs at different time intervals in predicting septic shock*

| VARIABLES | CUT POINT | SENSITIVITY (%) | SPECIFICITY (%) | PPV (%) | NPP (%) | AUC (%) |
|---|---|---|---|---|---|---|
| WBCS DAY-0 | 10 | 73.33% | 31.43% | 36.84% | 71.67% | 0.616 |
| WBCS DAY-3 | 10.5 | 46.67% | 85.71% | 58.33% | 78.95% | 0.643 |
| WBCS DAY-6 | 11.5 | 60% | 61.43% | 40% | 78.18% | 0.631 |
| WBCS DAY-9 | 13.5 | 63.33% | 64.29% | 43.18% | 80.36% | 0.650 |
| WBCS DAY-12 | 14.5 | 63.33% | 65.71% | 44.19% | 80.7% | 0.680 |

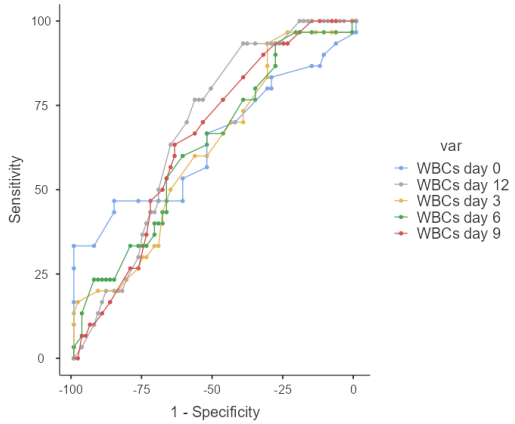


Figure 3. ROC curve analysis of WBCs at different time intervals in predicting septic shock.

## 4. Discussion

A dysregulated host response to infection consistently causes sepsis, a potentially fatal organ failure. The unnecessary overprescribing of antibiotics in situations where sepsis is not present would be reduced if diagnostic tests were more precise.[9]

PCT is related to Amylin, Procalcitonin, and Adrenomedullin, which is a family of proteins. Rhodes et al.,[10] suggested PCT as a useful indicator for stopping antibiotic treatment in sepsis, however the data was limited and the advice was weak as well.

There are a number of ongoing trials that aim to evaluate PCT-guided therapy in intensive care unit patients in order to determine its advantages and disadvantages. Nevertheless, PCT has been proposed to be somewhat useful in diagnosing pneumonia caused by various illnesses.[11]

An additional key cytokine that rises early in inflammatory cascades is interleukin-6 (IL-6). In reaction to a bacterial infection, monocytes and macrophages create it. It helps keep plasma cells alive, which are responsible for secreting antibodies and promoting the development of cytotoxic T-cells. One of the hepatocyte-stimulating factors that initiates the acute-phase response—which includes C-reactive protein—is IL-6.[11]

Among all the sepsis indicators being studied, CBC values may be the most helpful because they can be easily performed, are cheap, and are available in all medical facilities. This test is important for the early diagnosis of many health issues, which should then be further investigated through laboratory examination.[7]

The present study is a single-center prospective cohort in which patients with sepsis were treated in ICU with recent ICU guidelines (2021 surviving sepsis campaign). It aimed to assess and compare the diagnostic and prognostic capability of procalcitonin versus IL-6 versus complete blood count among 100-patients with sepsis.

According to our demographic data, 61% of our patients were male and 39% were female. Their ages ranged from 25 to 85 years, with a mean±SD of 56.6±16.3 years. The average age of the patients was 71.7±15.5 years, with 63.6% being male and 36.4% being female, according to Gómez et al.,[4].

Al-Zahrani et al.,[12] The most prevalent species detected in Saudi Arabia were Gram-negative (Klebsiella and E. coli) and GBS.

There was a mean±SD of 11.5±3.02 for TLC at day 0 in the present study, which varied from 7.5 to 18. The values at day 3 varied from 7.5-22.5, with an average±standard deviation of 13.4±4.26. With a mean±SD of 14.4±4.91, the results at day 6 ranged from 7.9 to 24.5. The data at day 9 varied from 8 to 25.5, with a mean±SD of 15±5.36. On day 12, the values varied from 8 to 26.5, with an average of 15.4±6.52. This was in consensus with Munford and Suffredini[13] According to the source, sepsis typically results in an increased white blood cell count, a higher number of neutrophils, and a higher percentage of immature forms.

In this study, interleukin-6 on day 0 ranged

between 54-790 pg/ml with a median (IQR) of 147(303). On day 3, it ranged between 40-750pg/ml with a median (IQR) of 100(323). On day 6, it ranged between 30-700pg/ml with a median (IQR) of 69(264). On day 9, it ranged between 20-600pg/ml with a median (IQR) of 45(250). On day 12, it ranged between 10-500pg/ml with a median (IQR) of 35(215). Takahashi et al.,[14] confirmed that IL-6 has a greater diagnostic value for sepsis than PCT and CRP.

By comparing patients with sepsis to those with septic shock, the current study found a statistically significant correlation between sepsis severity and procalcitonin levels at various time intervals (day 0, day 3, day 6, day 9, and day 12).

Heper et al.,[15] assessed the serum PCT level as a diagnostic and predictive metric in 21 patients diagnosed with sepsis and 18 patients diagnosed with severe sepsis, as well as in patients experiencing septic shock. High PCT levels were associated with a poor prognosis in the severe sepsis group when they persisted after 72 hours.

There was a statistically significant correlation between WBCs at various time intervals and mortality in the present investigation. Specifically, patients who did not survive had greater WBCs on days 3, 6, 9, and 12 compared to those who did. But, Yu et al.,[6] it was determined that IL-6 did not correlate with 28-day mortality in sepsis patients, indicating that IL-6 does not serve as a predictor of mortality in sepsis patients.

Limitations: The single medical center and the relatively small sample size.

### *4. Conclusion*

Serum biomarker concentrations were higher in patients who did not survive sepsis compared to those who did, which is in line with the high mortality rate in this condition. In contrast to other diagnostic tools, procalcitonin is useful for distinguishing between deaths caused by sepsis and those caused by other causes. This makes it an ideal sepsis marker. Patients can be stratified and identified with a higher risk of unfavorable outcomes when their procalcitonin levels are elevated, as it is a good predictor of mortality. In order to guide antibacterial treatment and reduce antibiotic duration, the PCT procedure is useful. IL-6 has the ability to serve as a biomarker for the diagnosis of sepsis and is a reliable predictor of this condition.

## Disclosure

The authors have no financial interest to declare in relation to the content of this article.

## Authorship

All authors have a substantial contribution to the article

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## Conflicts of interest

There are no conflicts of interest.

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