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Research Article

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# Analysis of leukocyte cell population data (CPD) as biomarkers in the diagnosis of sepsis

## Abstract

**Background:** Leukocyte cell population data (CPD) are parameters currently being studied as biomarkers in sepsis and other pathologies. CPD was procured with the BC 6800 Plus Mindray® hematology analyzer that also provides information on the internal cellular complexity, nucleic acid content, and size of leukocytes. This study aimed to assess the efficacy of CPD parameters as biomarkers in the diagnosis of sepsis by comparing these with the standard sepsis biomarker, procalcitonin (PCT).

**Methods:** In total 107 patients with suspected sepsis were included in the study, and serum procalcitonin levels were measured and WBC cell population data (CPD) were analyzed in a hemogram to confirm the diagnostic accuracy of these biomarkers. ROC curves were plotted for all parameters and patients were categorized based on their serum procalcitonin levels. IBM SPSS Stadistics version 24 was used for statistical analysis of the data.

**Results:** All parameters except the CPD NEU-X (neutrophil complexity), NEU-Z (neutrophil size), LYM-Z (lymphocyte size) and MON-Z (monocyte size) showed statistically significant results ($p<0.05$). ROC curve analysis showed that the CPD parameters MON-X and NEU-Y had area under the ROC curve (AUC) > 0.7, reflecting the better diagnostic performance in sepsis. A lower AUC of 0.650 was obtained for PCT; 87.8% of septic patients had serum PCT levels between ≥ 0.5 ng/mL and 51.2% ≥ 2 ng/mL.

**Conclusion:** This study suggests that some of the new CPD parameters (MON-X and NEU-Y) have the potential to be a useful diagnostic marker for sepsis.

**Keywords:** white blood cell count, leukocyte cell population data (CPD), sepsis, procalcitonin, Mindray®, inflammation

Volume 10 Issue 2 - 2022

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**Received:** May 11, 2022 | **Published:** June 01, 2022

## Introduction

Sepsis, a clinical syndrome characterized by severe organ dysfunction, is caused by the body's abnormal response toward an infection that can turn life-threatening (sepsis-3).[1] The current definition of sepsis-3 has a higher specificity but lower sensitivity, thus detecting a "sicker" cohort of patients. The degree of organ dysfunction can be measured with the Sequential Sepsis-Related Organ Failure Assessment (SOFA) scale or with the new rapid SOFA scale (qSOFA) that includes only three clinical criteria: determination of level of consciousness (Glasgow scale score <13), systolic blood pressure < 100 mmHg and respiratory rate ≥ 22 rpm. When at least two of the three criteria are present it has good predictive validity for the detection of those patients with suspected infection and probable sepsis (1). The incidence rate, associated mortality, morbidity, and high cost make it a very serious health problem. Sepsis is one of the main causes of admission to the hospital's Intensive Care Unit (ICU), affecting around 31 million people each year worldwide, causing approximately 6 million deaths.[2,3] It is a complex, time-dependent syndrome, difficult to diagnose, and should always be treated as a medical emergency.[3,4] The early diagnosis is crucial to initiate the most appropriate treatment, which is vital to improving the prognosis and survival rates of patients. Diagnosis of sepsis is difficult and mostly based on the evaluation of clinical signs and symptoms and the laboratory tests (microbiological, biochemical, and hematological).[5,6] Although blood culture remains the standard technique for the diagnosis of systemic infection, it has a major drawback: the waiting time to obtain the results, which is difficult to interpret as sample culture often gets contaminated. Procalcitonin has so far been the most studied candidate biomarker in this pathology. It is a polypeptide composed of 116 amino acids, a precursor of calcitonin, produced mainly by the C cells of the thyroid gland. It is a sensitive biomarker when distinguishing between bacterial infection and non-bacterial infection, but it does not present high specificity when elevated in other non-infectious circumstances (severe trauma, surgery, newborns, immunosuppressive treatments, paraneoplastic syndromes, etc...), therefore its diagnostic value in this pathology is controversial. Although its efficacy as a biomarker of sepsis is questionable, it is the most widely used and the only one currently included in treatment algorithms. In the laboratory, since it is the most studied biomarker and is easily accessible, and is the most widely used so far.[7,8] Currently, there is no single laboratory test to accurately diagnose sepsis: technological advances and research proposals for new biomarkers continue.[2]

The patients at risk of developing sepsis suffer from an immunological imbalance due to infection leading to the morphological and functional changes in the cells of the immune system (mostly leukocytes).[2,9,10] Recent researches have focused on finding new biomarkers related to the inflammatory immune response and blood cell count through hemogram.[11]

In addition to the data from the classic hemogram, the new generation of the hematological analyzer, fluorescence flow cytometry, can also provide the cell population data (CPD),[9,12–14] which offers quantitative and precise information on cellular changes in response to infection. These parameters are currently "under investigation" but have the potential to emerge as useful markers in pathologies such as sepsis and myelodysplastic syndromes, where the cells show prominent phenotypic changes.[12,13,15,16] Most of the studies performed in this field to date have been carried out using the hematological analyzer of the Sysmex® laboratory since it is one

of the few that incorporate CPD parameters.[17–20] This is one of the first studies to utilize the BC 6800 Plus Mindray® analyzer to obtain CPD parameters data for neutrophils (NEU), lymphocytes (LYM) and monocytes (MON). The emitted optical signals indicate changes in internal cellular complexity (NEU-X, LYM-X and MON-X), nucleic acid content (NEU-Y, LYM-Y, MON-Y) and cell size (NEU-Z, LYM-Z, MON-Z).[21,22]

At the beginning of our study, we hypothesized that sepsis affects the leukocyte cell population and the CPD parameter analyzer can determine precise quantitative changes. The main objective of this project was to determine and evaluate the diagnostic accuracy of CPD parameters versus procalcitonin levels (reference parameter) as useful biomarkers in the detection of sepsis.

## Materials and methods

### Study design

The retrospective observational study reviewed the clinical and analytical data of patients admitted to the Poniente Hospital (El Ejido, Almería, Spain) between September and December 2019, initially treated with suspected infection and/or sepsis from the Emergency Department. The study was approved by the Research Ethics Committee of Almeria (Pl_20_29 Sepsis).

### Patients

The study population included patients who had been admitted to the hospital in the aforementioned period with suspected infection and/or sepsis from the emergency department, who had procalcitonin determination and complete blood count requested in the initial request.

Inclusion criteria were established as follows: age ≥ 18 years with suspected infection and/or sepsis; serum PCT and complete blood count from initial blood samples collected in the emergency department in biochemistry tubes without anticoagulant (for PCT) and EDTA K2 tube for complete blood count. In the case of multiple samples from the same patient, the sample closest to the indication of suspected sepsis/sepsis in the clinical judgment section of the patient's medical history was selected. Patients aged ≤18 years, those with a history of hematological disorders, immunocompromised patients and pregnant women were excluded from this study.

### Data collection

**Laboratory tests:** leukocyte cell population data (CPD) and serum procalcitonin concentration.

**Other variables collected:** patient age, sex and the cause of infection in the positive sepsis cases. The leukocyte cell population data (CPD), was obtained from the BC 6800 Plus Mindray® analyzer (Table 1):

**Table 1** Description and information of the CPD provided by the hematological analyzer. Information adapted from[2]

| Parameter | Optical signal emitted | Cellular information |
|---|---|---|
| **X-AXIS** | | |
| NEU-X | Intensity of laterally scattered light in the neutrophil area | Internal cellularcomplexity: granulation,presence of vacuolesand other cytoplasmicinclusions. |
| LYM-X | Intensity of laterally scattered light in the lymphocyte area | |
| MON-X | Intensity of laterally scattered light in the monocyte area | |
| **Y-AXIS** | | |
| NEU-Y | Fluorescent light intensity in the neutrophil area | DNA/RNA nucleic acidcontent. Cell activation |
| LYM-Y | Fluorescent light intensity in the lymphocyte area | |
| MON-Y | Fluorescent light intensity in the monocyte area | |
| **Z-AXIS** | | |
| NEU-Z | Forward scattered light intensity in the neutrophil Cell volume/size area | |
| LYM-Z | Forward scattered light intensity in the lymphocyte area | |
| MON-Z | Forward scattered light intensity in the monocyte area | |

Modulab Werfen® laboratory software was used to collect sociodemographic data (age, sex), service where patients with sepsis were admitted, and analytical data (PCT, hemogram). The computer program Ariadna ® was used to obtain the diagnosis, clinical assessment and review the patients' medical history.

### Measuring instruments

EDTA K2 blood samples were processed by the BC 6800 Plus Mindray® hematology analyzer to obtain the results of the hemogram and CPD of neutrophils, monocytes, and lymphocytes. The methodology used was fluorescence flow cytometry (SF-Cube, laser light scattering, and fluorescence). The cells, after being treated with specific lysing agents, were labeled with a fluorochrome (which penetrates the cell due to the perforation of the membrane) and passed through a flow cell cytometer. A beam of laser light intercepted the labeled cells to yield three varied signals (X, Y, Z) that allowed the classification and characterization of cells (Figure 1).

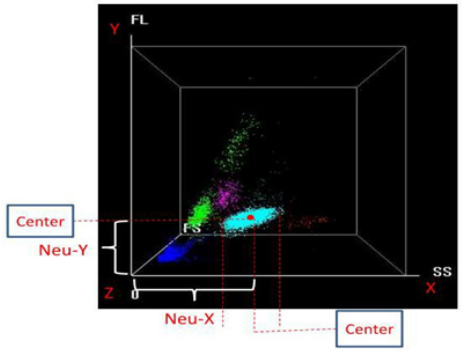


**Figure 1** Scatter plot of leukocytes obtained by the analyzer. X-axis, Z-axis, Y-axis visualization of neutrophils (t represented here as a graph).[21]

For the determination of PCT, neither an EDTA-K2 sample is used as in the case of CPDs nor the same equipment because they

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use different methodologies. In our laboratory, PCT is measured by one of the most commonly used methodologies in clinical laboratories for this test, by immunoassay, and a serum sample is required for analysis. In our study, the immunoassay equipment available and used to measure PCT was the Beckman Coulter DXI 800 (paramagnetic particle chemiluminescence chemiluminescence immunoassay methodology). Both analyzers met the quality specifications required to perform the analysis.

### Statistical analysis

The Kolmogorov Smirnov test was used to determine the normality of the variables. Using the Chi-square test, procalcitonin levels were compared with those at which sepsis developed in the patients. The diagnostic accuracy of the CPD parameters, as well as the comparison of the diagnostic performance of CPD with procalcitonin, were calculated using the ROC curve and AUC. Statistical analysis was performed with IBM SPSS v24. A parameter was considered an acceptable diagnostic biomarker when it was statistically significant ($p<0.05$) and had an AUC value >0.7.

## Results

This study included 107 patients (71% men) with suspected sepsis. The mean age of the participants was 60.5 years. Of the 107 patients, 41 were clinically confirmed to have sepsis according to diagnostic criteria (38.3%) (sepsis-3). The mean age of patients with confirmed sepsis was 55.2 years; 29 males (70.7%) and 12 females (29.3%). The patients were admitted to different departments: 31 cases of sepsis diagnosed in the ICU, 2 in the Emergency Department, 4 in the Digestive Department and 4 in Internal Medicine.

The results of the microbiological cultures of all patients with sepsis were collected to establish the origin of the infection. The following Table 2 lists the microorganisms responsible for causing sepsis in the patients:

**Table 2** Origin of sepsis in the 41 patients and microorganisms isolated

| Infection focus | Microorganisms at cause |
|---|---|
| Urinary n = 14 | *Escherichia coli* n = 6<br>*Klebsiella pneumoniae* n = 3<br>*Enterococcus faecalis* n = 3<br>*Enterobacter cloacae* n = 1<br>*ndidaCa krusei* n = 1 |
| Abdominal n = 9 | *Klebsiella pneumoniae* n = 1<br>*Enterococcus faecium* n = 2<br>*Enterococcus faecalis* n = 4<br>*Escherichia coli* n = 2 |
| Respiratory n = 14 | *Streptococcus pneumoniae* n = 7<br>*Klebsiella pneumoniae* n = 2<br>*Escherichia coli* n = 1<br>*Staphylococcus aureus* n = 1<br>*Enterobacter cloacae* n = 2<br>*Candida albicans* n = 1 |
| Others: | |
| Injury n = 2 | *Pseudomonas aeruginosa* n = 1<br>*Klebsiella pneumoniae* n = 1 |
| Catheter n = 1 | *Enterobacter cloacae* n = 1 |
| Ulcer n = 1 | *Klebsiella pneumoniae* n = 1 |

The infection in the studied patients reveals that most were of urinary (34%) or respiratory (34%) origin, with *Escherichia coli* and *Streptococcus pneumoniae* being the most common pathogens, followed by the abdominal source of infection (22%) with *Enterococcus faecalis* as the main causative pathogen.

The following Table 3 shows the results of the ROC curves for the parameters analyzed. Of all the parameters analyzed, statistically significant differences were found in the values of NEU-Y, LYM-X, LYM-Y, MON-X, MON-Y, and PCT.

**Table 3** ROC curve area results for CPD and PCT parameters. AUC values, standard error, and asymptotic significance level

| Parameter | AUC (IC 95%) | Standard error | P |
|---|---|---|---|
| NEU-X | 0.525 (0.412–0.638) | 0.058 | 0.661 |
| **NEU-Y** | **0.724 (0.625–0.822)** | **0.05** | **0.000** |
| NEU-Z | 0.523 (0.409–0.638) | 0.058 | 0.684 |
| LYM-X | 0.632 (0.518–0.746) | 0.058 | 0.022 |
| LYM-Y | 0.647 (0.539–0.754) | 0.055 | 0.011 |
| LYM-Z | 0.522 (0.408–0.635) | 0.058 | 0.708 |
| **MON-X** | **0.729 (0.632–0.826)** | **0.05** | **0.000** |
| MON-Y | 0.630 (0.519–0.741) | 0.057 | 0.024 |
| MON-Z | 0.576 (0.465–0.686) | 0.056 | 0.19 |
| **PCT** | **0.650 (0.547–0.752)** | **0.052** | **0.009** |

Of the CPDs that were statistically significant, those with a higher area under the ROC curve values were chosen to appropriately differentiate between sepsis/non-sepsis. CPD analysis revealed two parameters with higher ROC curve area AUC >0.7, MON-X (monocyte internal cellular complexity) with a ROC curve area value of 0.729 (72.9%), and NEU-Y (neutrophil nucleic acid content) with a value of 0.724 (72.4%).

PCT values were included in this study as it is the current standard clinical biomarker. We calculated a ROC curve area value of 0.650 (65%) for PCT. The ROC curves are presented in the following Figure 2:

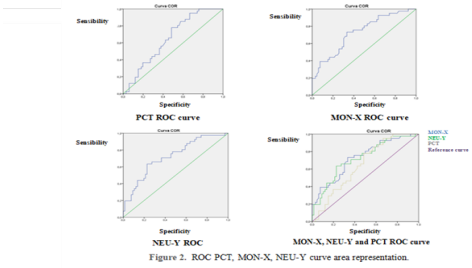

Figure 2. ROC PCT, MON-X, NEU-Y curve area representation.

**Figure 2** ROC, PCT, MON-X, NEU-Y curve area representation.

PCT levels correlate with sepsis severity and can be used to monitor patients' conditions and help in the antibiotic de-escalation. For this reason, patients were categorized according to their PCT levels, and the results are presented in Table 4. As per the results obtained from the patients with sepsis, 87.8% had serum PCT levels ≥0.5 ng/mL and 51.2% ≥2 ng/mL. About 26.8 % of patients had PCT concentrations ≥10ng/mL. The calculated p-value in the chi-square test was 0.036 ($p<0.05$), indicating the results were statistically significant.

**Table 4** Stratification of PCT values in patients with confirmed sepsis

| PCT level (ng/mL) | < 0.5 ng/mL | 0.5–2 ng/mL | 2–10 ng/mL | >10 ng/mL |
|---|---|---|---|---|
| Sepsis (n = 41) | 5 | 15 | 10 | 11 |
| % | 12.20% | 36.60% | 24.40% | 26.80% |

## Discussion

Sepsis is a time-dependent process in which early detection and initiation of appropriate antimicrobial therapy are crucial for a better

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prognosis. An early diagnostic biomarker would enable effective treatment. Obtaining a biomarker that is modified in the first hours would be very valuable and would allow a more effective treatment. Of all the biomarkers studied so far for the diagnosis of sepsis, none of them has high sensitivity and specificity, and for this reason research in this field continues.

Sepsis is a time-dependent process in which early detection and initiation of appropriate antimicrobial therapy are crucial for a better prognosis. Obtaining a biomarker that is modified in the first hours would be very valuable and would allow more effective treatment. Of all the biomarkers studied so far for the diagnosis of sepsis, none of them have high sensitivity and specificity, so research is still ongoing.

In this study the CPDs reported by the BC 6800 Plus Mindray® equipment have been evaluated and the results show that there are statistically significant differences for some of them ($p<0.05$). MON-X and NEU-Y stand out as the most relevant CPD parameters in the prediction of sepsis with AUC values on the ROC curve of 0.729 and 0.724 respectively, reflecting the production of changes at the structural level and cellular complexity in monocytes and nucleic acid content/cellular activation in neutrophils with an area under the ROC curve better than the reference biomarker studied, procalcitonin, with AUC = 0.650.

PCT, widely used in clinical practice, has the disadvantage that it does not rise until 6-12 hours after the presence of the stimulus (infectious in this case), and that it also rises in many other circumstances, so it has a low specificity as a biomarker of sepsis.[2] Its kinetics allow adequate seriation, and it is known that its levels correlate with the severity of the patients, where increasing levels are related to bacteremia and worse prognosis. For this reason, being the reference biomarker, PCT concentrations were studied in the septic patients in the study; 51.2% of the patients had PCT values greater than or equal to 2 ng/ml and of these patients, 26.8% had values greater than or equal to 10 ng/ml associated with worse prognosis and greater degree of organ failure. Likewise, blood culture, widely used for the diagnosis of bacteremia, also has the disadvantage of being a slow technique, with a high probability of contamination and delay in obtaining the results, which adds to the need for better biomarkers in sepsis.

Since sepsis triggers a response by the immune system, especially innate immunity (first line of defense) where leukocytes are the fundamental components of this system, new lines of marker research focus on cellular and humoral immunity, on the quantification of the different cell types and the changes they may undergo in septic patients. The new hematological analyzers such as the Mindray® BC 6800 Plus used to carry out this study, in addition to the basic hemogram, allow us to obtain detailed information on the morphological and functional modification of activated leukocytes in response to infection through the parameters in CPD research, which numerically provide us with rapid and accurate information regarding all the characteristics measured in these cells (cellular complexity, nucleic acid content and cell volume). Any condition that alters leukocytes can affect CPD values and through these parameters we can observe the changes that occur. Most of the studies performed in this field so far have been carried out using the hematological analyzer of the Sysmex® laboratory, since it is one of the few that incorporate CPD parameters.[15,18]

These parameters prove to be interesting in several aspects as biomarkers, in addition to providing information on changes in leukocytes in a quantitative way, they are obtained very quickly and more accurately during automated differential analysis without additional sample requirements, in an objective and cost-effective manner, They are considered very advantageous when working and analyzing in the laboratory, being useful for the management of hematological pathology, neoplasm and infection, being postulated as predictive and novel parameters in the detection of infection and sepsis.[20]

Regarding the results obtained from CPD in this study, they are in agreement with some published studies[2,9,10,12] where of the CPD parameters studied, they suggest that MON-X and NEU-Y parameters may provide useful information in the management of septic patients and be of CPD the best candidates as biomarkers. The limitations of our study, it is a retrospective study and therefore has the typical limitations of these studies, such as heterogeneity of data collection and population. Another limitation is the lack of a sepsis coding system in our hospital, as not all patients can be collected, only if indicated on request. And an important limitation was the time of availability of the equipment in our laboratory, which was only the indicated months and we could not process more samples. We are working on a prospective study in the near future regarding CPD and sepsis parameters.

## Conclusion

In conclusion, diagnosing sepsis early with certainty remains a challenge for clinicians even today. Clinical laboratories conduct tests for biomarkers that can help in the early diagnosis and subsequent follow-up of the infection in patients. This study demonstrates that CPDs, namely MON-X and NEU-Y, are useful in the early diagnosis of sepsis.

## Acknowledgements

The authors acknowledge Mindray® laboratory for making their equipment available for a certain period of time, which allowed this study to be carried out.

## Conflicts of interest

The author declares no potential conflicts of interest.

## Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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**Citation:** Portell RIM, Alarcón RR, Benayas BMP, et al. Analysis of leukocyte cell population data (CPD) as biomarkers in the diagnosis of sepsis. *Hematol Transfus Int J.* 2022;10(2):33–37. DOI: 10.15406/htij.2022.10.00278