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RESEARCH

The role of thrombocyte indices in early determination of sepsis agents in newborns

Yenidoğanlarda sepsis ajanlarının erken saptanmasında trombosit indekslerinin rolü

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Abstract

Purpose: Neonatal sepsis is an important cause of morbidity and mortality. The signs and symptoms of neonatal sepsis are nonspecific, and there is no ideal marker for diagnosis. Our study aimed to investigate the role of platelet indices in determining agents in sepsis.

Materials and Methods: A total of 90 records with sepsis data were examined retrospectively, demographic and clinical characteristics of gram-positive, gram-negative and Candida infection patients were evaluated by complete blood counts at the time of diagnosis and on the fifth day of infection and platelet amount (PLT), mean platelet volume (MPV), plateletcrit (PCT) and distribution width (PDW) values were compared by ROC curve analysis.

Results: No statistical difference was found between the groups in terms of gender, gestational week, birth weight, surfactant use, need for mechanical ventilator treatment, and necrotizing enterocolitis. When infection was first detected, the Area Under Curve (AUC) of PCT, PLT and MPV (without thrombocytopenia) values in detecting gram-positive bacterial infection were 0.764, 0.765 and 0.792 respectively.

Conclusion: The increase in PCT and PLT values at the time of initial diagnosis can be used to detect gram-positive bacterial infections. A decrease in MPV can be used for early diagnosis of fungal infections without thrombocytopenia.

Keywords:. : Neonatal, sepsis, mean platelet volume (MPV), plateletcrit (PCT), platelet (PLT)

Öz

Amaç: Yenidoğan sepsisi, morbidite ve mortalitenin önemli bir nedenidir. Yenidoğan sepsisinin belirtileri ve semptomları spesifik olmayıp, tanı için ideal bir belirteç bulunmamaktadır. Çalışmamız, sepsis ajanlarını belirlemede trombosit indekslerinin rolünü araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Sepsis tanısı olan toplam 90 hastanın kaydı retrospektif olarak incelenerek gram-pozitif, gram-negative ve Candida enfeksiyonu olan hastaların demografik ve klinik özellikleri karşılaştırıldı ve hastaların tanı anındaki ve enfeksiyonun beşinci günündeki tam kan sayımları değerlendirilerek, platelet sayıları (PLT), ortalama platelet hacmi (MPV), plateletkrit (PCT) ve dağılım genişliği (PDW) değerleri ROC eğrisi analizi ile karşılaştırıldı.

Bulgular: Cinsiyet, gestasyonel hafta, doğum ağırlığı, surfaktan kullanımı, mekanik ventilatör tedavisi gereksinimi ve nekrotizan enterokolit açısından gruplar arasında istatistiksel fark bulunamadı. İlk tespit edildiğinde, gram-pozitif bakteriyel enfeksiyonları tespit etmede PCT, PLT ve MPV (trombositopenisiz) değerlerinin ROC eğri-altı alan (AUC)'si sırasıyla 0,764, 0,765 ve 0,792 olarak bulundu.

Sonuç: İlk tanı anında PCT ve PLT değerlerindeki artış, gram-pozitif bakteriyel enfeksiyonları tanımak için kullanılabilir. MPV'de azalma ise trombositopeni görülmeyen mantar enfeksiyonları için erken tanı amaçlı kullanılabilir.

Anahtar kelimeler: Yenidoğan, sepsis, ortalama platelet hacmi (MPV), plateletkrit (PCT), platelet (PLT)

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INTRODUCTION

Neonatal sepsis is the leading cause of morbidity and mortality in newborns, which can occur in the first months and can be life-threatening, especially in developing countries. It is generally defined as a systemic inflammatory response that occurs as a result of a suspected or proven infection[1]. The incidence of sepsis is reported to be between 1-8.1 per 1,000 live births[2].

Symptoms are seen within the first 48 hours in early-onset sepsis, and more than one organ or system involvement can be observed; however, in late-onset sepsis, involvement can be seen as multisystem or as pneumonia, arthritis, osteomyelitis. Sepsis diagnosis is made by assessing the clinical and laboratory findings together, and since it has a unique factor in the blood culture, it can be identified[2]. Though research continues to identify reliable, rapid-resulting biomarkers to distinguish between infected and uninfected neonatal, blood culture analysis is accepted as the gold standard for diagnosis. However, this analysis is still slow today, and false positive or false negative results may occur[3].

The most common examination for diagnosis and follow-up of sepsis in all patients is blood culture analysis[4]. Thrombocytopenia [Platelet (PLT) <150 k/µl] and severe thrombocytopenia (PLT 0-30 k/µl) are common laboratory findings in neonatal sepsis, depending on the type and severity of sepsis. Platelet indices [Platelet Distribution Width (PDW), Mean Platelet Volume (MPV), Plateletcrit (PCT)] can contribute to the early diagnosis and follow-up of the organism-specific type of sepsis while awaiting cultures. As knowledge of the pathophysiological mechanisms and causation of sepsis-associated thrombocytopenia is increased, they may be helpful in starting the appropriate treatment early[5]. In the literature, it has been stated that platelet indices could be used in determining the inflammation, diagnosing various infections and their follow-up, determining the disease course severity, and efficacy of treatment[4,6]. We hypothesized that the suspicion or confirmation of sepsis could be narrowed down to its type through a hemogram test. This study aimed to investigate the role of platelet count and platelet indices such as MPV, PCT, and PDW in distinguishing between gram-positive, gram-negative, and fungal infections in neonates with proven hospital-acquired sepsis. Identifying potential markers for sepsis types could serve as an initiative for further research to enhance diagnostic accuracy.

MATERIALS AND METHODS

Study design and sample

This study is a retrospective observational cohort study conducted between January 1, 2011 and January 1, 2020 in by Cukurova University Neonatal Intensive Care Unit. In the case of a suspicion of infection in hospitalized patients, necessary blood tests are taken, and our clinic is informed, usually within two or three days, by the laboratory whether there is any growth signal in terms of cultures. However, as it is not yet clear what type of microorganism grows in the culture, control blood tests are taken from these patients on the 5th day in our clinic, and control cultures, especially from patients with gram-positive microorganism signal. Blood cultures of the patients with proven hospital-acquired neonatal sepsis whose infection types were determined were statistically compared under the framework of the analyses performed on the first day of infection diagnosis and on the 5th day for control purposes. Analyses included Platelet Count, Mean Platelet Volume (MPV), Plateletcrit (PCT), Platelet Distribution Width (PDW), and Platelet (PLT) values.

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by by Cukurova University Non-Interventional Clinical Research Ethics Committee (Date of Approval: 03/07/2020; Decision No: 101).

Power analysis results were based on three independent groups with two degrees of freedom belongs to gram positive, gram negative and Candida infection groups. Taking 0.35 as the f-effect size, 0.05 as the alpha-error, 0.80 as power and drop rate of 5%, the minimum sample size is calculated as 87. And a total of 90 newborn patients were included to the study. Since the Research Hospital where the study was conducted has only a 3rd Step Neonatal Intensive Care Unit, those who were admitted to the 3rd Step Neonatal Intensive Care Unit on the specified dates, had no clinical signs of sepsis on admission but developed clinical sepsis symptoms after 72 hours of hospitalization, had a Tollner sepsis score >10, or had Tollner sepsis. Those who had a score between 5 and 10, had positive clinical findings, and had gram-positive, gram-negative bacterial or

fungal strains growing in sterile fluids were included in the study. Hospital records were evaluated retrospectively. Only patients with nosocomial sepsis were included in the study.

Cases with Tollner sepsis score between 0-5 and only those with positive clinical findings were not included in the evaluation. Patients with early-onset neonatal sepsis were excluded from the study. In addition, patients who were given antibiotics for clinical sepsis but whose blood culture was not positive, who had major anomaly, arrhythmia, metabolic disorder, birth asphyxia, congenital heart defect, who died within 5 day of sepsis suspicion (As no blood controls on the 5th day), patients who were transfused due to thrombocytopenia from the day of suspected infection until the 5th day that control examinations were performed, and patients with missing data were not included in the study. A total of 90 patients were included in the study in accordance with these criteria.

Sepsis diagnosis

Nosocomial infections also called hospital-acquired infections or healthcare-associated infections are a subset of infectious diseases acquired in a healthcare facility. Newborns who were hospitalized with a different reason, that is, the infection cannot be present at admission, or newborns who were diagnosed with sepsis at least 72 hours after hospital admission were considered as neonatal nosocomial sepsis cases [7]. Clinical sepsis was defined as having two or more of the following: Poor perfusion (capillary recharge time >3 sec), muscle hypotonia or hypertonia, lethargy, enteral feeding intolerance, bloody stool, progressive increase in oxygen demand, bradycardia, unstable body temperature, unexplained and persistent metabolic acidosis. Though blood culture continues to be considered as the gold standard for diagnosis of sepsis, due to their limitations, urine, cerebrospinal fluid (CSF) and tracheal aspirate cultures (TAC) cultures were also used to diagnose gram-positive, gram-negative, and fungal infections [8].

Statistical analysis

Statistical analyses of the study were performed with IBM SPSS Statistics for Windows v.20.0 (IBM Corp. USA). The normal distribution of the data was tested by means of the Shapiro-Wilk test. The data that were not normally distributed were analyzed with the Kruskal-Wallis test for more than two categorical variables and with the Mann-Whitney U test for two categorical variables. Fisher's Exact test was used to compare categorical variables for 2x3 and 3x3. One-Way ANOVA was used to analyze normally distributed data in more than two categories, and Bonferroni method ($p < 0.05$) was used for Post Hoc multiple comparison. Values from the first day of infection and the fifth day were compared with ROC Curve analysis. The statistical significance level was determined as $p<0.05$.

RESULTS

Of the 90 patients, 29 were infected with gram-positive, 29 were infected with gram-negative microorganisms, and 32 with strains of Candida. First hospital-acquired infection attacks of the patients were included in the study. There was no difference between the groups in terms of gender, gestational week, birth weight, surfactant use, and mechanical ventilator treatment need. However, there were statistically significant differences between the groups in terms of death due to infection, multi-organ failure due to infection, need for ventilator due to infection (Table 1). Additionally, the number of patients with neutropenia and thrombocytopenia detected in the blood count taken at the beginning of the infection was statistically different between the groups.

PCT value did not show any statistical difference in all groups at the time of hospitalization. The difference in PCT values between the groups on the first and fifth days of infection was found to be statistically high. It was observed that the PLT value was lower in patients infected with gram-positive bacteria at the time of first hospitalization. However, when the first- and fifth-day infection values were compared, the PLT value of the patients with gram-positive bacterial infection was found to be statistically higher than the other groups. However, MPV value was found to be insufficient to make a diagnosis as it showed a statistically significant difference at the time of hospitalization before diagnosing sepsis. There was no statistical difference between the groups after the diagnosis of sepsis. The PDW value was not found to be statistically significant in determining gram-positive and gram-negative infections. However, a statistically significant difference was observed in determining fungal infections (Table 1).

Table 1. Demographic characteristics of the patients

		Gr+ (N=29) Mean±SD IQR	Gr- (N=29) Mean±SD IQR	Candida (N=32) Mean±SD IQR	P value
Maternal age (years)		29.4±5.4 7	31.28±5.7 9	30.5±6.2 7	0.506*
Gestational age (weeks)		31.4±5.3 9.80	33.1±5.1 9.35	31.2±4.9 9.63	0.906*
Birth weight (gr)		1713.1±1176.7 1578	2213.4±1207.4 2185	1791.8±1231.1 1931	0.239*
Starting day of infection		11.0 ±15.0 11	22.0±16.3 24	**40.2±35.8 20**	**<0.001***
		N	**N**	**N**	
Gender	Male	14	18	17	0.564†
	Female	15	11	15	
By week of birth	Premature	23	17	26	0.166†
	Mature	5	11	6	
	Postmature	1	1	0	
By birth weight	SGA	10	6	9	0.573*
	AGA	17	17	19	
	LGA	2	6	4	
Infection site detected	Blood	**29**	16	**26**	**0.012**†
	Urine	0	**5**	**6**	
	CSF	0	1	0	NA
	TAC	0	6	0	
	Other	0	1	0	
Death due to infection		2	4	9	0.090†
Multi-organ failure due to infection		1	**8**	**12**	0.006†
The need for ventilator due to infection		0	**13**	**14**	<0.001†
Neutropenia (+) at the time of infection diagnosis		0	0	**8**	<0.001†
Thrombocytopenia (+) at the time of infection diagnosis		6	**10**	**11**	<0.001†
Thrombocytopenia on the 5th day of infection		4	**13**	**17**	0.001†
PLT at First Hospitalization		219379.3±82117.6 128500	241931.0±69588.0 78500	245593.7±131420.7 174250	0.729
PLT on the first day of infection		235724.1±87063.1 124500	150896.5±152680. 8 200000	143668.7±160637.8 185250	<0.001
PLT on the 5th day of infection		293517.2±130011.7 176500	218517.2±172525. 2 278000	187750.0±178266.3 254000	0.014
PCT at First Hospitalization		0.22±0.08 0.10	0.23±0.06 0.07	0.23±0.12 0.16	0.548
PCT on the first day of infection		0.26±0.09 0.13	0.16±0.17 0.26	0.15±0.20 0.18	<0.001
PCT on the 5th day of infection		0.36±0.18 0.24	0.24±0.2 0.24±0.2	0.22±0.22 0.32	0.006
MPV at First Hospitalization		10.14±1.42 2.35	9.57±1.19 1.70	9.23±1.47 2.45	0.032
MPV on the first day of infection		11.03±1.77 2.45	10.49±1.46 2.60	10.2±1.64 2.30	0.114
MPV on the 5th day of infection		11.39±1.57 2.05	10.57±1.72 2.55	10.76±1.99 3.05	0.143
PDW at First Hospitalization		14.39±3.35 5.90	15.28±3.85 6.15	21.32±14.88 4.50	0.041
PDW on the first day of infection		16.3±3.85 6.80	16.8±2.98 4.40	20.7±1.20 2.93	0.164
PDW on the 5th day of infection		17.1±3.7 5.80	17.4±3.22 4.10	25.28±16.91 5.83	0.143

*, Kruskal-Wallis, †, Fisher's Exact, Gr- Gram negative bacteria, Gr+ gram positive bacteria, IQR Interquartile range, SGA Small for Gestational Age, AGA Appropriate for Gestational Age, LGA Large for Gestational Age, CSF Cerebrospinal fluid, TAC Tracheal aspirate culture, MPV Mean platelet volume, PCT Plateletcrit, PDW Platelet distribution width, PLT Platelet; Significant P values and variables with statistically significant differences in each row were written as bold

Table 2. Comparison of the performances of the tests determined for sepsis diagnosis with culture results in ROC curve analysis

	Gram+ Bacteria Culture Results vs PLT on the first day of infection	Gram-Positive Bacteria Culture Results vs PCT on the first day of infection	Gram-Positive Bacteria Culture Results vs PLT on the 5th day of infection	Gram-Positive Bacteria Culture Results vs PCT on the 5th day of infection	Candida Culture Results vs MPV on the first day of infection
AUC	0.765	0.764	0.681	0.709	0.792
Chosen Threshold*	>138500 mL/cell	>0.240%	>261000 mL/cell	>0.299%	<9.30 fl**
Sensitivity (%)	86.20	62.06	62.06	62.06	66.66
Specificity (%)	68.85	77.04	67.21	70.49	95.06
PPV (%)	56.81	56.25	47.36	50	60
NPV (%)	91.30	81.03	78.84	79.62	96.25
Accuracy (%)	74.44	72.22	65.55	67.77	92.22
LR+	2.76	2.70	1.89	2.10	13.5
LR -	0.20	0.49	0.56	0.53	0.29

AUC Area under curve, *PPV* Positive predictive value, *NPV* Negative predictive value, *LR+* Likelihood ratio positive, *LR-* Likelihood ratio negative; *All performance tests were calculated according to the chosen threshold.; ** In cases with Candida infections without thrombocytopenia

In order to determine the sensitivity and specificity of the tests for gram-positive bacterial infections, the values of the first day of infection and the fifth day were compared with ROC Curve analysis in Figure 1. The first day AUC value of PLT test for gram-positive infection cases was 0.765, and sensitivity was 86.20%, specificity 68.85%, Positive Predictive Value (PPV) 56.81%, Negative Predictive Value (NPV) 91.30%, accuracy 74.44%, Likelihood Ratio for Positive Results (LR+) 27.67 and the Likelihood Ratio for Negative Results (LR-) 0.20 (138500 cells/ml above PLT and p<0.001). AUC of the PLT test for gram-positive infection was found to be 0.681 on the fifth day, and its sensitivity was 62.06%, specificity 67.21%, PPV 47.36%, NPV 78.84%, accuracy 65.55% LR+ 18.93 and LR- 0.56 (261000 cells/mL above PLT and p:0.014). ROC Curve analysis of PCT test AUC was 0.764 and sensitivity was 62.06%, specificity 77.04%, PPV 56.25%, accuracy 81.03%, LR+ 2.70, and LR- 0.49 (0.240% PCT and p<0.001). AUC of PCT test for gram-positive infection was 0.709 on the fifth day and sensitivity was 62.06%, specificity 70.49%, PPV 50%, NPV 79.62%, accuracy 67.77%, LR+ 2.10, and LR- 0.53 (0.299% PCT and p: 0.006). Though the sensitivity of MPV tests on the first and the 5th day for gram-positive infection is very similar, it is not sufficient for the diagnosis of the disease. In addition, PDW test was not found to be sensitive in diagnosing gram-positive infection either (Table 2).

The means of PCT, PLT, MPV and PDW tests on the day of diagnosis and the 5th day for each infection are shown with the analysis in Figure 2. In addition, a comparison was made by including the mean of blood values at the time of hospitalization. The result of the comparison was that the mean basal PLT count was 200,000 cells/mL in patients with gram-positive bacterial infection, while it slightly increased at the time of diagnosis. It was observed that this value was approximately 300,000 cells/mL. on the 5th day of the diagnosis, whereas the mean basal PLT count was observed as approximately 250,000 cells/mL in patients with gram- and fungal infections. In patients with both infections, the PLT count decreased to approximately 150,000 cells/mL at the time of diagnosis. However, it increased again to approximately 250,000 cells/mL on the 5th day after diagnosis.

Basal PLT count was observed as approximately 0.2% in patients with gram-positive bacterial infection, while it was above 0.25% at the time of diagnosis. And on the 5th day after diagnosis, it was over 0.35%. However, while basal PLT count was about 0.2% in patients with gram-negative and with fungal infection, this value was found to be below 0.2% at the time of diagnosis. However, on the 5th day after diagnosis, PCT values were similar to baseline value. When the MPV test is examined, it is observed that the tests made at the time of diagnosis

and on the 5th day after diagnosis in patients with gram-positive bacterial infection were higher than the mean of the baseline values. But this increase is not significant. Finally, the PDW test was examined. Unlike other tests, PDW test did not show a significant difference in the mean values of patients with gram-positive and gram-negative. However, the mean value of the tests of the patients with fungal infection was found to be higher at the time of diagnosis and on the 5th day compared to the other groups.

In Figure 3a, platelet volume was evaluated for infections with normal platelet count (PLT > 150,000) and thrombocytopenia (PLT < 150,000). Thrombocytopenia was observed in most patients with gram-negative and with fungal infections throughout the study (65.5% and 71.9%, respectively). In patients with gram-positive bacterial infection and with PLT value of 150,000 cells/ml and above, the MPV value remained below 11.5 fl in cases and did not show any statistical change. Although MPV was detected approximately 14 fl in some cases with thrombocytopenia and with PLT value between 50,000 cells/mL and 150,000 cells/mL, this did not affect the MPV. In addition, there were no patients with PLT count below 50,000 mL/cell ($p = 0.487$). In patients with Gram-negative bacterial infection, there was no statistical difference in MPV values in patients with both normal platelets and thrombocytopenia ($p = 0.806$). A statistically significant decrease in MPV was observed in patients with fungal infection and with PLT value of 150,000 cells/mL and above. There was no visible change in MPV in patients with platelet count of between 50,000 cells/mL and 150,000 cells/mL, and platelet count of 50,000 cells/mL ($p=0.042$).

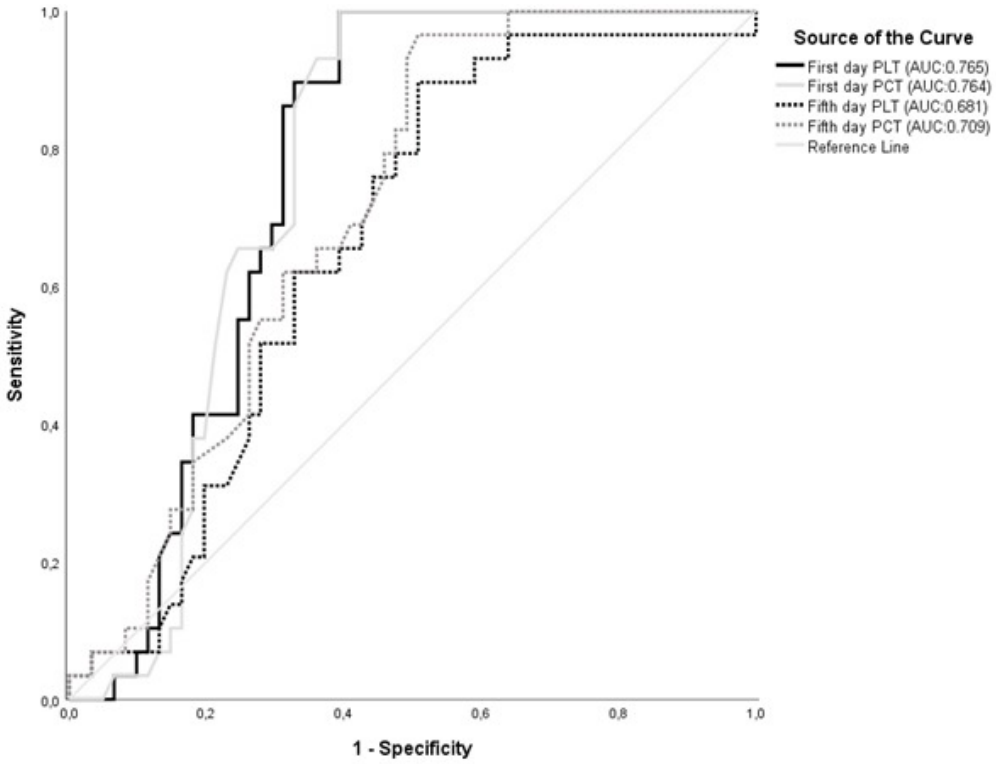

Figure 1. Blood values measured on the first and fifth day of infection for gram-positive bacterial infection.

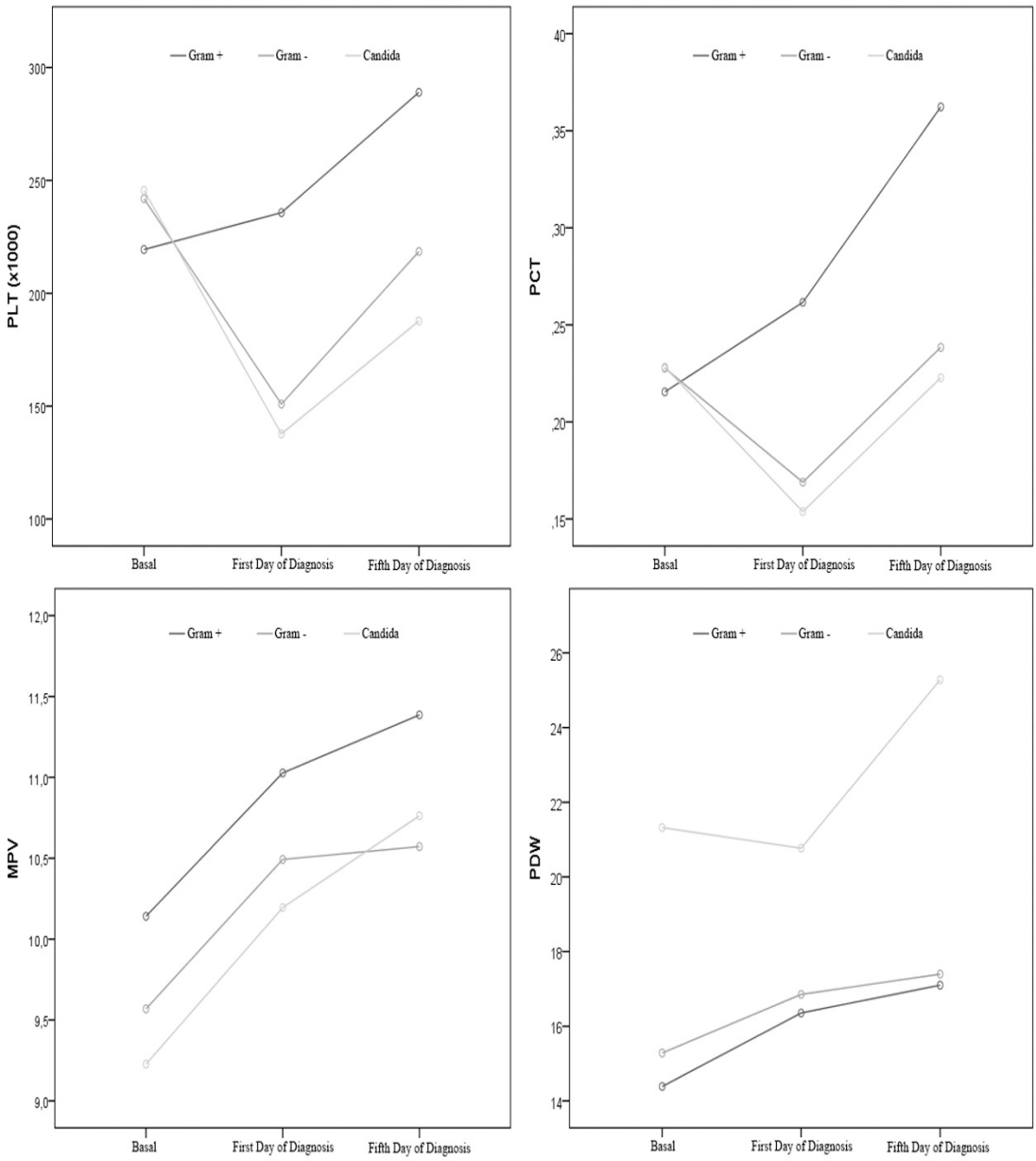

Figure 2. Distribution of blood values measured on the first day of hospitalization before sepsis diagnosis, and first and fifth day of sepsis diagnosis in sepsis subgroups.

ROC Curve analysis was performed for measuring the sensitivity of the MPV test in sepsis patients with fungal infection without thrombocytopenia (Figure 3b). According to the analysis, AUC in MPV test was found to be 0.792, with a sensitivity of 66.66%, a specificity of 95.06%, ppv 60%, npv 96.25%, accuracy 92.22%, LR+ 13.5, and LR-0.29 (9 MPV below .30 fl and p: 0.114).

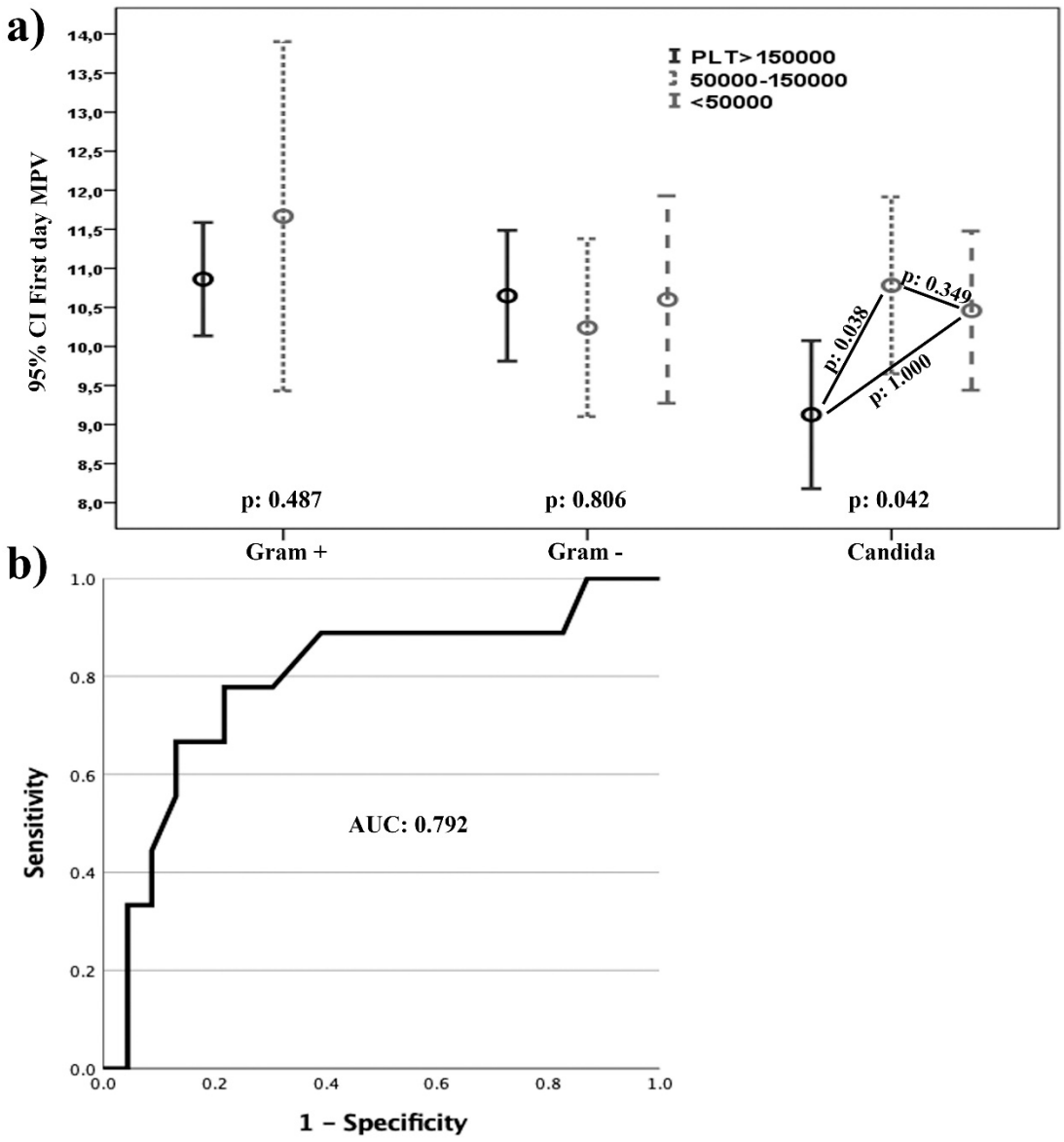

Figure 3. Evaluation of MPV test on the first day of the diagnosis of sepsis a) MPV values in cases with normal and low platelet values at the time of diagnosis. b) ROC Curve analysis of MPV test performed on the first day of infection in patients diagnosed with sepsis without thrombocytopenia.

DISCUSSION

The number of patients with thrombocytopenia at the time of diagnosis was found to be lower in group with gram-positive bacterial infection compared to other groups, and an increase in the number of patients with thrombocytopenia in the groups with gram-negative and fungal infection on the 5th day was observed compared to the 1st day. In a study conducted, it was stated that thrombocytopenia was more commonly seen in gram-negative cases in neonatal sepsis cases.[9]. It has been previously shown that there was a significant difference between control and sepsis group in terms of platelet count, PDW and MPV[10]. In this study, with the onset of the

disease, in patients with gram-positive bacterial infection, PCT and PLT values were higher than normal values both on the test day and on the 5th day of treatment. These values were found to be statistically sensitive in diagnosing sepsis in neonates with gram-positive bacterial infection.

It has been shown that in patients with gram-positive bacterial infection, a significant increase in PCT and PLT values in blood count at the time of diagnosis and on the 5th day of diagnosis could be associated with the diagnosis of sepsis caused by gram-positive bacteria. When the differential characteristics of blood values evaluated with ROC Curve analysis were examined in terms of sepsis sub-diagnosis, it was concluded that in patients with gram-positive bacterial infection on the first day of the infection, PCT and PLT tests were sensitive in detecting gram-positive infection. PCT and PLT tests which were performed on the 5th day of the disease detected the infection on the 5th day as well. As a result of the analysis, no significant relationship was found between gram-negative bacterial infections, fungal infections and blood tests. In another study, MPV test was not considered to be sufficient for the diagnosis of neonatal sepsis; instead, it was stated that PCT test could be used.[11]. Additionally, treatment for both gram-positive and gram-negative bacterial infections is applied to the patient until culture results are obtained in the sepsis treatment. As a result of our analysis, antibiotic resistance can be prevented by applying treatment for gram-positive bacterial infection only in cases with PCT 0.167% and PLT 1,338,000 cells/ml and above on the first day of infection.

In cases such as reduced platelet production, increased platelet destruction and more diluted blood than normal, thrombocytopenia may occur as the number of platelets in the unit blood will decrease. Therefore, platelet count in the blood and the mean structural volume of these platelets were examined. As a result of the study, a decrease in mean platelet volume was observed in the groups with thrombocytopenia, with fungal infection, with normal platelet count in the presence of gram-positive bacterial infection. Increase in MPV indicates increased production of platelet by the bone marrow due to destruction or consumption in the body. In similar studies, it was stated that MPV values did not show any change due to thrombocytopenia presence in patients with gram-positive and gram-negative bacterial infections[12,13]. This study conforms with these findings in terms of gram-positive and gram-negative ($p = 0.487$ and $p = 0.806$, respectively). Patients with fungal infection and without thrombocytopenia had a significantly lower MPV compared to patients with thrombocytopenia ($p = 0.038$). In Candida infection, as in other sepsis, thrombocytopenia develops due to factors such as hemodilution, increase in platelet consumption, decrease in production and capillary involvement, and the detailed mechanism is unknown [14]. Additionally, in this study, most patients with gram-negative and with Candida infection had thrombocytopenia as expected. However, in patients with Candida infection whose platelet counts are normal, but not above normal, low MPV may indicate that new platelet production is decreased due to complex indirect Candida-PLT interactions, as the PLT cells are old[14,15]. It is thought that MPV test can be used in sepsis cases with fungal infection and without thrombocytopenia. Additionally, IPF may be a distinguishing marker in patients with Candida and without thrombocytopenia, who usually have old PLT cells with a low MPV test[16].

According to the culture results, antibiotic treatments can be changed according to the gram-positive, gram-negative, and fungal infections of the patients, infection type can be predicted by performing only blood tests before culture, and the most appropriate antibiotic treatment can be decided early. Additionally, sepsis cases with fungal infection and without thrombocytopenia can be determined with the MPV test. In current treatment methods, antibiotic treatment administered to the patient after sepsis diagnosis until the infection type is determined usually targets gram-positive, gram-negative bacterial infections. Antibiotic treatment for fungal infection is not preferred without determining the infection type, both because the infection is seen less common and because of the side effects of the drugs. At the time of diagnosis, patients of this group can be examined more closely with MPV test. No test has been found to detect cases with gram-negative infection and sepsis caused by fungal infection with thrombocytopenia. However, after the study, in cases with thrombocytopenia but with no abnormalities in PCT, PLT, and MPV tests, the possibility of having gram-negative or fungal infection can be considered.

Neonatal sepsis has been defined as the third most common cause of neonatal death[17]. Many studies have shown that gram-positive infection is more common than gram-negative and fungal infection[18-

[22]. Studies conducted until now have found a relation between neonatal sepsis and MPW and PDW values[16]. It is considered that the maternal platelet parameters MPV, Immature Platelet Fraction (IPF) and PCT could be used as evidence of early predictors of neonatal sepsis development and respiratory distress, and that they could be accepted as predictive markers of adverse neonatal outcome[23].

Off-target antibiotic usage is undesirable and is often mitigated by using broad-spectrum antibiotics at the initial diagnosis. However, despite the limited clinical significance of our results, this study highlights the potential for immediate diagnosis or narrowing the diagnostic scope in cases of sepsis. Therefore, further multi-center studies are recommended to evaluate hemogram markers and to explore new potential markers from non-standardized hemogram variables to address gram-negative and Candida infections as well.

PCT and PLT tests can detect sepsis patients infected with gram-positive bacteria from the first day with high performance. Sepsis due to Candida infection cases without thrombocytopenia can be detected at a high rate of 95% specificity with MPV test. PLT, PCT and MPV tests alone are not sufficient to diagnose the disease. However, as the specificity of the tests is very high at the time of diagnosis, antibiotic treatment specific to these groups can be assessed. No method has been found to detect patients with fungal infections with thrombocytopenia and patients with gram-bacterial infections. The number of patients included in the study is small due to the high exclusion criteria.

In conclusion, newborn babies who are thought to have an infection, based on the platelecrit and platelet values at the time of first diagnosis, those with gram-positive bacteria infection can be diagnosed without waiting for the culture results. In accordance with these results, it will be possible to specify the type of infection and to choose the most appropriate antibiotic treatment. However, it is recommended that the results must be supported by further multi-centered studies, as the AUC values of the tests performed were rated as moderate.

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REFERENCES

1. Raimondi F, Ferrara T, Maffucci R, Milite P, Del Buono D, Santoro P et al. Neonatal sepsis: a difficult diagnostic challenge. Clin Biochem. 2011;44:463-4.
2. Satar M, Arısoy AE, Çelik İH. Turkish Neonatal Society guideline on neonatal infections - diagnosis and treatment. Turk Arch Pedıatr. 2018;53:88-100.
3. Jyothi P, Basavaraj MC, Basavaraj PV. Bacteriological profile of neonatal septicemia and antibiotic susceptibility pattern of the isolates. J Nat Sci Biol Med. 2013;4:306-9.
4. Guida JD, Kunig AM, Leef KH, McKenzie SE, Paul DA. Platelet count and sepsis in very low birth weight neonates: is there an organism-specific response? Pediatrics. 2003;111:1411-5.
5. Gao Y, Li Y, Yu X, Guo S, Ji X, Sun T et al. The impact of various platelet indices as prognostic markers of septic shock. PLoS One. 2014;9:e103761.
6. Kitazawa T, Yoshino Y, Tatsuno K, Ota Y, Yotsuyanagi H. Changes in the mean platelet volume levels after bloodstream infection have prognostic value. Intern Med. 2013;52:1487-93.
7. Solmaz A, Guzelcicek A. Çocuk yoğun bakım ünitesinde izlenen sepsis olgularının geriye dönük analizi. Harran Üniversitesi Tıp Fakültesi Dergisi. 2019;16:24-8.
8. Ershad M, Mostafa A, Dela Cruz M, Vearrier D. Neonatal sepsis. Curr Emerg Hosp Med Rep. 2019;7:83-90.
9. Arabdin M, Khan A, Zia S, Khan S, Khan GS, Shahid M. Frequency and severity of thrombocytopenia in neonatal sepsis. Cureus. 2022;14:e22665.
10. Tayman C, Tonbul A, Akca H, Bilici M. Mean platelet volume may simply predict the severity of sepsis in preterm infants. Clin Lab. 2014;60:1193-200.
11. Sarkhiz SG, Kilinc MY, Uygun SS, Konak M, Soylu H. Could plateletcrit, in the first 24 hours of life, be an early indıcator of poor etıology and prognosıs in preterm infants? Pediatric Practice and Research. 2019;7:176-81.
12. Shaaban HA, Safwat N. Mean platelet volume in preterm: a predictor of early onset neonatal sepsis. J Matern Fetal Neonatal Med. 2020;33:206-11.
13. Catal F, Tayman C, Tonbul A, Akça H, Kara S, Tatli MM et al. Mean platelet volume may simply predict the severity of sepsis in preterm infants. Clin Lab. 2014;60:1193-200.
14. Vardon-Bounes F, Ruiz S, Gratacap MP, Garcia C, Payrastre B, Minville V. Platelets are critical key players in sepsis. Int J Mol Sci. 2019;20:3494.
15. Eberl C, Speth C, Jacobsen ID, Hermann M, Hagleitner M, Deshmukh H et al. Candida: platelet

interaction and platelet activity in vitro. J Innate Immun. 2019;11:52-62.
16. Majumdar A, Biswas S, Jana A. Platelet indices as an earlier and economical marker of neonatal sepsis. Iraqi Journal of Hematology. 2021;10:108-11.
17. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1459-544.
18. Li J, Xia S, Liu Y, Zhang S, Jin Z. Bacteriological profile and antibiotic susceptibility pattern of neonatal septicemia and associated factors of ICU hospitalization days. Infect Drug Resist. 2022;15:427.
19. Dong H, Cao H, Zheng H. Pathogenic bacteria distributions and drug resistance analysis in 96 cases of neonatal sepsis. BMC Pediatr. 2017;17:44.
20. Sharma CM, Agrawal RP, Sharan H, Kumar B, Sharma D, Bhatia SS. "Neonatal sepsis": bacteria & their susceptibility pattern towards antibiotics in neonatal intensive care unit. J Clin Diagn Res. 2013;7:2511.
21. Moges F, Eshetie S, Yeshitela B, Abate E. Bacterial etiologic agents causing neonatal sepsis and associated risk factors in Gondar, Northwest Ethiopia. BMC Pediatr. 2017;17:137.
22. Muller-Pebody B, Johnson AP, Heath PT, Gilbert RE, Henderson KL, Sharland M et al. Empirical treatment of neonatal sepsis: are the current guidelines adequate? Arch Dis Child Fetal Neonatal Ed. 2011;96:F4-8.
23. Mishra S, Jaiswar S, Saad S, Tripathi S, Singh N, Deo S et al. Platelet indices as a predictive marker in neonatal sepsis and respiratory distress in preterm prelabor rupture of membranes. Int J Hematol. 2021;113:199-206.