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Evaluation of Biomarkers in Patients with Sepsis Diagnosis in Pediatric Intensive Care Unit

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Introduction: Sepsis is one of the leading causes of mortality and morbidity in intensive care units. In this study, we aimed to investigate the etiological cause, focus of infection, culture sample results, and inflammatory markers among patients treated for sepsis at pediatric intensive care units (PICUs).
Materials and Methods: We retrospectively reviewed the medical records of 70 patients aged 1 month to 18 years who were treated for sepsis at PICU between January 2014 and May 2019.
Results: The median age of the patients was 37 months. The most common underlying etiology was respiratory failure (70%). The most common site of infection causing sepsis was the respiratory system (n:40, 57%). The most commonly isolated agents were Proteus mirabilis and Acinetobacter baumannii. Whereas C reactive protein (CRP) was normal at the time of the diagnosis of sepsis in 28.5% (n=20) of the patients, procalcitonin (PCT) was elevated in all of them. A comparison of the laboratory parameters in the first 24 hours after the diagnosis of sepsis and at the end of the treatment revealed a significant difference between White blood cell (WBC) count, neutrophil-lymphocyte ratio (NLR), the levels of C reactive protein (CRP) and Procalcitonin ($p<0.05$). In addition, positive correlations were detected between NLR, CRP and PCT ($p=0.036$, $p=0.012$/ $r=0.251$, r:0.299, respectively).
Conclusion: We believe that PCT, CRP, and NLR can be used as biomarkers for monitoring patients with sepsis.
Keywords: CRP, NLR, PICU, procalcitonin, sepsis

Introduction

Sepsis is one of the leading causes of mortality and morbidity in intensive care unit. Multiorgan failure and death may occur unless the infection causing sepsis is effectively treated. Thus, it is of vital importance to have a thorough knowledge of sepsis and start appropriate treatment as quickly as possible (1, 2).

Sepsis is a clinical syndrome characterized by systemic inflammatory response syndrome, which is associated with infection-mediated immune system abnormalities, microcirculatory disorders, and end-organ failure. It has complex pathophysiology mediated by cytokine release, and it results from the effects of the circulating products of bacteria originating from constant

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bacteremia. There are some clues that the pathophysiology of pediatric sepsis is multi factorial, thus no single pathogen, mediator, or pathway is the sole culprit (3-6).

The introduction of advanced pediatric intensive care procedures, guidelines for early diagnosis and treatment, and support programs have all contributed to lower sepsis-related pediatric mortality, particularly in developed countries (7). Many laboratory parameters are used to diagnose inflammatory diseases and to monitor immune system response. Several specific laboratory tests determine the type and severity of an ongoing infection; however, only a few parameters exist for monitoring critically ill patients and assessing their treatment response (8-13).

In the present study, we aimed to investigate the effects of the etiological cause, focus of infection, culture sample results, and inflammatory markers on monitoring patients treated for sepsis at Dicle University Faculty of Medicine, Department of Pediatrics, Pediatric Intensive Care Units between 2014 and 2019.

Materials and Methods

This study enrolled 70 patients of any sex and age between 1 month and 18 years who were treated for sepsis at Dicle University Faculty of Medicine, Pediatric Intensive Care Unit (PICU) between January 2014 and May 2019. The patients' clinical and laboratory data were retrospectively obtained from the medical records and available digital media. We recorded full blood count parameters, C-reactive protein (CRP), procalcitonin, culture samples, neutrophil-lymphocyte ratio (NLR), thrombocyte lymphocyte ratio (PLR), and other laboratory parameters, which were studied in the first 24 hours after the diagnosis of sepsis and immediately after the treatment for sepsis was completed at the Pediatric Intensive Care Unit. NLR and PLR were calculated from the full blood count data.

Full blood count samples were collected in tubes containing 1-2 ml EDTA and studied with CELL DYN 3700 Hematology Analyzer device. Procalcitonin was studied with a RADIOMETER AQT90 device using the immune assay method; a level above 0.1 mg/dl according to the reference value was considered to be elevated. CRP was studied with nephelometer (SIEMENS) NnII model device using the nephelometry technique, with the normal reference range being 0-0.5 mg/dl and levels above >0.5 mg/dl being considered high. Blood cultures were obtained at a volume of at least 3 ml under sterile conditions. The samples were studied with the BACTEC FX fully automatic blood culture system at the microbiology laboratory. Aerobic blood culture samples were monitored in the device for 5 days. A sample was prepared from a culture sample signaling proliferation, and a preliminary microbiological identification was performed with Gram staining of that sample. The colonies that grew in the growth medium were identified by genus and/or species with Maldi Biotyper 3.1 (Bruker, Germany) system using the MALFU TOF mass spectrometry technique. Among hematological parameters, leucocyte count was evaluated by age. The values below the lower limit of normal by age were defined as leukopenia, and those above the lower limit of normal by age were defined as leukocytosis. Body temperature above 38.5 °C was defined as hyperthermia and below 36.0 °C as hypothermia.

Patients with the following features were excluded: contaminated blood culture receiving chemotherapy/glucocorticoids, HIV infection, underlying immune deficiency syndrome.

Sepsis was diagnosed based on the criteria established by the International Pediatric Sepsis Consensus Conference dated 2005 (7). These criteria are as follows;

SIRS: The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

1. A core temperature of 38.5°C or 36°C.
2. Tachycardia, defined as a mean heart rate 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to a 4-hr time
3. Mean respiratory rate 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or 10% immature neutrophils

Sepsis: SIRS in the presence of or as a result of suspected or proven infection.

Ethical statement

The study was conducted in compliance with the criteria of the Helsinki Declaration. All the participants (family members) accepted the informed/written consent. It was approved by the Dicle University Faculty of Medicine Institutional Ethics Committee (Date: 23.05.2019 No: 200).

Statistical Method

Statistical analysis of the data was done using the IBM Statistics Version 22 package program with 95% confidence. Chi-Square test, Fisher's exact Chi-Square test, and Chi-Square Trend were used for comparison of categorical data between groups, and Mann-Whitney U statistical analyzes were used for comparison of continuous variables between groups since the data were not suitable for normal distribution. The power of NLR values to predict bacteremia with ROC analysis; The survival times according to bacteremia, medical/surgical status, and NLR groups were evaluated by Kaplan Meier survival analysis, $p<0.05$ was considered significant.

Results

Out of 70 patients enrolled in the study, 36 (51.4%) were male, and 34 (48.6%) were female ($p>0.05$). The median age of the patients was 37 (min 3-max 188) months. The age range of the study population was 0-5 years for 49 patients (70%); 5-10 years for 18 (25.7%); and 10-18 years for 3 (4.3%). The most common indication for PICU admission was respiratory failure(70%). The indications for PICU admission were shown in Table 1, with some patients having more than one indication.

Table 1. Indications for intensive care unit admission

Parameters	n	%
Respiratory Failure	49	70
Spinal Muscular Atrophy	9	12.6
Convulsion	6	8.5
Cerebral Palsy	6	8.4
Hypoxic-İschemic Encephalopathy	5	7.1
Laringomalacia / Tracheomalacia / Bronchomalacia	4	5.6
Down Syndrome	4	5.6
Neurometabolic Disease	3	4.2
Neuropathy & Myopathy	3	4.2
Trauma	2	2.8
Intracranial Bleeding	2	2.8
Bronchiolitis Obliterans	2	2.8
Shunt Infections	2	2.8

* More than one etiology was found in the same patient

The most common foci of infection-causing sepsis in decreasing frequency were respiratory infections (n: 40, 57%), urinary system infections (n:14, 20%), circulatory system infections (n:9, 12.8%), and gastrointestinal system infections (n:9, 12.4%) (Table 2).

Table 2. Focus of infection-causing sepsis

Focus of Infection	N	%
Respiratory System	40	57
Urinary System	14	20
Gastrointestinal System	9	12.8
The Circulatory System	9	12.8
Others	2	2.8

* More than one focus of infection existed in 4 (4.2%) patients

A microorganism proliferated in the culture samples of 52 (74.2%) of 70 patients while no proliferation occurred in the samples of 18 (25.8%) patients. Culture positivity was detected in the tracheal aspirate fluid in 44.2% of the patients, urine samples in 27%, blood samples in 17.3%, stool samples in 17.3%, and other samples in 2%. An analysis of microorganism proliferation in culture samples showed that Proteus mirabilis proliferated in 9 (17.3%) patients, Acinetobacter baumannii in 8 (15.3%), Carbapenem-resistant enterococci (CRE) in 8 (15.3%), Pseudomonas aeruginosa in 7 (13.4%), Methicillin-resistant staphylococcus aureus (MRSA) in 6 (11.5%), Klebsiella pneumoniae in 4 (7.7%), E.coli in 4 (7.7.%), Candida albicans in 4 (7.7%), Vancomycin-resistant enterococci (VRE) in 2 (3.8%), and other microorganisms in 2 (3.8%) (Figure 1).

Two patients were found to have multiple simultaneous proliferation in different culture samples. An analysis of the acute phase reactants in septic patients in the first 24 hours after the diagnosis of sepsis showed that 20 (28.5%) patients had CRP levels within the normal reference range and 50 (71.5%) patients had CRP levels above the normal reference range. Procalcitonin level was high in all patients (100%).

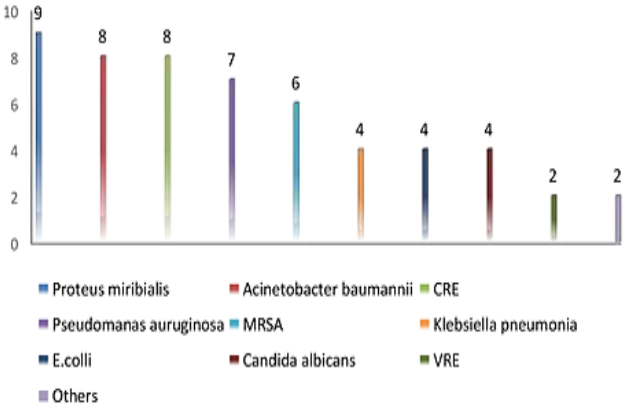


Figure 1. Distribution of the microorganisms detected in the culture samples

A comparison of the laboratory parameters measured in the first 24 hours after the diagnosis of sepsis and at the end of the treatment showed significant differences between WBC, NLR, CRP, and Procalcitonin levels ($p<0.05$, Table 3, Figure 2). There was no significant difference regarding the other parameters. A correlation analysis between NLR and the other parameters showed a positive correlation between NLR, CRP and PCT ($p=0.036$, $p=0.012$/ $r=0.251$, $r:0.299$, respectively).

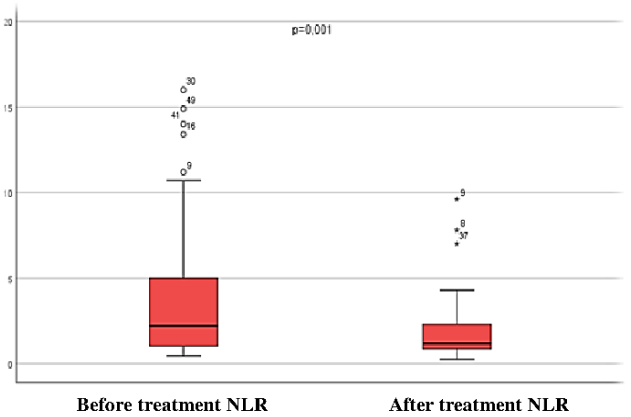


Figure 2. Comparison of pre and post-treatment NLR levels using Box plot analysis

Table 3. Comparison of the laboratory results at the time of the diagnosis of sepsis, before and after the treatment

Parameters	Before treatment *(Mean±Sd)*	After treatment *(Mean±Sd)*	P value
WBC *(10^3/uL)*	14,51±5,52	12,03±4,43	<0.001
Neutrophil count *(10^3/uL)*	8,9±5,06	33,02±227,2	0,377
Lymphocyte count *(10^3/uL)*	4,04±2,78	4,57±2,64	0,066
Hemoglobin *(g/dl)*	10,97±1,6	11,17±1,49	0,31
MPV *(fl)*	8,28±1,9	8,04±1,61	0,247
NLR	3,71±3,76	1,79±1,69	<0,001
PLR	118,3±85,4	106,49±75,33	0,335
Prokalcitonin *(ng/ mL)*	2,58±9,68	0,17±0,25	0,04
CRP *(mg/dL)*	4,55±6,51	2,1±10,11	0,029

WBC: White blood cell, **CRP**: C-reactive protein, **MPV**: Mean platelet volume, **NLR:** Neutrophil-Lymphocyte Ratio, **PLR:** Platelet-Lymphocyte Ratio. *****Pre-treatment laboratory parameters were measured in the first 24 hours after the diagnosis of sepsis was considered.

Discussion

Pediatric intensive care units are services that serve diverse groups of patients requiring a multidisciplinary approach. Mortality risk can be high in patients managed in intensive care units. Sepsis is one of the leading risk factors for increased mortality (14,15).

Pediatric intensive care units admit patients aged 1 month to 18 years for treatment. According to our literature review, Xiao et al.(16) reported that 80.8% of patients admitted to PICU for treatment of sepsis were children aged 1 month to 5 years; Navin et al. reported that the same age group comprised 68% of patients. Our study findings showed similarity with literature data, with 70% of our patients being 1 month to 5 years old. Sepsis can be observed in any age group, and care should be exercised to detect sepsis during intensive care unit follow-up of children under the age of 5 and to remember that early diagnosis may be life-saving in those patients. A review of the previous studies investigating the cause of intensive care unit admission showed that respiratory infections were the most common cause, affecting 76% of patients in the study of Xiao et al. (16), 34.6% of patients in the study of Workman et al. (17), 21% of patients in the study of Rey et al. (10), and 36.8% of patients in the study of Aygün (13). Similarly, our study found that respiratory infections were the most common etiological cause, being responsible for 70% of PICU admissions. A separate analysis of the former studies regarding the focus of the infection-causing sepsis showed that respiratory and urinary infections were the most common foci (10,16,17). In our study, the most common foci of infection-causing sepsis, in decreasing order of frequency, were respiratory and urinary infections. It is of vital importance to determine the foci causing sepsis and to start empirical antibiotic therapy as fast as possible at an early stage. It should be kept in mind that the respiratory and urinary systems are typically responsible for sepsis, and empirical therapy against these foci should be initiated until culture results become available.

Variable results have been reported in the literature regarding the detection of micro organisms in culture samples of children with sepsis. Katu et al. (18) found culture positivity in 66.7% of patients, Demirdağ et al. (19) in 77%,

and Workman et al. (17) in 67%. We detected culture positivity in 74.2% of our patients. The most commonly isolated bacteria in our patients, in decreasing order of frequency, were Proteus mirabilis, Acinetobacter baumanii, Pseudomonas aeruginosa, Carbapenem-resistant enterococci and Methicillin-resistant staphylococcus aureus (MRSA). Using blood samples to diagnose sepsis is of great importance for preventing mortality in critically ill patients with a life-threatening infection. However, it is not always a simple task to obtain an adequate blood volume for cultures in children and infants. Furthermore, possible contamination of blood culture samples especially by skin saprophytes despite efforts to reduce contamination continues to be an important clinical problem. Despite several challenges posed by blood cultures, they continue to guide clinicians for the treatment of sepsis for the sake of efficacy and, if necessary, modification of the treatment.

Sepsis is a pathophysiological process rather than a specific syndrome and is too complex to be defined by a single parameter. A perfect marker is yet to be found to diagnose sepsis. Since the clinical signs and symptoms of sepsis are not specific and may frequently vary, there is a potential for some biomarkers to be used for determining the severity of sepsis, clinical monitoring, and assessing treatment response. There are a plethora of studies in this field (8-12, 19).

Among such biomarkers, PCT and CRP are the most widely used ones. Procalcitonin is a protein containing 116 amino acids, which is a precursor protein of the calcitonin hormone released by the medullary neuroendocrine C cells of the thyroid gland, typically in response to a high calcium level in blood. Procalcitonin level is thought to increase 2 hours after the onset of an infection, to become detectable by 4 hours, to peak at 6 hours, and to maintain its level for 8-24 hours. Thanks to such favorable kinetics, PCT is an ideal candidate for use as a biomarker (20). C-reactive protein (CRP) is a pentameric acute-phase protein of hepatic origin circulating in the blood. Serum CRP level rises dramatically in the case of inflammation, tissue injury, and cytokine-mediated reaction against an infection. Quantification of acute-phase reaction may provide clinical information about the presence of tissue injury or inflammation as well as the treatment response (21). Serum CRP level is elevated by all inflammatory processes including infections and sepsis. Despite being a classical and sensitive biomarker of inflammation, CRP cannot distinguish bacterial and other types of inflammatory infections (20). Using PCT for the diagnosis of sepsis may offer an advantage since it may have better specificity for bacterial infections, unlike many other biomarkers that may be elevated in conditions other than bacterial infection (22).

Bustos et al. (8) reported that, unlike CRP and lactate, PCT was a good predictor of mortality and septic shock, being capable of categorizing patients by the severity of sepsis at the time of pediatric intensive care unit admission. In a study in adults, Luzzani et al. (22) found that PCT was a better marker of sepsis and showed a better correlation to the severity of infection and organ dysfunction than CRP. Rey et al. (10) found that PCT was a better diagnostic marker than CRP among critically ill children with sepsis. Nargis et al. (23). studied the specificities of PCT and CRP in patients treated for sepsis and reported a specificity of 72.2% for PCT and 33.3% for CRP.

Our comparison of the laboratory parameters measured in the first 24 hours after the diagnosis of sepsis and at the end of the treatment detected significant differences in WBC, CRP, PCT, and NLR levels. While 20 (28.5%) of our patients had a normal CRP level and 50 (71.5%) of them had an elevated CRP level in the first 24 hours of sepsis, all of our patients had an elevated PCT level. These results support the literature data indicating that PCT rapidly rises and reaches a detectable level in blood at an earlier stage than CRP; they also suggest that PCT may be a better parameter than CRP for assessing bacterial sepsis. In addition, we believe that CRP and PCT should be effectively used to monitor patients with sepsis and to assess their treatment response.

Neutrophils are the first-line cellular defense cells of innate immunity against infectious agents. Lymphocytes play an important role in adaptive immunity. The immune response against various triggers causes an increase in neutrophil count and a decrease in lymphocyte count. Neutrophil lymphocyte ratio (NLR) is a readily available, rapidly obtained, and inexpensive parameter. Several researchers have studied NLR with CRP and PCT as an important marker for an early diagnosis of bacteremia and assessment of the outcomes of sepsis (24, 25, 26). Several studies have shown that, in comparison to standard diagnostic biomarkers, NLR made meaningful contribution to the early prediction of sepsis (25-27). Furthermore, several studies in infants and newborns have indicated that NLR was an accurate predictor of sepsis along with CRP (28,29). We detected a significant difference between the NLR levels at the onset of sepsis and at the end of the treatment; we also demonstrated that NLR had a positive correlation with CRP and PCT. We believe that the neutrophil-lymphocyte ratio can be used for disease monitoring similarly to CRP and PCT.

Conclusion

Respiratory and urinary infections are the most common foci of infection among patients treated for sepsis at pediatric intensive care units. The proliferation of microorganisms in culture samples is time-consuming and sometimes even not possible; we, therefore, believe that empirical antibiotic treatment should be commenced as soon as possible after determining the most probable focus and microorganism.

We believe that PCT, CRP, and NLR, the effectiveness of which has been recently shown, may be used as biomarkers to support the diagnosis of sepsis and to assess treatment efficacy. In the light of our results, we may suggest that PCT is a more effective marker than CRP in the first 24 hours among patients suspected to have sepsis. In conclusion, markers such as PCT, CRP, and NLR should not be used alone as the definitive tests but should be used in conjunction with physical examination, clinical features, and microbiological culture results to diagnose sepsis and to assess treatment response.

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Conflicts of Interest

The authors declared no conflict of interest for the present article.

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