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Original Article

Anorectal Pathologies in the Course of Acute Leukaemias; Predictive Parameters

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Abstract. ***Introduction.*** **Patients with leukaemia are exposed to infections as long as they are neutropenic. During this period, anorectal pathologies are among the common foci of infection with high mortality. In this study, we aim to investigate the factors that may have a predictive effect on early diagnosis and rapid intervention in perianal complications occurring in neutropenic patients diagnosed with leukaemia.**
Materials and Methods. **A total of 90 patients with acute leukaemia, including 45 patients with anorectal pathology and 45 patients without anorectal pathology, were analysed. Demographics, blood group, BMI, haemogram and biochemical parameters at the time of diagnosis, and types of perianal pathology were recorded.**
Results. **In the group of patients with anorectal pathology, WBC, lymphocytes, monocytes, and LDH were significantly ($p<0.05$) higher, and platelets, MPV, and PCT were significantly ($p<0.05$) lower. The multivariate model showed significant-independent ($p<0.05$) efficacy of WBC and MPV values in differentiating patients with and without anorectal pathology. A significant efficacy was observed at the WBC cut-off of 17000 [area under the curve 0.656 (0.542-0.770)] and the MPV cut-off of 10 [area under the curve 0.667 (0.554-0.780)] in differentiating patients with and without anorectal pathology.**
Discussion. **Anorectal pathologies are common foci of infection in patients with acute leukaemia. Having predictive parameters that may help for early intervention will help the clinician. This is the first study in the literature to compare a control group with a group with anorectal pathologies in leukaemia patients providing a cut-off for WBC.**

Keywords: Acute Leukemia; Leukocyte count; MPV; Perianal pathologies.

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Introduction. Acute leukaemia is diagnosed with a blast rate of ≥20% in the bone marrow. Leukemias, which are characterised by abnormal leukocyte production, are categorised into subgroups based on proliferation rate, source cell and genotypic characteristics.[1] Patients with leukaemia are exposed to infections as long as they are neutropenic. During this period, anorectal pathologies are among the common foci of infection. Although the diagnosis is difficult, the diagnosis can be made based on the findings from physical examination and imaging modalities. Although symptoms may be masked in immunosuppressed patients, they are usually

accompanied by complaints such as pain, swelling and constipation, which may progress to systemic infection.[2] A wide spectrum of conditions can be encountered, ranging from mild lesions to more severe conditions such as abscesses, and has a high mortality rate of 11-57% in patients with neutropenia.[3] Early recognition of anorectal pathologies and rapid intervention in neutropenic patients are among the factors that will significantly affect mortality.

In this study, we aim to investigate the factors that may have a predictive effect on early diagnosis and rapid intervention in perianal complications occurring in the neutropenic period in patients with leukaemia receiving cytotoxic chemotherapy.

Materials and Methods. Patients with newly diagnosed leukaemia who received induction cytotoxic chemotherapy in the Haematology Department between June 2022 and October 2023 were retrospectively analysed. Patients were questioned about their complaints daily during the neutropenia period, and routine physical examinations, including perianal examinations, were performed and recorded in their files. Perianal MRI was performed on patients with suspicious complaints (anal pain, difficulty sitting, fever) or physical examination findings (anal tenderness, redness, discharge) during the febrile neutropenia period. Patients diagnosed with haemorrhoids, abscesses, fistula and fissures by perianal MRI were included in the 'patient with perianal pathology' group. The 'patients without perianal pathology' group included patients who were newly diagnosed with leukaemia and received induction therapy and who had no perianal complaints or findings during the neutropenia period (the focus of infection was not in the perianal region). Patients with a history of perianal pathology or surgery before the diagnosis of leukaemia and those with a diagnosis of diabetes mellitus were excluded from the study. A total of 90 patients, including 45 patients with perianal pathology and 45 patients without perianal pathology, were enrolled in the study. Demographics, blood group, BMI (body mass index), haemogram and biochemical parameters at the time of diagnosis, and types of perianal pathology were recorded. The types of perianal pathology of the patients were classified according to the Perianal MRI results.

Statistical Analysis. Mean, standard deviation, median, minimum, maximum value frequency and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov-Smirnov test. Independent Samples t-test and Mann-Whitney U test were used to compare the quantitative data. A chi-square test was used to compare the qualitative data. Univariate and multivariate logistic regression was used to show the effect level. ROC analysis was used to show the effect level. SPSS 27.0 was used for statistical analyses.

Ethical Approval and Informed Consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Etlik City Hospital, Ankara, Turkey (AEŞH-EK1-2023-179).

Results. The study in which 90 patients, including 45

Table 1. Descriptive statistics of the data and distribution of demographic parameters of the patients.

		Mean±sd/n-%
Age (years)		44.9±15.0
Gender	Female	42 (46.7%)
	Male	48 (53.3%)
Weight (kg)		72.1±15.7
BMI (kg/m^2)		26.1± 5.4
Diagnosis	ALL	24 (26.7%)
	AML	66 (73.3%)
Abscess		10 (11.1%)
Fissure		5 (5.6%)
Fistula		10 (11.1%)
Haemorrhoids		20 (22.2%)
WBC (10^3/µL)		37.1±56.2
Haemoglobin (g/dL)		8.8±2.3
Platelet (10^3/µL)		71.9±114.9
MPV (fL)		10.4±1.5
PCT (%)		0.07±0.10
PDW (%)		13.0±3.4
Lymphocytes (10^3/µL)		13.2±34.9
Neutrophils (10^3/µL)		6.16±12.06
Monocytes (10^3/µL)		17.8±29.9
Glucose (mg/dL)		118.1±39.2
Urea (mg/dL)		32.8±31.6
Creatinine (mg/dL)		0.84±0.27
ALT (U/L)		31.1±31.3
AST (U/L)		39.0±68.7
LDH (U/L)		771.6±895.5
Albumin (g/dL)		3.70±0.59
Vitamin B12 (pg/mL)		507.9±460.9
Folate (ng/mL)		6.3±5.2
Ferritin (ml/ng)		871.8±1236.1

BMI:Body Mass İndex, ALL:Acute Lymphoblastic Leukaemia, AML:Acute Myeloid Leukaemia, WBC:White Blood Cell, MPV:Mean Platelet Volume, PCT:Plateletcrit, PDW:Platelet Distribution Width, ALT:Alanine Aminotransferase, AST:Aspartate Aminotransferase, LDH:Lactate Dehydrogenase

Table 2. Comparison of group parameters with and without anorectal pathology.

		Anorectal Pathologies (-)	Anorectal Pathologies (+)	P	
		Mean±sd/n-%	Mean±sd/n-%		
Age (years)		47.6±15.9	42.2±13.8	0087	t
Gender	Female	17 (37.8%)	25 (55.6%)	0091	X^2
	Male	28 (62.2%)	20 (44.4%)		
Weight (kg)		72.7±13.2	71.6±17.9	0733	t
BMI (kg/m^2)		25.8±4.5	26.4±6.2	0637	t
Diagnosis	ALL	11 (24.4%)	13 (28.9%)	0634	X^2
	AML	34 (75.6%)	32 (71.1%)		
WBC (10^3/µL)		23.5±40.2	50.7±66.3	***0004***	m
Haemoglobin (g/dL)		8.9±2.4	8.7±2.3	0620	t
Platelets (10^3/µL)		91.4±146.7	52.3±66.4	***0024***	m
MPV (fL)		11.0±1.4	9.8±1.3	***0000***	m
PCT (%)		0.09±0.12	0.05±0.06	***0012***	m
PDW (%)		13.4±3.5	12.7±3.4	0176	m
Lymphocytes (10^3/µL)		4.7±6.3	21.8±47.7	***0002***	m
Neutrophils (10^3/µL)		7.4±16.0	5.0±5.9	0377	m
Monocytes (10^3/µL)		10.6±22.0	24.3±34.8	***0015***	m
Glucose (mg/dL)		124.7±40.2	111.5±37.4	0180	m
Urea (mg/dL)		33.0±17.2	32.6±41.5	0176	m
Creatinine (mg/dL)		0.8±0.3	0.8±0.3	0725	m
ALT (U/L)		26.5±20.0	35.7±39.2	0631	m
AST (U/L)		30.2±27.4	47.7±93.0	0188	m
LDH (U/L)		753.1±1107.0	790.1±629.2	***0041***	m
Albumin (g/dL)		3.7±0.6	3.7±0.6	0570	t
Vitamin B12 (pg/mL)		564.8±548.5	451.0±349.8	0611	m
Folate (ng/mL)		5.7±3.5	6.8±6.5	0678	m
Ferritin (mL/ng)		855.5±1568.6	888.2±793.4	0329	m

BMI:Body Mass İndex, ALL:Acute Lymphoblastic Leukaemia, AML:Acute Myeloid Leukaemia, WBC:White Blood Cell, MPV:Mean Platelet Volume, PCT:Plateletcrit, PDW:Platelet Distribution Width, ALT:Alanine Aminotransferase, AST:Aspartate Aminotransferase, LDH:Lactate Dehydrogenase. [t]Independent Samples t-test / [m]Mann-Whitney u test / X^2 Chi-square test.

patients with anorectal pathology and 45 control group, were analysed consisted of 42 (46.7%) men and 48 (53.3%) women. The mean age of the patients included in the study was 44.9±15.0 years, and 66 (73.3%) were receiving treatment for AML (Acute Myeloid Leukaemia) and 24 (26.7%) for ALL (Acute Lymphoblastic Leukaemia). The distribution of age, gender and diagnosis did not differ significantly (p>0.05) between the groups with and without anorectal pathology. In our study, 20 patients (22.2%) were diagnosed with haemorrhoids, 10 (11.1%) with abscess, 10 (11.1%) with fistula and 5 (5.6%) with fissure. BMI was 25.8±4.5 and 26.4±6.2, respectively, in the groups with and without anorectal pathology, and no statistically significant difference was found between the two groups. Demographics and other general characteristics of the patients are analysed in detail in **Table 1**. In the group without anorectal pathology, WBC (White Blood Cell) was 23.5±40.2, lymphocyte count was 4.7±6.3, monocyte count was 10.6±22, LDH (Lactate Dehydrogenase) was 753.1±1107, while in the group with anorectal pathology WBC was 50.7±66.3, lymphocyte count 21.8± 47.7, monocyte count 24.3± 34.8, LDH 790.1±629.2 and these values were statistically significantly (p<0.05) higher in the group with anorectal pathology. Haemoglobin, PDW (Platelet Distribution Width), neutrophil, glucose, urea, creatinine, ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), albumin, vitamin B12, folate, ferritin levels did not differ significantly (p>0.05) between the groups. Platelets were 52.3± 66.4, MPV (Mean Platelet Volume) 9.8± 1.3, PCT (Plateletcrit) 0.05± 0.06 in the group with anorectal pathology and were significantly (p<0.05) lower than the group without anorectal pathology (**Table 2**).

The parameters in **Table 2** were evaluated with the appropriate method (Independent Sample t-test ([t]) / Mann-Whitney U test ([m]) / Chi-square test (X^2)), and

Table 3. Univariate and Multivariate Model.

	Univariate Model			Multivariate Model		
	OR	%95 GA	p	OR	%95 GA	p
WBC (x10³)	1.011	1.001 - 1.022	***0.036***	1.012	1.001 - 1.024	***0.036***
Platelet (x10³)	0.996	0.991 - 1.001	0.150			
MPV	0.463	0.304 - 0.706	***0.000***	0.454	0.292 - 0.706	***0.000***
PCT	0.007	0.000 - 6.594	0.156			
Lymphocyte (x10³)	1.075	1.011 - 1.142	***0.021***			
Monocyte (x10³)	1.019	1.001 - 1.037	***0.043***			
LDH	1.000	1.000 - 1.001	0.844			

Logistic Regression (Forward LR). WBC: White Blood Cell, MPV: Mean Platelet Volume, PCT: Platelet, LDH: Lactate Dehydrogenase.

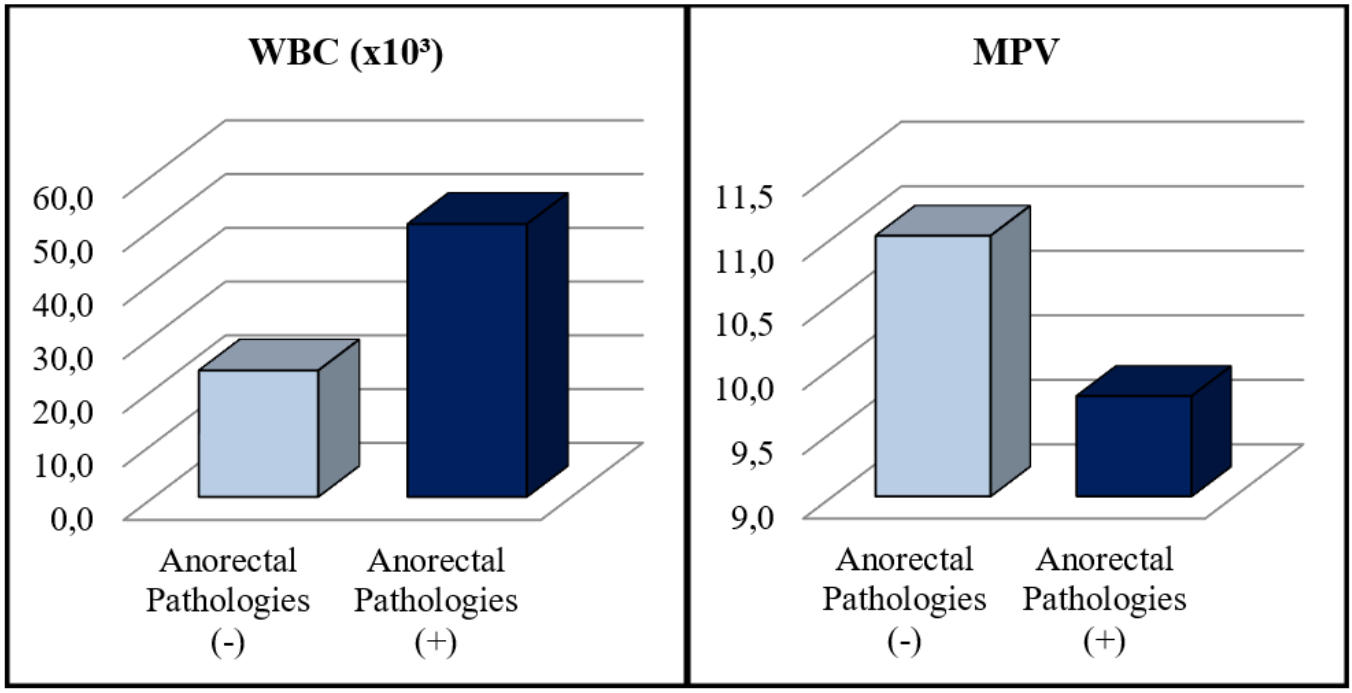


Figure 3 and 4. WBC and MPV values.

univariate regression analysis was performed on the parameters that were found to be statistically significant ($p < 0.05$). The univariate model showed significant ($p<0.05$) activity of WBC, MPV, lymphocyte, and monocyte in differentiating patients with and without anorectal pathology. WBC, MPV, lymphocyte and monocyte parameters that showed statistically significant effect in distinguishing patients with and without anorectal pathology in the univariate model were analysed by multivariate regression. The multivariate model showed significant-independent ($p<0.05$) efficacy of WBC and MPV values in differentiating patients with and without anorectal pathology (**Table 3, Figure 3 and 4**).

A significant cut-off for differentiation of intergroup patients was 17000 [area under the curve 0.656 (0.542-0.770)] for WBC and 10 [area under the curve 0.667 (0.554-0.780)] for MPV. The sensitivity, positive predictive rate, specificity, specificity and negative predictive rate were 66.7%, 65.2%, 64.4% and 65.9%, respectively, for the intergroup differentiation of patients at the WBC cut off of 17000 (**Table 4, Figure 1**).

The sensitivity, positive predictive rate, specificity, specificity and negative predictive rate were 60.0%, 69.2%, 73.3% and 64.7%, respectively, for the intergroup differentiation of patients at the MPV cut off of 10 (**Table 5, Figure 2**).

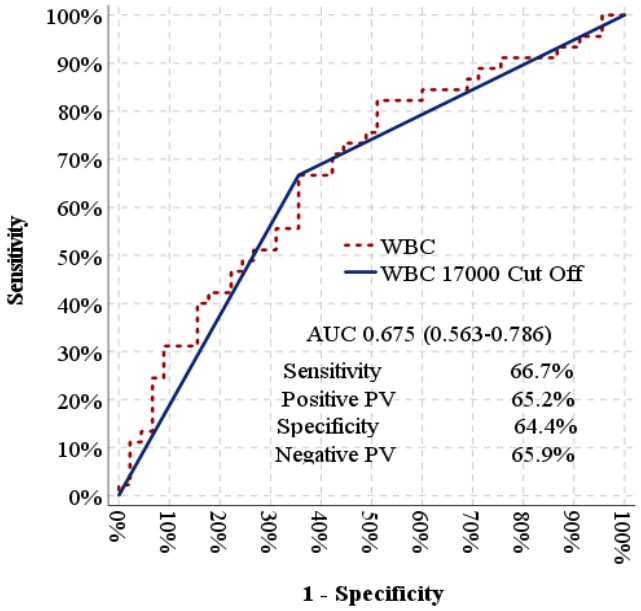
Discussion. There are many factors affecting clinical susceptibility, especially for infections in patients with haematological malignancies. Factors affecting the risk of infection can generally be analysed into three main groups: disease-related, patient-related, and treatment-related.[4] Factors associated with the disease include neutropenia, impaired granulocyte function,[5] the potential of immature myeloid cells to inhibit the antigen-specific T-cell response,[6] and immunoglobulin deficiency due to dysregulation of the humoral immune system.[6] Patient-related factors include age, malnutrition and low baseline BMI. Both T and B cell functions

Table 4. For WBC, cut off.

		Area Under the Curve		%95 Confidence Interval	p
WBC		0675		0563 - 0786	***0004***
WBC 17000 Cut off		0656		0542 - 0770	***0011***
		Anorectal Pathologies (-)	Anorectal Pathologies (+)		%
WBC	≤ 17000	29	15	Sensitivity	66.7%
	> 17000	16	30	Positive PV	65.2%
				Specificity	64.4%
				Negative PV	65.9%

ROC Curve (WBC: White Blood Cell).

Figure 1. White Blood Cell.



deteriorate with age, and the function of the immune system decreases. Prolonged neutropenia with high-dose chemotherapy[7] may result in mucositis and impaired gastrointestinal flora after broad-spectrum antibiotic use.[8]

Pneumonia, skin and soft tissue infections, anorectal pathologies, urinary tract infections, mucositis, neutropenic enterocolitis, and catheter infections can be listed as possible foci of infection that may occur during neutropenia in haematological malignancies.[9]

In patients with haematological malignancies, anal and perianal pathologies are among the common complications with the contribution of mucosal damage during neutropenia, and infections are the most common cause.[10] In this patient population, diagnosis of anorectal pathologies may be difficult, but the diagnosis can be made based on redness, swelling, tenderness, fluctuation and imaging findings on physical examination.[3] The incidence was 7.3% in a study by Büyükaşık Y et al., [11] 5.8% in a study by Greval et al.,[12] and 6.7% in a study by Chen C et al.[2] In neutropenic process, perianal infections tend to recur in every cycle.[2]

These infections are observed in a wide spectrum from mild lesions, e.g. local cellulitis and haemorrhoids, to more severe conditions, e.g. abscesses and are associated with a mortality rate of 11-57% in patients with neutropenia.[3] In addition to the serious mortality risk, they cause severe anal pain, discomfort, and management difficulties in the course of treatment.[13] In the study by Perazzoli et al., anorectal pathologies were observed as abscesses in 27%, anal fissures in 23% and haemorrhoids in 19%.[14] In our study, haemorrhoids were reported in 22.2% (20), abscesses in 11.1% (10), fistulas in 11.1% (10) and fissures in 5.6% (5).

The study included 42 (46.7%) men and 48 (53.3%) women. The mean age of the patients included in the study was 44.9±15.0 years, and 66 (73.3%) were receiving treatment for AML and 24 (26.7%) for ALL. No significant ($p>0.05$) difference was found between the groups with and without anorectal pathology according to age, gender, diagnosis distribution and BMI. In some studies in the literature, abscesses were more frequent in patients diagnosed with AML than in patients diagnosed with ALL.[2,10] In contrast, in other literature studies, no correlation was found between the diagnosis and the development of anal abscess.[11,15] In the study by Chang H et al., the group with perianal abscess was younger than the group without perianal abscess.[16]

In our study, WBC, lymphocyte, monocyte and LDH were significantly ($p<0.05$) higher in the group with anorectal pathologies, while platelets, MPV and PCT were significantly ($p<0.05$) lower in the group without anorectal pathologies.

In a study by Orhan B et al., the prognosis was found to be worse, and the need for the operation was higher in patients with anorectal pathology with elevated WBC.[10]

A high monocyte count at the time of diagnosis was considered a poor prognostic factor for overall survival.[17,18] In our study, the presence of leucocytosis in the group with anorectal pathology and the associated lymphocytosis and monocytosis can be considered consistent with the literature.

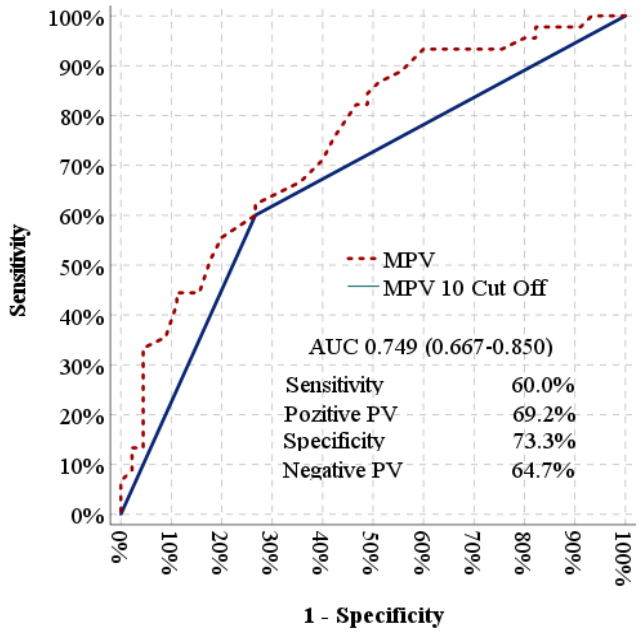
Platelet count at the time of diagnosis varies in AML patients. Higher leukocyte and blast counts were observed in the group with low platelet count at the time of diagnosis (<20,000/10^9/L) compared to the group with

Table 5. MPV cut off.

		Area Under the Curve		%95 Confidence Interval			p
MPV		0749		0667	-	0850	***0000***
MPV 10 Cut off		0667		0554	-	0780	***0006***
		Anorectal Pathologies (-)	Anorectal Pathologies (+)				%
MPV	> 10	33	18			Sensitivity	60.0%
	≤ 10	12	27			Positive PV	69.2%
						Specificity	73.3%
						Negative PV	64.7%

ROC Curve.

Figure 2.



moderately high and very high platelet counts.[19] Thus, the association of thrombocytopenia with elevated WBC is a finding also observed in our study and is consistent with this literature data.

Survival was higher in AML patients with a platelet count between 50,000 and 120,000 at the time of diagnosis compared to patients with low or high platelet counts.[20] In our study, platelet count was lower in the group with anorectal pathology. In other words, low platelet count at the time of diagnosis is associated with more frequent anorectal pathology and higher mortality.

The blood level of LDH increases with cell damage and tends to increase as the severity of infection increases. Studies in the literature show that LDH level has prognostic significance for infection.[21,22] In our study, LDH level was also found to be higher in patients with anorectal pathology. Elevated LDH is parallel with the occurrence of anorectal pathology.

MPV and PCT are platelet parameters that are automatically calculated in whole blood tests. MPV is one of the main platelet parameters, which also reflects the proliferation, metabolism, platelet enzymatic activity, and functional status of megakaryocytes. MPV can be used as a reference to evaluate platelet production and function and to determine the cause of thrombocytopenia.[23,24]

Studies have shown that a decrease in myeloproliferative function leads to a decrease in platelets, while MPV decreases or remains unchanged.[25] In a 2014 study, Vinholt et al. suggested that bleeding symptoms in patients with thrombocytopenia may be due to a decrease in MPV.[26]

The literature contains studies demonstrating the relationship between PCT and infection severity.[27,28] PCT was lower in the group with anorectal pathology compared to the group without anorectal pathology.

The univariate model showed significant ($p<0.05$) activity of WBC, MPV, lymphocyte, and monocyte in differentiating patients with and without anorectal pathology, whereas no significant ($p>0.05$) activity of platelet, PCT, and LDH was observed (**Table 4**).

The multivariate model showed significant-independent ($p<0.05$) efficacy of WBC and MPV values in differentiating patients with and without anorectal pathology (**Table 4**).

A significant cut-off for differentiation of intergroup patients was 17000 [area under the curve 0.656 (0.542-0.770)] for WBC and 10 [area under the curve 0.667 (0.554-0.780)] for MPV. The sensitivity, positive predictive rate, specificity, specificity, and negative predictive rate were 66.7%, 65.2%, 64.4% and 65.9%, respectively, for the intergroup differentiation of patients at the WBC cut-off of 17000 (**Table 4, Figure 1**).

The sensitivity, positive predictive rate, specificity, specificity and negative predictive rate were 60.0%, 69.2%, 73.3% and 64.7%, respectively, for the intergroup differentiation of patients at the MPV cut off of 10 (**Table 5, Figure 2**).

Conclusion. Anorectal pathologies are common foci of infection in patients with acute leukaemia. Early intervention is an important factor that will affect the patient's survival in the neutropenic period. Having predictive parameters that may help for early intervention will help the clinician. Setting a cut-off for WBC and MPV can be a serious guide. Multicentre

studies with a larger number of patients are needed to set a standard for these cut-off values. In the literature, this study is the first to compare a control group with a group of patients with anorectal pathologies in leukaemia patients and to provide a cut-off for WBC and MPV, which were considered significant independent variables in the multivariate model.

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