



**Original Article**

## The Role of White Blood Cell Count in Perianal Pathologies: A Retrospective Analysis of Hematologic Malignancies

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**Competing interests:** The authors declare no conflict of Interest.

**Abstract. Background and Objective:** Infections are the most common cause of anal and perianal pathologies in patients with hematological malignancies. Perianal infection diagnosis in this group of patients is difficult; thus, a careful anorectal examination is necessary with imaging modalities. In addition, the literature reveals a knowledge gap in the approach to anal pathologies in patients with neutropenia during diagnosis or chemotherapy. This study aimed to examine our institutional data on perianal complications and investigate the relationship between the white blood cell-neutrophil count, perianal lesion, and the type of treatment in patients with hematologic malignancies during the neutropenic period.

**Methods:** Patients with a hematologic malignancy, hospitalized for cytotoxic chemotherapy, complicated by perianal pathology, documented by at least one imaging method, were included in the study.

**Results:** A total of 42 patients were included in the study. Most of them had acute leukemia, 31 were affected by acute myeloid leukemia (AML), and 7 by Acute lymphoid leukemia (ALL). There was no statistically significant relationship between the anal abscess formation, the neutrophil count, and a previous perianal pathology. Anal abscess development was significantly more frequent in acute myeloid leukemia. An inverse relationship was found between the total white blood cell number at onset and having a surgical intervention for anal pathology.

**In conclusion,** this article has shown that white blood cell count at the time of hospitalization can affect the surgical intervention in patients with hematological malignancy (in the majority with acute leukemia) affected by anal pathologies occurring in the neutropenic period.

**Keywords:** Perianal; Acute leukemia; White blood cell.

**Citation:** Orhan B., Özkalemkaş F., Özkocaman V., Gürbüz B., Ersal T., Pınar İ.E., Yalçın C., Candar Ö., Çubukçu S., Koca T.G., Ali R. The role of white blood cell count in perianal pathologies: A retrospective analysis of hematologic malignancies. *Mediterr J Hematol Infect Dis* 2022, 14(1): e2022051, DOI: <http://dx.doi.org/10.4084/MJHID.2022.051>

**Published:** July 1, 2022

**Received:** February 9, 2022

**Accepted:** June 14, 2022

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**Introduction.** Infections are the most common cause of anal and perianal pathologies in patients with hematological malignancies.<sup>1</sup> The incidence of perianal infections is 8%–9% in patients with acute leukemia.<sup>2</sup>

Immunosuppression due to chemotherapies or underlying disease causes the onset of perianal infections due to opportunistic organisms.<sup>3</sup> When blood neutrophil count falls below 500/mm<sup>3</sup> and the patient becomes

thrombocytopenic, delayed healing and opportunistic infections become imminent. Furthermore, mucosal and mechanical barrier damage provide additional entry of pathogens in the neutropenic stage.<sup>4</sup>

Anorectal infections in patients with cancer are diagnosed for the presence of redness or tenderness, which are infection findings during a physical examination, abscess by incision or drainage, or pathognomonic findings revealed by imaging methods.<sup>5</sup> The clinical evaluation of anorectal infections in patients with cancer differs from healthy individuals. These evaluations include immunosuppression status, steroid use, chemo, and radio treatment-related toxicities.<sup>6</sup> Perianal infection diagnosis in this group of patients is difficult; thus, a careful anorectal examination is necessary with imaging modalities.<sup>4</sup> These infections have a large spectrum ranging from local cellulitis to severe sepsis and have a mortality rate of 11%–57% in patients with neutropenia; thus, prompt treatment and the type of intervention (surgical or medical) becomes a challenge.<sup>7</sup> Non-septic conditions, such as hemorrhoids and fissures, should be conservatively approached, whereas septic conditions should be more carefully approached, and surgery should be performed as necessary.<sup>8</sup> A literature review on the treatment of perianal pathologies in patients with neutropenic hematologic malignancy recommended surgical intervention only in patients with frank abscess formation and those without non-surgical treatment response.<sup>7</sup>

Therapy decisions must consider the risks and benefits of treatment and the clinical course related to chemotherapy and oncologic prognosis.<sup>6</sup> The literature revealed a knowledge gap in the approach to anal pathologies in patients with hematologic neutropenia during diagnosis or chemotherapy. Demonstrating a correlation between grade and duration of neutropenia

with complications of surgical intervention could be useful to improve the management of these challenging cases. Therefore, this study aimed to examine our institutional data on perianal pathologies during the neutropenic period and investigate the relationship among the total white blood cell (WBC; neutrophils, monocytes, eosinophils, basophils, lymphocytes, and blasts)-neutrophil count, perianal lesion, and the type of treatment in patients with hematologic malignancies.

**Material and Methods.** The demographic and clinical characteristics of 480 adult patients with a hematologic malignancy and hospitalized for cytotoxic chemotherapy at the Bursa Uludag University Hospital Department of Hematology between January 2010 and May 2021 were retrieved from the medical files and then retrospectively analyzed. Patients who are complicated by perianal pathology and with at least one imaging method (computerized tomography, magnetic resonance imaging, and ultrasonography) were included in the study. The median age, gender, diagnosis, complete blood count analysis at the time of hospitalization for hematologic malignancy, biochemical parameters, duration of neutropenia, active disease at hospitalization, perianal pathology types, anorectal disease history, and surgical history were evaluated. Our study was conducted under the institutional research committee's ethical standards and according to the 1964 Helsinki Declaration. This study was approved by the clinical research ethics committee of Bursa Uludag University Faculty of Medicine (Decision No: 2021-15/6).

Continuous variables were expressed as median (range) values and categorical variables as frequency and corresponding percentage values. Statistical analyses were done using the Statistical Package for the Social Sciences version 23 package program. The Mann-Whitney U test was used for group comparison.

**Table 1.** Demographic data and diagnostic features of patients.

<b>Age; median (min-max)</b>		n = 42; 63.6 (39.4–85.8)
<b>Gender</b>	<i>Male</i>	29 (69.1%)
	<i>Female</i>	13 (30.9%)
<b>WBC (K/<math>\mu</math>L); median (min-max)</b>		6810 (330–232900)
<b>Diagnosis</b>	<i>AML</i>	31 (73.8%)
	<i>ALL</i>	7 (16.6%)
	<i>Burkitt's Lymphoma</i>	3 (7.1%)
	<i>Multiple Myeloma</i>	1 (2.5%)
<b>ARD History</b>	<i>Yes</i>	18 (42.9%)
	<i>No</i>	24 (57.1%)
<b>Anal Pathology</b>	<i>Anal Abscess</i>	30 (71.4%)
	<i>Anal Fistula</i>	7 (16.6%)
	<i>Anal Fissure</i>	4 (9.5%)
	<i>External Hemorrhoid</i>	1 (2.5%)
<b>Active Disease</b>	<i>Yes</i>	27 (64.2%)
	<i>No</i>	15 (35.8%)
<b>Surgical Intervention</b>	<i>Yes</i>	13 (30.9%)
	<i>No</i>	29 (69.1%)

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; ARD: anorectal disease; WBC: white blood cell.

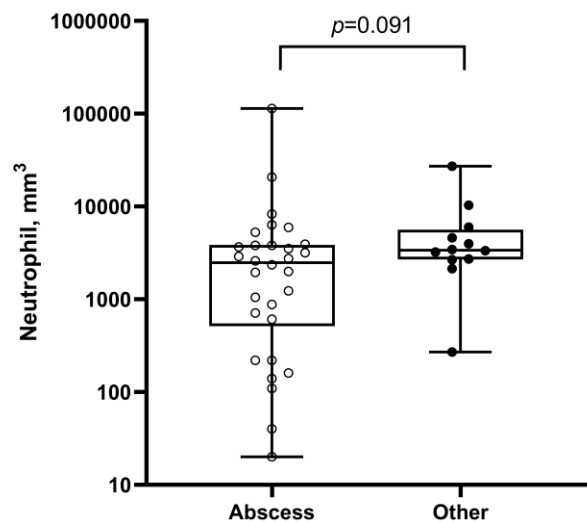
Categorical data were evaluated using the Chi-square test. Statistical significance was accepted as  $p < 0.05$ . Correlations were determined using the Spearman correlation coefficient.

**Results.** The study included a total of 42 patients. The demographic data and treatment characteristics of patients are shown in **Table 1**. The incidence of perianal pathology was 8.7% (42/480). The median age of patients during the diagnosis was 41 (18–70) years. Of the patients, 29 were males, 13 were females, 31 had acute myeloid leukemia (AML), 7 had acute lymphoblastic leukemia (ALL), 3 had Burkitt's lymphoma, and 1 had multiple myeloma. Patients with a history of anorectal disease before diagnosis or treatment accounted for 18, and those without were 24. Perianal complications that developed after cytotoxic therapy included anal abscess in 30, anal fistula in 7, anal fissure in 4, and external hemorrhoid in 1 patient.

Additionally, 13 were operated on, and 29 did not require surgical intervention. While 27 patients had active disease, 15 received consolidation therapy. The comparison between the groups revealed no statistical significance between the anal abscess formation and neutrophil count (**Figure 1**;  $p = 0.091$ ). No correlation could be found between the neutrophil count at the time of hospitalization for hematological disease and the development of an anal abscess. However, a statistically significant association was found between AML diagnosis and anal abscess development (**Table 2**;  $p = 0.002$ ,  $X^2 = 11.638$ ). The incidence of the anal abscess was found to be higher in AML patients than in ALL patients. When the patients were compared according to their white blood cell counts at the time of hospitalization for hematological malignancy, the surgical intervention for the anal abscess was found to be low in patients with high white blood cell counts, and this relationship is statistically significant (**Figure 2A**;  $p = 0.0209$ ). There was no correlation between neutrophil counts at hospitalization for hematological malignancy and surgical intervention for anal abscess (**Figure 2B**;  $p =$

0.3486). Although there was no statistical significance between the duration of neutropenia and the development of anal abscess (**Figure 2D**;  $p = 0.1023$ ), a positive correlation statistically significant was observed between the duration of the neutropenia and the outcome of the surgical intervention requested for the anal abscess (**Figure 2C**;  $p = 0.0297$ ). No statistical significance was found between the anal abscess formation ( $p = 0.924$ ) or surgical intervention ( $p = 0.520$ ) and the history of perianal pathology (**Table 3**). The median overall survival (OS) of patients was 30.1 months (95% confidence interval [CI]: 21.2–38.9), and the overall mortality rate was 52.3%. The comparison of patient survival to their anal abscess status revealed no significant difference between the two groups (**Figure 3**;  $p = 0.3587$ ). Only one patient with an anal abscess died during the first month due to perianal sepsis.

Abscess material cultures of 14 (14/30) patients with anal abscesses were positive. Isolated species under which antibiotic coverage cultures were positive are

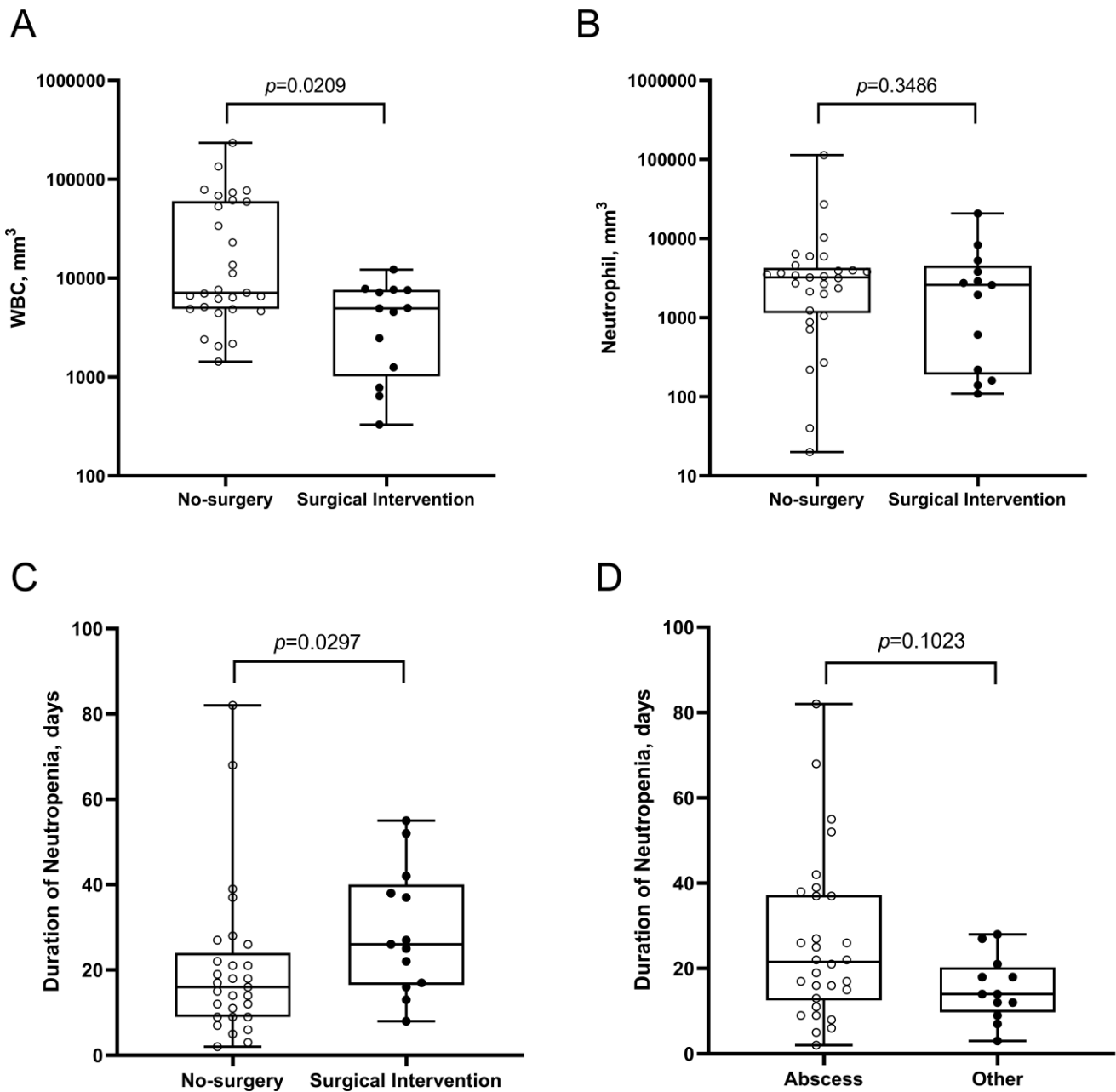


**Figure 1.** Comparison of neutrophil count at the time of hospitalization for hematological malignancy and the development of anal abscess.

**Table 2.** Anal abscess in AML, ALL, and other group of patients.

	AML	ALL	Other	p-value* X <sup>2</sup> value
Anal Abscess	25/31 (80.6%) <sup>a</sup>	1/7 (14.3%) <sup>b</sup>	4/4 (100%) <sup>a</sup>	$P = 0.001$ $X^2 = 11.817$
Pairwise comparisons				
	AML –	ALL		$p = 0.002$ $X^2 = 11.638$
	AML –	Other		$p = 0.999$ $X^2 = 0.934$
	ALL –	Other		$p = 0.015$ $X^2 = 7.543$

a-b: a statistically significant difference between the groups with different letters in the same line ( $p < 0.05$ ). \*Fisher's Exact Chi-square Test was used ( $p < 0.05$ ). ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia.

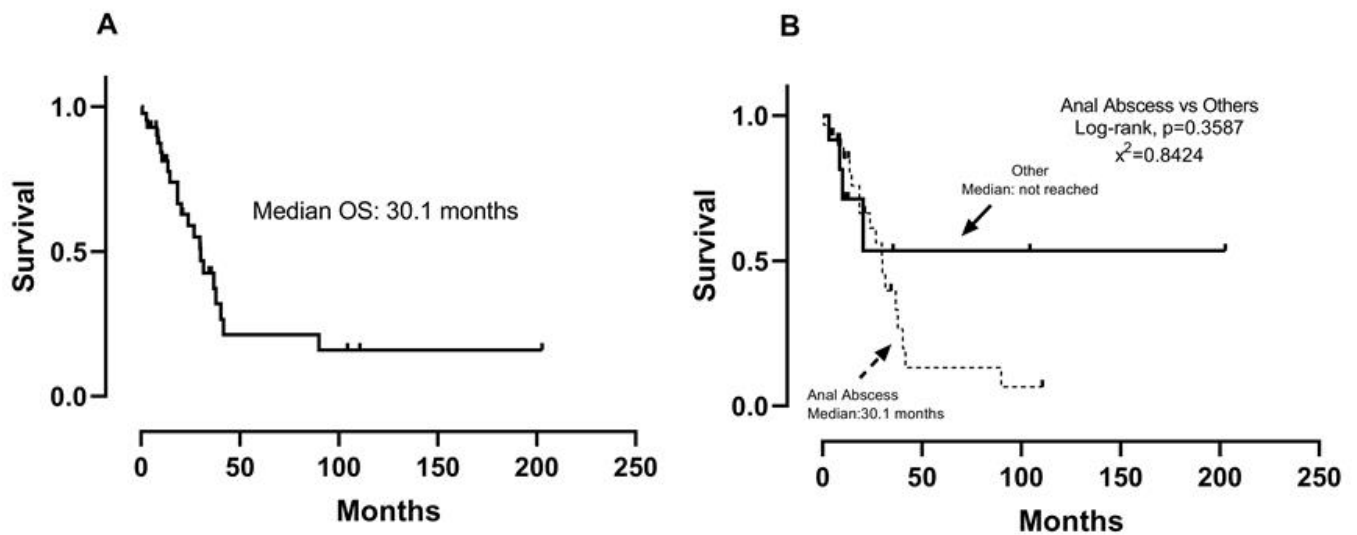


**Figure 2.** Total white blood cell (WBC) counts at the time of the hospitalization for hematologic malignancy with and without surgery (A). Neutrophil counts at the time of hospitalization for hematological malignancy with and without surgery (B). The duration of neutropenia in anal abscess with and without surgery (C). The duration of neutropenia in patients with anal abscess and anal pathology other than anal abscess (D). Data are shown as median, minimum, maximum, and points for each data as a Whisker-plot graphic. The difference between the groups was evaluated using the Mann-Whitney U test ( $p < 0.05$ ).

**Table 3.** The association between surgical intervention and anal abscess as determined by ARD history.

		History of ARD
Surgical Intervention	Correlation Coefficient	-0.102
	<i>p-value</i>	0.520
Abscess	Correlation Coefficient	0.015
	<i>p-value</i>	0.924

ARD: anorectal disease.



**Figure 3.** The overall survival of patients with perianal pathologies (A). The comparison of the overall survival between the patients with anal abscesses and other perianal pathologies (B).

**Table 4.** Isolated species and empirical antibiotic use in patients with anal abscess.

#	Spp.	Antibiotic	Disease type
1	<i>Escherichia coli</i>	Piperacillin/tazobactam + Teicoplanin	ALL
2	<i>Escherichia coli</i> <i>Enterococcus faecium</i>	Meropenem + Amikacin	AML
3	<i>Enterococcus faecium</i>	Meropenem + Teicoplanin	AML
4	<i>Klebsiella Pneumoniae</i>	Meropenem + Daptomycin + Metronidazole	AML
5	<i>Enterococcus faecium</i>	Meropenem + Metronidazole	AML
6	<i>Enterococcus faecium</i>	Imipenem + Metronidazole	AML
7	<i>Klebsiella pneumoniae</i>	Meropenem + Teicoplanin	AML
8	<i>Escherichia coli</i>	Meropenem + Linezolid	AML
9	<i>E Escherichia coli</i> <i>Enterococcus faecium</i>	Meropenem + Vancomycin	AML
10	<i>Acinetobacter baumannii</i> <i>Escherichia coli</i>	Meropenem + Vancomycin + Metronidazole	AML
11	<i>Escherichia coli</i> <i>Enterococcus faecium</i> <i>Klebsiella pneumoniae</i>	Meropenem + Vancomycin + Metronidazole	AML
12	<i>Escherichia coli</i> <i>Enterococcus faecium</i> <i>Klebsiella pneumoniae</i>	Meropenem + Vancomycin	AML
13	<i>Escherichia coli</i> <i>Enterococcus faecium</i>	Meropenem	Burkitt Lymphoma
14	<i>Enterococcus faecium</i>	Meropenem + Teicoplanin + Metronidazole	AML

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; spp: species, #: number.

shown in **Table 4**. The most commonly isolated species are *Escherichia coli* (*E.coli*), *Enterococcus faecium*, and *Klebsiella pneumoniae*. Since the patients in the study were diagnosed with a hematological malignancy in the neutropenic period, the patients were under empirical antibiotherapy at the time of anal abscess development. Patients were usually given carbapenems (13/14) for gram-negative bacteria and glycopeptides (8/14) for gram-positive bacteria when their cultures were positive. All 13 patients were put on piperacillin/tazobactam after the initial febrile neutropenic episode. The switch to

Carbapenem was done when the surgery material cultures were taken.

**Discussion.** Patients with neutropenia are susceptible to anorectal complications, and symptomatic anorectal pathology affects 2%–32% of patients with hematology-oncology.<sup>9</sup> The absence of inflammatory cells masks the clinical manifestations of anorectal infections in patients with neutropenia; thus, detecting the symptoms in these patients is difficult. If left untreated, anorectal infections can progress between tissue layers and cause an abscess

or necrotizing fasciitis.<sup>10</sup>

Our study's rate of perianal pathology was 8.7%, and 29 of the patients were male, and 14 were female. Previous studies revealed a male-to-female ratio between 3–3.5, with AML predominance in patients with perianal infections. Male and AML predominance was similar to previous studies.<sup>1,2</sup> Male predominance is explained by the higher incidence of patients with AML in our series and the higher incidence of AML in males.<sup>11</sup> A previous history of anorectal disease did not favor, in a way statistically significant, anal abscess development and surgical intervention in our study, according to Badgwell et al., who compared the presence or no of anorectal history in patients submitted to surgical intervention for anal pathologies in the neutropenic period.<sup>6</sup> On the contrary, another study comparing the patients with anorectal history with anal abscesses or not revealed a statistical significance.<sup>9</sup> Multicenter studies with a large number of patients are needed to evaluate better the anorectal disease history and perianal infections in the neutropenic period.

The incidence of anal abscess varies in retrospective studies on perianal complications in patients with hematological malignancies.<sup>1,2</sup> In our research, anal abscess constituted the majority of perianal complications. Additionally, the incidence of anal abscesses was higher in AML patients than in ALL patients with statistical significance ( $p = 0.002$ ). Some similar studies revealed no relationship between the disease type and anal abscess development.<sup>1,2,9</sup> However, other studies showed that recurrent perianal infections are more common in patients with AML than in ALL.<sup>1,12</sup> The small number of patients may explain the higher incidence of perianal complications in patients with AML than ALL included in this study and myeloid leukemias, the use of high-dose cytarabine-based regimens with more mucositis side effects.<sup>13</sup>

In our study, *E. coli*, *Enterococcus faecium*, and *Klebsiella pneumoniae* were the most common agents in cultures from anal abscess surgery material. Similarly, *E. coli*, *Enterococcus spp.*, and *Non-Bacteroides fragilis* were the most prevalent agents recovered from cultures sent from anal abscess surgery material in a study of cancer patients.<sup>10</sup> The most frequently isolated pathogens in another investigation of anal infections in individuals with acute leukemia were *Enterococcus spp* and *E.coli*, respectively, and carbapenems, piperacillin/tazobactam, cefepime, and vancomycin were the most often utilized antibiotics.<sup>1</sup> It was highlighted again that, in accordance with the relevant literature, the antibiotics used empirically should be active versus enteric agents such as *Enterococcus spp.* and *E. coli*, as well as isolated agents and medications employed in this study. Another noteworthy finding in this study is that a bacterium known to cause complications in cancer centers, *Pseudomonas aeruginosa*, was not found in the cultures.

This could be because of the prophylactic use of ciprofloxacin in acute leukemia remission/induction regimens.<sup>14</sup>

Buyukasik et al. revealed that the neutrophil count during diagnosis affected the surgical intervention due to anal abscess and possible cure after the surgical intervention. Still, the authors did not mention the number of leukocytes.<sup>2</sup> Our study revealed that the neutrophil count did not statistically affect the anal abscess development or the surgical intervention; however, statistical significance was found between the total WBC counts during the diagnosis of hematologic malignancy and the surgical intervention. Furthermore, the frequency of surgery in patients with high WBC count (most of them with AML) was lower than in those with low WBC count. This relationship has been demonstrated for the first time in the literature. However, it needs to be further discussed and validated, which may be explained by the worse clinical course of patients with high WBC count during diagnosis and the early use of antibiotics.

In our study, the comparison of the duration of neutropenia with the anal abscess development revealed no statistical significance, and more neutropenic days increased the incidence of undergoing anal abscess surgery. This relationship was statistically significant. However, a study showed no statistical significance in the duration of neutropenia compared with the perianal complication development.<sup>9</sup> Therefore, it is difficult to say that there is a relationship between the time of neutropenia and the surgical intervention for anal abscess.

Mortality rates and survival times differ in studies that evaluated anal pathologies of patients with cancer. A study that assessed the anorectal complications of patients with hematological cancer in the neutropenic period revealed a 41.2% overall mortality rate.<sup>9</sup> A similar study showed a 2.4% mortality rate within one month.<sup>4</sup> A cohort study of most patients with leukemia revealed that the median survival was 14.4 months (95% CI: 7.9–19.5).<sup>6</sup> The OS in our study was 30.1 months, and the overall mortality rate was 52.3%. Only one patient died in the first month (mortality rate: 2.3%). The survival of patients with anal abscesses compared with other anal pathologies revealed no statistical significance in our study. Therefore, the OS seems to be better, and the mortality rates were compatible with other studies.

**Study Limitations.** Limitations of this study are its retrospective nature, its small sample size, and the inclusion of patients having both induction and consolidation chemotherapy. The study, even if includes a small proportion of nonleukemic patients, reflects the behavior of leukemic patients, considering that also the Burkitt lymphoma assumes a leukemic character.

**Conclusions.** In conclusion, this article has shown that

white blood cell count at the time of hospitalization in patients with hematological malignancy can affect the surgical intervention due to anal pathologies that may occur in the neutropenic period. Therefore, large-scale

randomized studies with more patients are needed to predict the course of anal pathology, the need for surgery, and appropriate treatment in those groups of patients.

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