DOI: 10.4274/MMJ.galenos.2024.94884
Medeni Med J 2024;39:261-267

Original Article

The Serum Biomarkers in Ulcerative Colitis

Ülseratif Kolitte Serum Biyobelirteçleri

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ABSTRACT

Objective: In this study, the aim was to evaluate the diagnostic effectiveness of more easily applicable and cost-effective serum biomarkers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP) to albumin ratio (CAR), and CRP-to-lymphocyte ratio (CLR), instead of the endoscopic activity index (EAI) used to determine disease activation in ulcerative colitis (UC) patients.

Methods: Blood tests performed during the same period as colonoscopy were reviewed, and NLR, PLR, CAR, and CLR values were calculated. Based on the EAI score, patients with a score <4 were classified as having UC in remission, those with a score ≥4 as having active UC, and those with normal colonoscopy results as the control group.

Results: The study included 66 patients with active UC, 31 with UC in remission, and 99 controls. The CLR and CAR values of active and remission UC patients were found to be higher compared with the control group ($p<0.001$), while no significant difference was found between the groups in terms of PLR and NLR values ($p>0.05$). The AUC calculated for CLR in diagnosing active UC was significant ($p<0.001$), and the best cut-off value was determined as >1,75. For CAR, the best cut-off value was calculated as >0.11.

Conclusions: This study demonstrated that the CLR and CAR had high sensitivity and specificity for detecting UC activity, whereas the PLR and NLR had low diagnostic value.

Keywords: Ulcerative colitis, inflammation markers, colonoscopy, endoscopic activity index

ÖZ

Amaç: Bu çalışmada, ülseratif kolit (ÜK) hastalarında hastalık aktivasyonunu belirlemek için kullanılan endoskopik aktivite indeksi (EAI) yerine nötrofil-lenfosit oranı (NLO), trombosit-lenfosit oranı (PLO), C-reaktif protein (CRP) albümin oranı (CAO) ve CRP-lenfosit oranı (CLO) gibi daha kolay uygulanabilir ve maliyet etkin serum biyobelirteçlerinin tanısal etkinliğinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Kolonoskopi ile aynı dönemde alınan kan testleri gözden geçirilmiş ve NLO, PLO, CAO ve CLO değerleri hesaplanmıştır. EAI skoruna göre, skoru<4 olan hastalar remisyonda ÜK, skoru ≥4 olanlar aktif ÜK ve kolonoskopi sonuçları normal olanlar kontrol grubu olarak sınıflandırılmıştır.

Bulgular: Çalışmaya 66 aktif ÜK, 31 remisyondaki ÜK ve 99 kontrol grubu katılımcısı dahil edilmiştir. Aktif ve remisyondaki ÜK hastalarının CLO ve CAO değerleri kontrol grubuna göre yüksek bulunurken ($p<0,001$), PLO ve NLO değerlerinde anlamlı fark bulunmadı ($p>0,05$). Aktif ÜK tanısında CLO için hesaplanan AUC anlamlıydı ($p<0,001$) ve en iyi cut-off >1,75 olarak belirlendi. CAO için en iyi cut-off >0,11 olarak hesaplanmıştır.

Sonuçlar: Bu çalışma, CLO ve CAO'ın ÜK aktivitesini saptamada yüksek duyarlılık ve özgüllüğe sahip olduğunu, PLO ve NLO'nun ise düşük tanısal değere sahip olduğunu göstermektedir.

Anahtar kelimeler: Ülseratif kolit, inflamasyon belirteçleri, kolonoskopi, endoskopik aktivite indeksi

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease[1]. During disease course, periods of relapse and remission are often observed. Disease activity was assessed using clinical symptoms and endoscopic findings. The Rachmilewitz Endoscopic Activity Index (EAI) is an index used to determine disease severity. Based on findings such as mucosal erythema, ulceration, granularity, vascular pattern, and bleeding, the EAI is used to evaluate the remission and activation status of the disease[2]. Early detection of disease activity and appropriate treatment are crucial for improving prognosis and quality of life[3,4].

Colonoscopy is the most important examination for evaluating disease activity in UC. However, this procedure is invasive, requires bowel preparation, and is not

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Received: 05 October 2024
Accepted: 01 November 2024
Online First: 04 December 2024

Cite as: Sezer S, Demirci S, Kara MI, Korkmaz M. The Serum Biomarkers in Ulcerative Colitis. Medeni Med J. 2024;39:261-267

always easily performed on demand. Numerous serum biomarkers that are easy to implement, non-invasive, and inexpensive have been investigated as alternatives to endoscopic evaluation for determining disease activation in UC[5]. C-reactive protein (CRP) is a test used to assess the activation of UC; however, their sensitivity and specificity are not satisfactory[6]. Recently, various integrated indices, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), CRP-to-albumin ratio (CAR), and CRP-to-lymphocyte ratio (CLR), have been utilized for the assessment of infectious illnesses[7-10].

The aim of this study was to determine the diagnostic effectiveness of more easily applicable and low-cost serum biomarkers (NLR, PLR, CAR, CLR) as alternatives to EAI for detecting disease activation in UC.

MATERIALS and METHODS

For this retrospective study, patients aged over 18 years with UC who underwent colonoscopy at Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital between January 2022 and August 2024 were screened from the hospital information system. Patients diagnosed with UC through endoscopic and histopathological evaluations and assessments based on the Rachmilewitz EAI were included in the study. The control group consisted of consecutive patients without a diagnosis of UC who had normal colonoscopy findings.

The exclusion criteria were as follows: individuals with suspected UC, Crohn's disease, patients who were not graded according to the Rachmilewitz EAI, individuals with solitary rectal ulcers, those with radiation colitis, patients with missing routine blood test results, individuals who had undergone total or subtotal colectomy, patients with inflammatory conditions unrelated to UC (trauma, liver cirrhosis, malignancy), acute and chronic renal failure, pregnancy, other autoimmune diseases (Behçet's disease, psoriasis, rheumatoid arthritis), and those with active viral or bacterial infections that could potentially affect laboratory parameters were excluded from the study. The exclusion criteria were similar for the control group and the UC group. Ethical approval was obtained from the Health Sciences University Türkiye, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Non-interventional Clinical Research Ethics Committee (decision no: 2024-07/103, date: 25.07.2024). The Helsinki Declaration was waived for the requirement of written informed consent, as only medical data from the patients' electronic records were extracted.

Data Collection

Blood tests performed concurrently with colonoscopy were included in the evaluation.

The following inflammatory indices were computed for analysis. The NLR was calculated by dividing the neutrophil count (10^9/L) by the lymphocyte count (10^9/L)[7]. The PLR was calculated by dividing the platelet count (10^9/L) by the lymphocyte count (10^9/L)[8]. The CAR was calculated by dividing the CRP levels (mg/L) by the albumin levels (g/L)[9]. CLR was calculated by dividing CRP levels (mg/L) by the lymphocyte count (10^9/L)[10]. The activity of UC was assessed by scoring according to the Rachmilewitz EAI (Figure 1)[11].

Groups

According to the Rachmilewitz EAI, patients with a score <4/12 were classified as being in remission from UC, those with a score ≥4/12 were classified as having active UC, and individuals with normal colonoscopy results and no UC were designated as the control group.

Sample Size

For the sample size calculation, a significance level of 5% and statistical power of 80% were utilized in accordance with the retrospective study methodology. According to the literature, studies on biomarker ratios require a minimum of 30-50 participants in each group to detect medium effect sizes[12]. This study included 66 participants in the active UC group, 31 in the remission group, and 99 in the control group, achieving a sufficient sample size to detect differences in biomarkers among the groups.

Endoscopic Activity	**0**	**1**	**2**	**3**
Mucosal Erosions	None	Mild	Moderate	Severe
Ulcers	None	Single-surfaced	Superficial, multiple	Deep, localized
Mucosal Hyperemia	None	Mild	Moderate	Severe
Loss of Vascular Pattern	None	Mild	Moderate	Severe
Hemorrhagic Mucosal Surface	None	Minimal	Moderate	Widespread

Figure 1. Rachmilewitz endoscopic activity index

Statistical Analysis

Descriptive statistics for continuous data included mean, standard deviation, median, minimum, maximum, and interquartile range with the 25^{th}-75^{th} percentile values, while counts and percentages were reported for categorical data. The Shapiro-Wilk test was used to assess the normality of the data distribution. Comparisons of continuous variables among patients in the active, remission, and control groups were performed using the Kruskal-Wallis variance analysis. The sources of the differences among the groups were examined using the Kruskal-Wallis multiple comparison test. For nominal variable group comparisons (in cross-tabulations), the chi-square test was utilized. The diagnostic performance of the CLR and CAR values was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). The optimal cut-off point was determined using Youden's index. The diagnostic accuracy metrics for the CLR and CAR values (sensitivity, specificity, positive predictive value, and negative predictive value) were assessed. IBM SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL) was used for the analyses, with a significance level set at $p<0.05$.

RESULTS

In total, 4,056 colonoscopy reports were screened, and 422 patients with UC were identified. Following the application of the exclusion criteria, 196 patients were enrolled in the study: 66 with active UC, 31 in remission, and 99 in the control group (Figure 2).

The distribution of sex among patients in the active, remission, and control groups did not reveal any meaningful distinction ($p>0.05$) (Table 1).

In contrast, a notable variation in white blood cell (WBC) counts was observed between the groups ($p<0.05$). Using the Kruskal-Wallis multiple comparison test, we observed that the WBC counts in the active UC group were significantly elevated compared with the control cohort, whereas no notable differences were found among the other group comparisons ($p>0.05$). Moreover, no meaningful distinction was found in hemoglobin (HB) levels across the active, remission, and control groups ($p>0.05$). No meaningful distinction was observed in the NLR values among the active, remission, and control groups ($p>0.05$). The PLR values did not exhibit

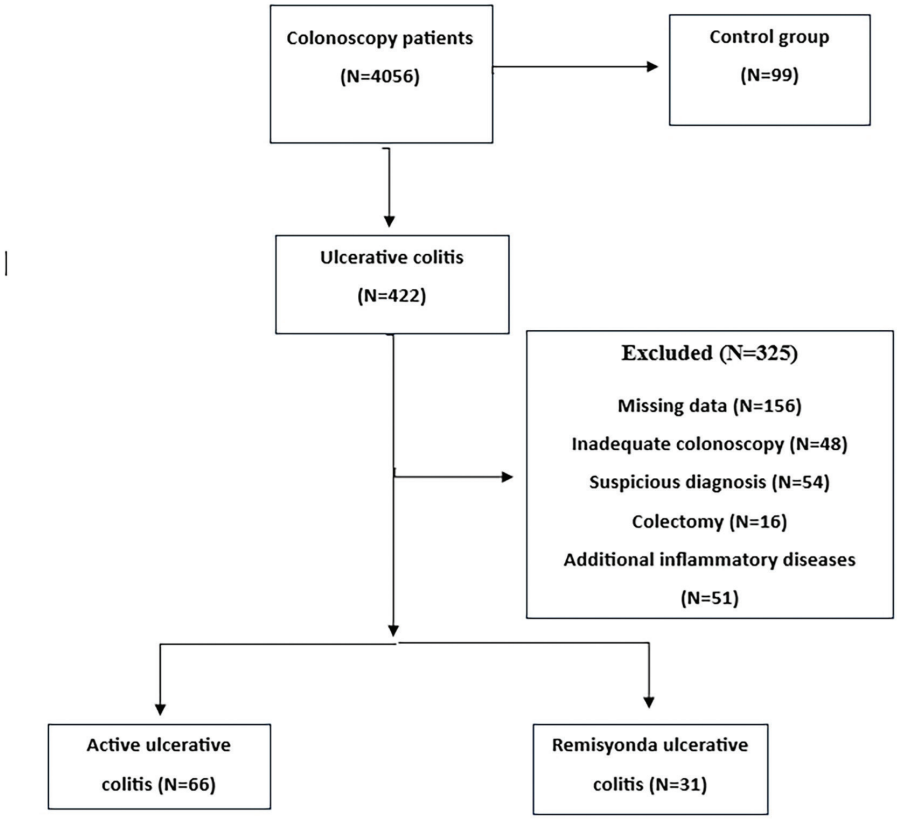

Figure 2. Flow chart of the study

significant variations between the active, remission, and control groups (p>0.05). However, a statistically significant distinction was detected in the CLR values among the active, remission, and control groups (p<0.001). The CLR values in the active and remission UC groups were significantly elevated compared with the control group. There was no noteworthy difference between the CLR values of the active and remission UC groups (p>0.05). Additionally, a meaningful distinction was observed in CAR values among patients across the three groups (p<0.001). Further analysis using the Kruskal-Wallis multiple comparison test revealed that the CAR values in the active and remission UC groups were significantly higher than those in the control group, with no meaningful distinction between the CAR values of the active and remission UC cohorts (p>0.05) (Table 2).

The AUC for CLR values in distinguishing active UC diagnosis was found to be significant (p<0.001), with the cut-off point for CLR values established at >1.75 (Figure 3A) (Table 3).

Similarly, the calculated AUC for CAR values in differentiating active UC diagnosis was found to be significant (p<0.001). The cut-off threshold for CAR values was set to greater than 0.11 (Figure 3B) (Table 3).

The AUC calculated for CLR values in distinguishing remission UC was found to be significant (p<0.01). The cutoff threshold for CLR values was found to be greater than 1.28 (Table 4).

The AUC calculated for CAR values in distinguishing remission UC was found to be significant (p<0.01). The cut-off threshold for CAR values was set to greater than 0.07 (Table 4).

Table 1. Comparison of sex between the active, remission, and control groups

	Active UC (n=66)	Remission UC (n=31)	Control (n=99)	
	n (%)	n (%)	n (%)	
Sex				
Famale	22 (33.3)	9 (29.0)	41 (41.4)	0.358[c]
Male	44 (66.7)	22 (71.0)	58 (58.6)	

[c]; Chi -Square test, UC; Ulcerative colitis

Table 2. Comparison of findings among patients in the active, remission, and control groups

	Active UC (n=66)	Remission UC (n=31)	Control (n=99)		
	Median (IQR)	Median (IQR)	Median (IQR)	p-value	Post hoc
WBC	7.69	6.71	6.64 (5.61-7.83)	0.012[k]	a-b p=0.843
(10^3/µL)	(5.98-9.40)	(6.04-8.72)			**a-c p=0.009**
					b-c p=0.751
HB (g/dL)	14.1 (12.8-15.0)	14.2 (12.6-15.5)	14.0 (12.3-15.5)	0.968[k]	
NLR	2.28 (1.73-3.10)	1.94 (1.66-2.55)	1.89 (1.46-2.57)	0.057[k]	
PLR	140.25	127.50	127.71	0.054[k]	
	(112.24-198.21)	(102.20-172.60)	(102.52-166.53)		
CLR	3.21 (1.36-6.25)	1.61 (0.83-3.0)	0.93 (0.37-1.44)	<0.001[k]	a-b p=0.099
					a-c p<0.001
					b-c p=0.010
CAR	0.14 (0.06-0.26)	0.07 (0.03-0.20)	0.05 (0.02-0.07)	<0.001[k]	a-b p=0.155
					a-c p<0.001
					b-c p=0.024

[k]:Kruskal-Wallis test, data are presented as median (25%-75%), UC: Ulcerative colitis, a: Active ulcerative colitis, b: Remission ulcerative colitis, c: Control, WBC: White blood cell, HB: Hemoglobin, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet lymphocyte ratio, CLR: C-reactive protein lymphocyte ratio, CAR: C-reactive protein albumin ratio, IQR: Interquartile range

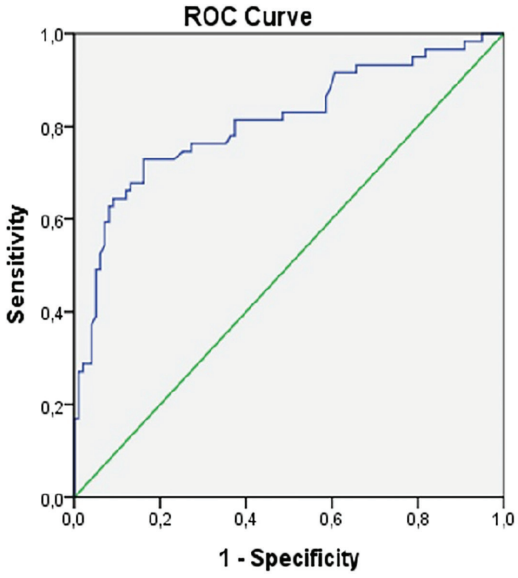

Figure 3A. Cut-off point for CLR values

CLR: C-reactive protein lymphocyte ratio, ROC: Receiver operating characteristic

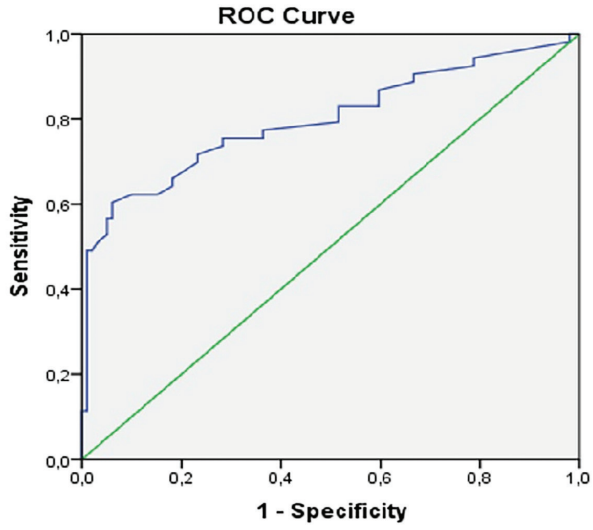

Figure 3B. Cut-off point for CAR values

CAR: CRP-to-albumin ratio, ROC: Receiver operating characteristic

Table 3. Diagnostic performance of CLR and CAR in the identification of active ulcerative colitis patients.

	AUC 95% CI	p-value	Cut-off	Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI
CLR	**0.810**	**<0.001**	>1.75	72.8%	83.8%	72.8%	83.8%
	0.735-0.885			60.4-82.5	75.3-89.8	65.1-79.5	76.9-89.0
CAR	0.798	**<0.001**	>0.11	60.3%	92.9%	82.0	81.4
	0.716-0.881			46.9-72.4	86.1-96.5	74.8-87.6	74.1-87.1

AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value, CLR: C-reactive protein lymphocyte ratio, CAR: C-reactive protein albumin ratio, CI: Confidence interval

Table 4. Diagnostic performance of CLR and CAR values in distinguishing remission ulcerative colitis patients.

	AUC 95% CI	p-value	Cut-off 95% CI	Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI
CLR	0.698	**<0.001**	>1.28	65.5	68.6	38.0	87.2
	0.589-0.806			47.3-80.0	59.0-76.9	29.6-47.0	79.8-92.2
CAR	0.668	**0.008**	>0.07	55.5	76.7	39.4	86.3
	0.547-0.789			37.3-72.4	67.5-83.9	31.0-48.6	78.8-91.6

PPV: Positive predictive value, NPV: Negative predictive value, CLR: C-reactive protein lymphocyte ratio, CAR: C-reactive protein albumin ratio, CI: Confidence interval

DISCUSSION

Our study demonstrated that the serum biomarkers CLR and CAR had high sensitivity and specificity for detecting active UC according to the Rachmilewitz EAI, whereas the PLR and NLR values proved ineffective in determining the activation status. Additionally, we identified a cut-off value for CLR of >1.75 and CAR of >0.11 for active UC.

Lymphocytes secrete cytokines and intestinal proteases, resulting in mucosal layer damage. These immune cells tend to accumulate in the inflamed region of the lamina propria[13,14]. In individuals with

active inflammatory bowel disease (IBD), lymphocytes translocate from the peripheral circulation to inflamed intestinal tissues, thereby resulting in peripheral lymphopenia. Patients with IBD frequently exhibit increased levels of thrombopoietin and interleukin-6, both of which contribute to the maturation of megakaryocytes[15]. The platelets present in peripheral blood may be activated and exhibit spontaneous aggregation, as well as increased sensitivity to pro-aggregatory agents[16]. Therefore, peripheral thrombocytosis is frequently observed in patients with active UC[17].

Although the precise mechanism linking CRP to disease activity remains somewhat ambiguous, multiple biologically plausible explanations have been proposed. CRP and albumin are widely used as markers of acute inflammation in clinical practice, with albumin also reflecting the nutritional status. Cytokines produced by inflammation may suppress albumin production in the liver[18]. Increased levels of cytokines as a result of inflammation may cause malnutrition[19]. This may explain why CAR better reflects disease activity in patients with longer disease durations.

Lin et al.[20] Found that CLR and CAR had high predictive accuracy for diagnosing severe UC, with AUC values of 0.732 and 0.714, respectively. The higher sensitivity of CLR (67%) compared with CAR suggests its broad applicability in screening for inflammation. Zhang et al.[21] demonstrated that CAR had high specificity in diagnosing active UC according to the Rachmilewitz EAI, but its sensitivity was relatively low. Similar to our study, we found that the sensitivity of CLR (72.8%) for predicting active UC was higher than that of CAR (60.8%). In patients with active UC, the AUC values for CLR and CAR were 0.810 and 0.798, respectively. The cut-off values for active UC were >1.75 for CLR and >0.11 for CAR. The higher sensitivity of CLR in patients with active UC in our study indicates that CLR is more effective than CAR for detecting inflammation. However, although the specificity of CLR (83.8%) is not as high as that of CAR (92.9%), it is still quite robust. The difference in our cut-off values compared with Lin et al.[20] may be attributed to our comparison of CLR and CAR with the EA score instead of the Mayo Clinic score.

The presence of parameters more closely associated with chronicity, such as albumin, in the CAR calculation may have contributed to its slightly lower sensitivity in active inflammatory conditions compared with CLR.

In remission UC, the cutoff values for CLR and CAR (>1.28 and >0.07, respectively) and their negative predictive values (87.2% and 86.3%) indicate that these markers may serve as reliable indicators for ruling out remission.

In a study conducted by Feng et al.[22], the PLR and NLR ratios in patients with active and remission UC were compared with those of CRP, ESR, and fecal calprotectin. The sensitivity of NLR in active UC was 78.8% with a specificity of 65%, whereas that of PLR was 58.3% with a specificity of 75%.

Samuel et al.[23] did not identify any relationship between PLR and NLR values and UC activation. Similarly, in our study, we did not find an association between NLR and PLR values and disease activation. The differing results compared with those of Feng et al.[22] may be due to our comparison of the PLR and NLR values with the EAI.

The strengths of our study include its ability to be one of the rare studies to evaluate biomarkers in conjunction with the Rachmilewitz EAI in the Turkish population. Second, it provides a cost-effective and easily applicable option for disease activity assessment.

Study Limitations

The limitations of our study include its retrospective nature, which led to missing demographic data for some patients. Second, although the diagnosis of UC in our participants was confirmed through past pathology reports, there were deficiencies in pathological evaluations that could have added additional insight for determining disease remission alongside the EAI. Third, the limited number of patients in remission has restricted the statistical interpretation of this patient group.

CONCLUSION

Our study demonstrated that both CLR and CAR have high sensitivity and specificity for detecting UC activity. There is a need for further investigation into the dynamic changes in these inflammatory indices in relation to the activity and severity of UC. Additionally, we determined the cutoff values for active UC to be >1.75 for CLR and >0.11 for CAR. Similarly, our findings indicate that CLR has a higher sensitivity (72.8%) compared to CAR (60.8%) in predicting active UC. On the other hand, the PLR and NLR values were ineffective in indicating UC activation. Future studies should evaluate the relationship between these indices and UC in greater detail.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Health Sciences University Türkiye,

Abdurrahman Yurtaslan Ankara Oncology CPSU Non-Interventional Clinical Research Ethics Committee (decision No: 2024-07/103, date: 25.07.2024)

Informed Consent: The Helsinki Declaration was waived for the requirement of written informed consent, as only medical data from the patients' electronic records were extracted.

Footnotes

Author Contributions

Concept: S.S., M.K., Design: S.S., M.K., Data Collection and/or Processing: S.S., M.I.K., Analysis and/or Interpretation: S.D., M.I.K., Literature Search: S.S., M.I.K., Writing: S.S.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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