Original Investigation / *Özgün Araştırma*

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Predictive Values of Biomarkers in Identifying Bacterial and Fungal Nosocomial Bloodstream Infections in Children

Çocuklarda Bakteriyel ve Fungal Nozokomiyal Kan Dolaşımı Enfeksiyonlarının Tanımlanmasında Biyobelirteçlerin Öngörücü Değerleri

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Abstract

Objective: Nosocomial bloodstream infections have become a major concern in pediatric intensive care units. Early diagnosis and treatment are important as these infections have high morbidity and mortality. This study aims to determine the predictive values of complete blood count parameters, C-reactive protein, and procalcitonin in determining the causative agent of nosocomial bloodstream infections.

Material and Methods: We retrospectively evaluated all patients diagnosed with nosocomial bloodstream infections in our pediatric intensive care unit over an 18-month period. Predictive values of the complete blood count, C-reactive protein, and procalcitonin to determine the presence of gram-positive, gram-negative, or *Candida* spp. infections were calculated.

Results: Gram-positive bacteria were the most common microorganisms causing nosocomial bloodstream infections (n=41, 41%). The mean white blood cell (11.5 x 10^9/L) (p< 0.001), polymorphonuclear leukocyte (6.36 x 10^9/L) (p= 0.008), and lymphocyte (3.47 x 10^9/L) (p= 0.02) counts of patients with bacterial infections were significantly higher than those with *Candida* spp. infections. The CRP levels were significantly higher in gram-negative infections (74 mg/L) compared to gram-positive (8.8 mg/L) infections (p= 0.009).

Conclusion: White blood cell and its subgroups counts were found to be significantly higher in bacterial agents than *Candida* spp. infections. However, white blood cell count and C-reactive protein were the most effective parameters in differentiating gram-negative infections from gram-positive and *Candida* spp. infections.

Keywords: Child, nosocomial infection, bacterial agent, *Candida* spp.

Öz

Giriş: Nozokomiyal kan dolaşımı enfeksiyonları, çocuk yoğun bakım ünitelerinde önemli bir sorun haline gelmiştir. Bu enfeksiyonların morbidite ve mortalitesi yüksek olduğundan erken tanı ve tedavi önemlidir. Bu çalışma, nozokomiyal kan dolaşımı enfeksiyonlarına neden olan etkenin belirlenmesinde tam kan sayımı parametreleri, C-reaktif protein ve prokalsitoninin prediktif değerlerini belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: Çalışmanın planlandığı 18 aylık dönemde çocuk yoğun bakım ünitemizde takibi sırasında nozokomiyal kan dolaşımı enfeksiyonu gelişen tüm hastaları geriye dönük olarak değerlendirdik. Gram-pozitif, gram-negatif veya kandida enfeksiyonlarının ayrımını yapabilmek için tam kan sayımı, C-reaktif protein ve prokalsitoninin tahmin değerleri hesaplanıldı.

Bulgular: Gram-pozitif bakteriler, nozokomiyal kan dolaşımı enfeksiyonlarına neden olan en yaygın mikroorganizmalardı (n= 41, %41). Bakteriyel enfeksiyonlu hastaların ortalama beyaz kan hücresi sayısı (11.5 x 10^9/L) (p< 0.001), polimorfonükleer lökosit sayısı (6.36 x 10^9/L) (p= 0.008) ve lenfosit sayısı (3.47 x 10^9/L) (p= 0.02) kandida enfeksiyonu olanlara göre istatistiksel olarak anlamlı derecede daha yüksekti. CRP düzeyleri ise gram-negatif bakteriyel enfeksiyonlarda (74 mg/L), gram-pozitif (8.8 mg/L) enfeksiyonlara göre istatistiksel olarak anlamlı yüksekti (p= 0.009).

Sonuç: Bakteriyel ajanlarda beyaz kan hücresi ve alt gruplarının sayısı *candida* enfeksiyonlarına göre anlamlı olarak daha yüksek bulundu. Bununla birlikte, beyaz kan hücresi sayısı ve CRP, gram-negatif enfeksiyonları gram-pozitif ve kandida enfeksiyonlarından ayırmada en etkili parametreler olarak belirlendi.

Anahtar Kelimeler: Çocuk, nozokomiyal enfeksiyon, bakteriyel ajan, kandida

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Introduction

Patients in pediatric intensive care units (ICUs) are more susceptible to nosocomial infections resulting from invasive devices and procedures in the critically ill. Bloodstream infections are the most common cause of nosocomial infections in pediatric ICUs and an important cause of in-hospital morbidity and mortality (1,2). Despite the advances in antimicrobial therapy, nosocomial bloodstream infections can prolong hospital stay and increase mortality (2). Indeed, early diagnosis and treatment are essential to reduce mortality (3). These infections are most common in children less than one-year-old, with gram-positive bacteria as the commonest causative pathogens (2,4).

A few studies have shown the significance of biomarkers, such as white blood cells (WBCs), C-reactive protein (CRP), and procalcitonin (PCT), in predicting nosocomial infections in adult populations (5-7). However, fewer studies have reported biomarkers in pediatric patients (8-10). Biomarkers to predict the infectious agent before receiving blood culture results are not yet available. Therefore, ampirical antibiotics are used to reduce the mortality and morbidity risk when nosocomial infections are suspected (7). However, if the ampiric antibiotic is not effective on the causative infectious agent, the patient's health status may deteriorate rapidly.

This study aimed to determine the predictive value of complete blood count (CBC), CRP, and PCT levels in determining the causative agent of nosocomial bloodstream infections in pediatric ICU patients.

Materials and Methods

Study Design and Participants

This is a retrospective study of patients between one month and 18 years of age who developed nosocomial bloodstream infection during follow-up in a pediatric ICU between January 2018 and June 2019. Bacteremia and fungemia diagnoses were made according to the Centers for Disease Control and Prevention (CDC) criteria (11). Nosocomial bacteremia and fungemia were defined as follows:

1. Fever≥ 38°C, chills or hypotension, (for patients< 1 year= fever≥ 38°C/ hypothermia, apnea, or bradycardia) and not related to other infection sites.
2. Blood culture isolation of one or more pathogens outside the skin flora or at least one of the following if the pathogen(s) is from the skin flora:

a. two or more separate positive blood cultures,

b. one positive blood culture in the presence of an intravascular device.

Nosocomial bloodstream infection was defined as the presence of any microorganism cultured in the blood taken under sterile conditions during clinical infection investigation, 48 hours after admission to the ICU. Since the patient reports were reviewed retrospectively, the information of the patients who did not have microorganism growth in the blood culture taken with the suspicion of nosocomial bloodstream infection could not be reached. Patients with polymicrobial growth in the blood culture, and any second-time infections in the same patient were excluded from the study. One doctor reviewed each medical record and extracted baseline epidemiological and clinical data, including age on admission, sex, and results of the complete blood count, CRP, PCT, urine analysis, urine culture, blood culture, and chest radiography. Patients were divided into three groups depending on their blood cultures= gram-negative, gram-positive, and *Candida* spp. infection groups. Due to the retrospective nature of the study, informed consent was not required from the patients, but any patient identifying features were removed from the data collected. Ethical approval was obtained from the local ethics committee (21.01.2021/274).

Laboratory Evaluations

At our hospital, complete blood count parameters are made using an automated whole blood cell counter Sysmex XN-9000 analyzer (Sysmex Corporation, Kobe, Japan). The CRP is measured using a standard turbidimetric assay. Procalcitonin is measured by electrochemiluminescence immunoassays. The BacTec 9240+ continuous monitoring blood culture system is used for blood culture evaluation.

Statistical Analysis

Descriptive statistics were used to summarize the data obtained. Mean ± standard deviation or median/range were used for continuous variables. Categorical variables were summarized as frequencies and percentages. When comparing two independent groups, the independent samples t-test was used when numerical variables showed normal distributions, and the Mann-Whitney U test was used for non-normal distributions. The one-way ANOVA test was used to compare more than two independent groups when the numerical variables showed normal distributions and the Kruskal-Wallis H test for non-normal distributions. Pearson's Chi-squared or Fisher's exact test were used to compare differences between categorical variables. Statistical analysis was performed with Jamovi Software Version 1.0. (Retrieved from https://www.jamovi.org). The DeLong method, 95% confidence interval, standard error, and area under the curve (AUC) were calculat-

ed with MedCalc Statistical Software Package. The significant level for all variables was considered. p-value< 0.05.

Results

Between January 1, 2018, and June 30, 2019, there were 1600 admissions to our pediatric ICU. Microorganism growth was detected in 145 of these patients whose blood culture was taken with suspicion of nosocomial bloodstream infection during hospitalization. Twenty-five patients whose culture growth was accepted as contamination and 20 patients who developed nosocomial bloodstream infection for the second time were excluded from the study. Of these 100 patients diagnosed with nosocomial bloodstream infection, 41 (41%) were gram-positive, 35 (35%) gram-negative, and 24 (24%) *Candida* infections. The median age of patients who developed nosocomial bloodstream infections was eight months (3.9-12 months). The most common cause for hospitalization of patients with nosocomial infections were lower respiratory tract infections (bronchiolitis and pneumonia) 70 (70%), followed by sepsis 9 (9%), metabolic diseases 8 (8%), central nervous system infections 3 (3%). The remaining 10 patients were spinal muscular atrophy and cerebral palsy who presented with respiratory distress.

Seventy-five patients (75%) were hospitalized for more than seven days at the time of diagnosis of nosocomial infection. When gram-negative, gram-positive, and *Candida* spp. infections were compared in terms of length of hospital stay no significant difference was found (p= 0.257). All patients were receiving broad-spectrum antibiotic therapy for their primary disease at the time of diagnosis of nosocomial bloodstream infection; and 56 (56%) had central venous catheters. Forty-eight (85.8%) of these patients had a central venous catheter for more than 96 hours during nosocomial bloodstream infections (Table 1).

The laboratory parameters, according to the microorganism group, are shown in Table 2. White blood cell (p< 0.01) and polymorphonuclear leukocyte (PMNLs) (p= 0.019) in *Candida* spp. infections was lower than the gram-positive and gram negative bacterial infections. However, the CRP value was found to be significantly lower in gram-positive agents compared to the other two agent groups (p= 0.004).

The mean WBCs (p< 0.001), PMNLs (p= 0.08), lymphocyte (p= 0.02), and platelet (p= 0.023) counts of those with bacterial infections were significantly higher than *Candida* infections. When both bacterial agent groups were compared with *Candida* spp. groups, no significant difference was found in the CRP value (p= 0.134) (Table 3). Comparisons of the WBC, PMNLs, lymphocyte, and CRP values of the patients in pairs are shown in Table 4. The CRP values of patients in the gram-negative groups were significantly higher than the gram-positive groups (p= 0.009).

In the ROC curve analysis, the WBC value for predicting bacterial infection was found to be >9.470 x 10^9 with 77.63% sensitivity and 62.5% specificity (AUC=0.747, p< 0.001), while the PMNLs predicting value for bacterial infection was found to be >5.33 x 10^9/L, with 59.21% sensitivity and 70.83% specificity (AUC= 0.681, p= 0.003). Moreover, the lymphocyte count for predicting bacterial infection was >2.43 x 10^9/L with 78.95% sensitivity and 54.17% specificity (AUC= 0.658, p= 0.021), while the platelet count for predicting bacterial infection was >236 x 10^9/L, with 60.53% sensitivity and 75% specificity (AUC= 0.655, p= 0.025). The predictive value of CRP to distinguish gram negative bacterial agent from gram positive agent, with 82.86% sensitivity and 53.66% specificity, was 102 gr/L (AUC= 0.697, p< 0.001). The effectiveness of hemoglobin, PMNL/lymphocyte, platelet/lymphocyte, red cell distribution width, mean platelet volume, and procalcitonin in predicting

Table 1. Comparison of patient age and other clinical parameters in terms of growing microorganism groups

	Gram (+) agent 41 (41%)	**Gram (-) agent 35 (35%)**	***Candida* spp. 24 (24%)**	**p**
Age (month)	8 months * (3-12 months)	8 months* (5.5-10 months)	7.2 months* (3-29 months)	0.74
Length of stay 3-5 days 5-7 days >7 days	 10 (24.4%) 3 (7.3%) 28 (68.3%)	 2 (5.7%) 4 (11.4%) 29 (82.9%)	 4 (16.7%) 2 (8.3%) 18 (75%)	0.257
Presence of catheter No Yes	 27 (65.9%) 14 (34.1%)	 10 (28.6%) 25 (71.4%)	 7 (29.2%) 17 (70.8%)	**0.01**
Catheter time 0-96 hours >96 hours	 2 (25%) 12 (25%)	 3 (37.5%) 22 (45.8%)	 3 (37.5%) 14 (29.1%)	**0.02**

* Median (25-75%).

Table 2. Growing microorganism groups and laboratory parameters

	Gram (+) n= 41	**Gram (-) n= 35**	***Candida* n= 24**	**p**
WBCx10^9/L	11.05 (9.74-16.03)	12.57 (9.93-17.89)	8.76 (6.125-11.19)	**<0.001**
Hb g/L	104 ± 18	100 ± 9	100 ± 16	0.523
PMNL x 10^9/L	5.81 (3.99-9.17)	6.5 (4.27-11.81)	4.74 (2.63-6.2)	**0.019**
Lymphocyte x 10^9/L	3.65 (2.68-4.56)	3.26 (2.4-3.98)	2.385 (1.98-3.51)	0.040
Platelet x 10^9/L	346 (146-417)	270 (177-396)	181 (875-250)	0.059
PMNL/Lymph	1.7 (1.1-3.3)	2.0 (1.4-4.2)	1.8 (1.0-3.8)	0.458
Plt/Lymph	73.5 (41.0-107.0)	92.2 (60.1-125.2)	84.7 (33.9-110.4)	0.513
RDW	15.2 (14.2-16.4)	15.7 (14.6-16.4)	15.6 (14.3-16.3)	0.550
MPV fL	9.7 (9.2-11.1)	9.6 (9.2-10.2)	10.5 (9.5-11.2)	0.195
C-reactive protein mg/L	8.8 (2.1-85.0)	74.0 (19.8-155.0)	66.3 (30.4-106.0)	**0.004**
Procalcitonin ng/mL	0.5 (0.2-2.4)	1.6 (0.4-7.8)	0.6 (0.3-1.6)	0.27

WBC: White blood cell, Hb: Hemoglobin, PMNL: Polymorphonuclear leukocyte, RDW: Red cell distribution width, MPV: Mean platelet volume.

Table 3. Laboratory parameters of bacterial and fungal agents

	Bacterial agent n= 76	***Candida* n= 24**	**p**
WBC x 10^9L*	11.54 (9.79-16.9)	8.76 (6.12-11.19)	**<0.001**
Hb g/L**	102 ± 15	100 ± 16	**0.617**
PMNL x 10^9/L*	6.36 (4.09-11.45)	4.74 (2.63-6.20)	**0.008**
Lymphocyte x 10^9/L*	3.47 (2.54-4.53)	2.38 (1.98-3.51)	**0.020**
Platelet count x 10^9/L*	306 (151.25-401)	181 (875-250.5)	**0.023**
PMNL/lymphocyte*	1.9 (1.1-3.5)	1.8 (1.0-3.8)	0.818
PLT/lymphocyte*	79.2 (44.5-118.6)	84.7 (33.9-110.4)	0.859
RDW*	15.6 (14.3-16.4)	15.6 (14.3-16.3)	0.698
MPV fL*	9.7 (9.2-10.5)	10.5 (9.5-11.2)	0.127
CRP g/L*	37.2 (4.9-104.3)	66.3 (30.4-106.0)	0.134
PCT ng/mL*	0.7 (0.3-4.4)	0.6 (0.3-1.6)	0.657

* Median (25-75%).
**Mean ± standard deviation.
WBC: White blood cell, Hb: Hemoglobin, PMNL: Polymorphonuclear leukocyte, RDW: Red cell distribution width, MPV: Mean platelet volume, CRP: C-reactive protein, PCT: Procalcitonin, PLT: Platelet count.

Table 4. Intergroup comparison

	WBC P	**PMNL P**	**Lenfosit P**	**CRP P**
Gram (+) - Gram (-)	0.666	0.656	0.505	**0.009**
Gram (+) - *Candida*	**0.009**	0.109	**0.042**	**0.021**
Gram (-) - *Candida*	**0.001**	**0.013**	0.206	0.987

WBC: White blood cell, PMNL: Polymorphonuclear leukocyte; CRP: C-reactive protein.

the infective agents were not statistically significant (p> 0.05).

Discussion

Early diagnosis and treatment is crucial for improving the clinical course of nosocomial bloodstream infections because of the associated high morbidity and mortality. We evaluated the predictive values of laboratory parameters in pediatric patients with nosocomial bloodstream infections to distinguish between gram-positive, gram-negative, and *Candida* spp. infections. Since gram-negative bacterial and *Candida* spp. infections are more dangerous in terms of morbidity and mortality, predicting these factors before blood culture results will save time for clinicians who treat critical patients. White blood cell, PMNL, lymphocyte, and platelet counts were found significantly higher in bacterial infections than *Candida* spp. infections. The most effective laboratory parameters in distinguishing gram-negative bacterial infections from gram-positive and *Candida* spp. infections were determined as CRP and WBC.

Most literature related to nosocomial bloodstream infections are from adult ICU patients; however, the literature in children is sparse (10,11). Nosocomial bloodstream infections are more common under 1-year of age, and the frequency of nosocomial infection is inversely related to age (12-14). Consistent with the literature, the median age of our patient group was eight months.

Consistent with the literature (15,16), the most common reason for our patients' hospitalization in PICU was lower respiratory tract infections. In addition, 75% of nosocomial infections in our PICU occured in patients hospitalized for more than seven days. Although there are publications stating that the length of stay in hospital is not a risk factor for the development of nosocomial bloodstream infection (1), there are also publications reporting that it is seen more frequently after seven days of hospitalization (2).

The presence of arterial and central venous catheters increases the risk of developing nosocomial bloodstream infections (1). Central venous catheters were present in 56% of our patients, and 85.8% of these patients had a catheter for more than 96 hours.

It has been reported that the most common cause of nosocomial bloodstream infections were gram-positive bacterial infections, with gram-negative bacterial infections being the second commonest cause (2,4,12). We found similar results in our study.

In one study (8) conducted in an adult ICU, the PCT levels were higher in patients with gram-negative sepsis than those with gram-positive and fungal sepsis. In other studies on adults with suspected sepsis, PCT levels were found to be significantly higher in gram-negative bacterial infections compared to infection from other organisms (17,18). A study involving pediatric hematology and oncology patients also showed a lower PCT level in gram-positive bacterial infections than in gram-negative bacterial infections (9). The reason for the different inflammatory responses to different pathogens is not entirely clear. It may be explained by the fact that lipoteichoic acid or lipopolysaccharide of gram-positive or gram-negative bacteria bind to different TLRs (Toll-like receptors) expressed in human cells triggering different pathways. Gram-positive bacteria activate the TLR2 pathway, whereas gram-negative bacteria the TLR4 pathway (17,19). The PCT level did not differ between the pathogen groups in our patients. This may be due to the use of broad-spectrum antibiotics during the diagnosis of nosocomial bloodstream infections.

In a study (20) evaluating nosocomial bloodstream infections in adults, the CRP and WBC levels in gram-negative bacterial infections were significantly higher than in gram-positive bacterial infections. In our study, it was observed that the WBC and PMNL values were higher in bacterial nosocomial bloodstream infections compared to *Candida* spp. infections. However, the CRP value in gram-negative bacterial infections was also significantly higher than gram-positive bacterial infections.

Our study has some limitations. First, the limited number of patients, and it was a single-center study. Second, biomarker concentrations were measured at the onset of sepsis symptoms with no further follow-up. Another limitation is the lack of information about patients whose blood cultures were taken for suspected nosocomial infection but did not have any microorganisms.

However, it is important because it gives an idea of which biomarker will be more useful in predicting the causative agent of nosocomial bloodstream infections to clinicians who follow up and treat critically ill children.

Conclusion

White blood cell, PMNL, lymphocyte counts, and CRP values were important laboratory parameters in predicting the causative agent in nosocomial bloodstream infections with high mortality and morbidity. The high WBC, PMNL, and lymphocyte values were significant in distinguishing bacterial agents from *Candida* spp. infections. In contrast, the high CRP was significant in distinguishing gram-negative infections from other agents.

Ethics Committe Approval: Ethical approval was obtained from the Kayseri City Hospital Ethics Committee (Decision no: 274, Date: 21.01.2021)

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- BÇ, HS; Design- BÇ, HS, BÖ; Supervision- BÇ, HS; Resource- BÇ, HS; Data Collection and/or Processing- BÇ, BÖ, HS; Analysis and/or Interpretation- BÇ, HS; Literature Search - BÇ; Writing- All of authors; Critical Review- All of authors.

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