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RESEARCH

A new prognostic index associated with pathological complete response in rectal cancer

Rektum kanserinde patolojik tam yanıt ilişkili yeni bir prognostik index

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Abstract

Purpose: Approximately half of rectal cancer cases are diagnosed at a locally advanced stage. It is important to identify biomarkers that can predict pathological complete response in patients undergoing surgery following neoadjuvant chemoradiotherapy.

Materials and Methods: This retrospective study included 205 patients with locally advanced rectal cancer who underwent surgery and adjuvant chemotherapy following neoadjuvant chemoradiotherapy. Inflammatory biomarkers were assayed in the complete blood count before neoadjuvant therapy.

Results: A pathological complete response was detected in 20.5% of the patients. The neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and pan-immune inflammation value were significantly lower in the pathological complete response (+) group than in the pathological complete response (-) group. The cut-off of the pan-immune inflammation value was ≤ 331.2, and this parameter had the best diagnostic performance of 90.4%.

Conclusion: Neoadjuvant chemoradiotherapy followed by surgery and adjuvant chemotherapy remains the standard treatment approach for rectal cancer. Since pathological complete response improves oncological outcomes, it is important to identify biomarkers that can predict pathological complete response in rectal cancer

Keywords:. Rectal cancer, pathological complete response, inflammatory biomarkers, pan-immune inflammation value

Öz

Amaç: Rektal kanserlerin yaklaşık yarısı lokal ileri evrede tanı almaktadır. Neoadjuvan kemoradyoterapiyi takiben cerrahi uygulanan hastalarda patolojik tam yanıtı öngörecek biyobelirteçlerin saptanması önemlidir.

Gereç ve Yöntem: Retrospektif planlanan çalışmaya neoadjuvan kemoradyoterapiyi takiben cerrahi geçirmiş ve adjuvan kemoterapi almış lokal ileri evre rektum kanserli 205 hasta dahil edildi. Neoadjuvan tedavi öncesinde bakılan tam kan sayımında inflamatuvar biyobelirteçler çalışıldı.

Bulgular: Hastaların %20.5'inde patolojik tam yanıt saptandı. Nötrofil-lenfosit oranı, platelet-lenfosit oranı ve pan-immün inflamasyon değeri patolojik tam yanıt (+) grupta patolojik tam yanıt (-) gruptan anlamlı düşük bulundu. Pan-immün inflamasyon için cut-off ≤331.2 bulundu ve %90.4 ile en iyi tanısal test olarak saptandı.

Sonuç: Rektum kanserinde neoadjuvan kemoradyoterapi, sonrasında cerrahi ve adjuvan kemoterapi standart tedavi yaklaşımı olarak önemini korumaktadır. Patolojik tam yanıt onkolojik sonuçları iyileştirdiğinden; rektum kanserinde de patolojik tam yanıtı öngörecek biyobelirteçlerin bilinmesi önemlidir. Nötrofil-lenfosit oranı, platelet-lenfosit oranı ve pan-immün inflamasyon değeri patolojik tam yanıt (+) grupta anlamlı düşük saptandı ve pan-immün inflamasyon en iyi tanısal test olarak saptandı.

Anahtar kelimeler: Rektum kanseri, patolojik tam yanıt, inflamatuvar biyobelirteçler, pan-immün inflamasyon değeri

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INTRODUCTION

Colorectal cancer (CRC) is the third most common and second-leading cause of cancer-related mortality in the world[1]. Rectal cancer constitutes approximately 30% of CRC cases, of which nearly half are diagnosed at locally advanced stage[2]. In these patients, the standard treatment is neoadjuvant chemoradiotherapy (nCRT), followed by surgery, and then adjuvant chemotherapy; however, total neoadjuvant therapy has also come into prominence in the current studies[3, 4]. Although total neoadjuvant therapy results in a higher rate of pathological complete response (pCR) and longer disease-free survival (DFS) than the standard treatment approach both in the short and long terms, the standard treatment option remains important in current clinical practice[2-4]. 16-22% of patients who received nCRT before surgery achieved pCR in Allegra's study[5]. However, there is limited information that can assist in the prediction of patients who will have pCR after nCRT.

The role of inflammation in carcinogenesis is important[6]. The inflammatory response is involved in different processes of cancer, such as initiation, prognosis, and metastasis. High neutrophils and platelets are associated with a poor prognosis, while a high lymphocyte count has the opposite effect. Therefore, parameters such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR), which evaluate the status of neutrophils, platelets, monocytes, and lymphocytes, have been investigated as possible prognostic markers in many malignancies, including rectal cancer[7, 8]. A tumor's course can be predicted using systemic inflammatory biomarkers[9]. The neutrophil-lymphocyte ratio (NLR), the lymphocyte-monocyte ratio (LMR), and the platelet-lymphocyte ratio (PLR) indicate a systemic inflammatory response[10]. In addition, the pan-immune inflammation value (PIV), which is determined using neutrophil, platelet, monocyte, and lymphocyte levels, has been investigated as a new prognostic biomarker in various malignancies [11].

Biomarkers derived from the complete blood count reflect systemic inflammation and have prognostic and predictive value in diverse malignancies. Also, they are easily accessible and inexpensive parameters. The novelty of this study is that it is the first to evaluate PIV in rectal cancer. We hypothesized whether there is a relationship between NLR, PLR, LMR, PIV and pCR prediction in patients with locally advanced rectal cancer receiving nCRT.

MATERIALS AND METHODS

Patients and study design

We performed a retrospective study. The data of 1100 patients diagnosed with rectal cancer in Adana City Education and Research Hospital between 2012 and 2022 were screened. Of them, 205 patients who received nCRT and met the eligilibity criteria were included to the study. Patient information and data were archived in the hospital database and patient files. The Local Ethics Committee of Adana City Education and Research Hospital approved the study (approval number=2380, date=02.02.2023).

Patients over the age of 18, diagnosed with locally advanced rectal cancer (stages II and III), receiving standard neoadjuvant concurrent chemoradiotherapy (nCRT), and patients who could be operated on (curative surgery with R0 resection) after neoadjuvant therapy were included in the study. Patients with secondary malignancies, patients under 18 years of age, those with additional comorbidities (such as rheumatological, immunological, and infectious diseases), those who did not receive the treatment completely, and those with conditions that may impact systemic inflammatory markers such as active infection, chronic inflammatory or autoimmune disease, and steroid use were excluded from the study.

The sample of the study was calculated using the G*Power 3.1.9.2. program. Based on the effect size of Karakaya et al.'s study titled "High Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio and Low Lymphocyte Levels Are Correlated With Worse Pathological Complete Response Rates" conducted in 2022[12], the medium effect size was accepted as 0.8 difference in our study. The alpha significance level was calculated as 0.05, and the sample size in 95% Power was calculated as a total of 205 patients, 163 in Group 1 and 42 in Group 2.

Treatment regimen

All patients received a total dose of 45-50 Gray radiotherapy in 25-28 fractions and simultaneous capecitabine chemotherapy (orally 825 mg/m^2 twice a day on radiotherapy days). Radiotherapy was applied by the doctor in the radiation oncology department of our hospital. After a recovery period

of 6-8 weeks, surgery was performed by general surgeons who are experts in oncology. All patients received adjuvant chemotherapy arranged by the oncologist. (modified FOLFOX 6= Oxaliplatin 85 mg/m^2 intravenous (IV), day 1, leucovorin 400 mg/m^2 IV day 1, 5-Fluorouracil 400 mg/m^2 IV bolus on day 1, followed by 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46–48 hours) continuous infusion. Repeat every 2 weeks to a total of 6 months perioperative therapy or CAPEOX Oxaliplatin 130 mg/m^2 IV day 1. Capecitabine 1000 mg/m^2 PO twice daily for 14 days every 3 weeks. Repeat every 3 weeks to a total of 6 months perioperative therapy.)

Patients' data

Age, gender, preoperative stage, preoperative lymph node status, surgery type, response status, and complete blood count values (neutrophil, platelet, monocyte, and lymphocyte counts) measured before neoadjuvant therapy were recorded retrospectively. Postoperative histopathological results were also recorded. NLR was calculated by dividing the neutrophil count by the lymphocyte count, PLR by dividing the platelet count by the lymphocyte count, and LMR by dividing the lymphocyte count by the monocyte count, and PIV using the following formula: neutrophil count x platelet count x monocyte count / lymphocyte count.

Pathological evaluation

Staging was performed using the American Joint Committee on Cancer (AJCC) staging manual (7th edition). Tumor regression grades (TRG) were determined according to AJCC (7th edition) as follows: TRG0, no residual tumor cells; TRG1, single cells or small groups of cells; TRG2, residual cancer but predominant fibrosis behind; and TRG3, minimal or no tumor response. The patients with TRG0 were included in the pCR group, and those with TRG1, 2, and 3 were in the non-pCR group.

Statistical analysis

The Statistical Package for the Social Sciences v. 25.0 was used for the statistical analyses of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where appropriate). The chi-square test was used to compare patients' gender, preoperative stage, preoperative lymph node number, operation type and differences between groups. The shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution. The Mann Whitney U test was used to examine the differences between groups in non-normally distributed age, neutrophil, platelet, lymphocyte, monocyte, NLR, PLR, LMR and PIV values. The sensitivity (sensitivity) and specificity (specificity) values of the NLR, PLR and PIV values of the patients included in the study were calculated, and the cut-off value was determined by examining the area under the ROC curve. The statistical significance level was accepted as 0.05 in all tests.

RESULTS

1100 rectal cancer patients were evaluated for this study, and 205 patients who received nCRT and met the study criteria were included in the sample (Figure 1). The mean age of the 205 patients with locally advanced rectal cancer was 59.7 ± 13.0 years, and 40% were female. The preoperative stage was II in 22% and III in 78%. 42 (20.5%) of the patients were pCR (+), and 163 (79.5%) were pCR (-) (Table 1). Patients' gender, age, preoperative stage, lymph node number, surgery type, pCR status, neutrophil, platelet, monocyte, and lymphocyte counts, NLR, PLR, LMR, and PIV were in Table 1.

The neutrophil, platelet, NLR, PLR, and PIV values of the patients in the pCR group were statistically significantly lower than those of the non-pCR group. The two groups were similar in terms of other parameters (Table 2).

When the diagnostic test performances of the NLR, PLR, and PIV values were examined, the area under the cut-off values were determined to be 83.4%, 78.5%, and 90.4%, respectively (Figure 2). Accordingly, PIV had the best diagnostic test performance (Table 3).

Table 1. Clinical characteristics of the patients

	n	%
Gender		
Male	123	60
Female	82	40
Preoperative stage		
II	45	22
III	160	78
Preoperative lymph node number		
None	45	22
1	12	5.9
More than 1	148	72.2
Surgery type		
APR	53	25.9
LAR	152	74.1
pCR status		
Negative	163	79.5
Positive	42	20.5
	Mean ± SD	Median (min-max)
Age	59.7 ± 13.0	61 (25-88)
Neutrophil	4.72 ± 1.6	4.5 (1.9-11.4)
Platelet	297.6 ± 89.5	299 (2.2-694)
Lymphocyte	1.65 ± 0.7	1.7 (0.3-3.8)
Monocyte	0.62 ± 0.2	0.6 (0.3-1.2)
NLR	3.60 ± 2.8	2.8 (0.84-22.67)
PLR	222.2 ± 152.8	176.6 (1.38-1190)
LMR	2.84 ± 1.2	2.66 (0.58-6.33)
PIV	685.6 ± 693.9	491.4 (3.99-5940.4)

APR: abdominoperineal resection, LAR: low anterior resection, pCR: pathological complete response, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LMR: lymphocyte-monocyte ratio, PIV: pan-immune inflammation value, SD: standard deviation

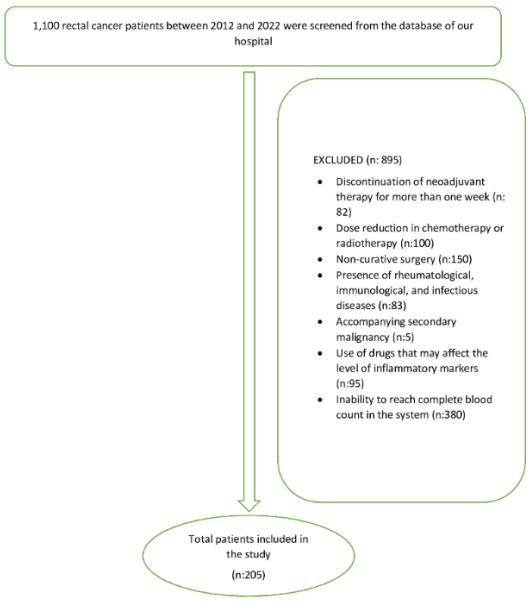

Figure 1. Flow chart of number of patients

Table 2. Comparison of the pCR and non-pCR groups in terms of demographic characteristics and inflammation parameters

	Non-pCR (n = 163)	**pCR (n = 42)**	**p[a]**
Gender, n (%)			
Male	95 (58.3)	28 (66.7)	0.323
Female	68 (41.7)	14 (33.3)	
	Mean ± SD	Mean ± SD	p[b]
Age	59.6 ± 13.1	60.3 ± 12.9	0.908
Neutrophil	5.15 ± 1.5	3.05 ± 0.8	<0.001*
Platelet	319.9 ± 80.9	210.9 ± 65.4	<0.001*
Lymphocyte	1.63 ± 0.7	1.73 ± 0.6	0.609
Monocyte	0.62 ± 0.2	0.61 ± 0.2	0.905
NLR	4.03 ± 3.0	1.93 ± 0.8	<0.001*
PLR	244.7 ± 161.2	134.8 ± 59.7	<0.001*
LMR	2.79 ± 1.3	3.02 ± 1.1	0.178
PIV	800.9 ± 732.0	238.1 ± 142.5	<0.001*

*p < 0.001, [a]Chi-square and Fisher's exact tests, [b]Mann-Whitney U test
pCR: pathological complete response, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LMR: lymphocyte-monocyte ratio, PIV: pan-immune inflammation value, SD: standard deviation

Table 3. Diagnostic test performances of NLR, PLR, and PIV

	NLR	**PLR**	**PIV**
AUC (95% CI) (%)	0.834 (0.776-0.882)	0.785 (0.722-0.839)	0.904 (0.856-0.941)
Cut-off	≤2.08	≤153.3	≤331.2
Sensitivity (95% CI) (%)	73.81 (58-86.1)	73.81 (58-86.1)	88.1 (74.4-96)
Specificity (95% CI) (%)	82.21 (75.5-87.7)	71.78 (64.2-78.5)	83.44 (76.8-88.8)
PPV (95% CI) (%)	51.7 (42.3-60.9)	40.3 (33.2-47.7)	57.8 (48.8-66.3)
NPV (95% CI) (%)	92.4 (87.9-95.3)	91.4 (86.4-94.7)	96.5 (92.3-98.4)
p	<0.001*	<0.001*	<0.001*

*p < 0.001; receiver operating characteristic analysis
NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LMR: lymphocyte-monocyte ratio, PIV: pan-immune inflammation value, AUC: area under the curve, CI: confidence interval

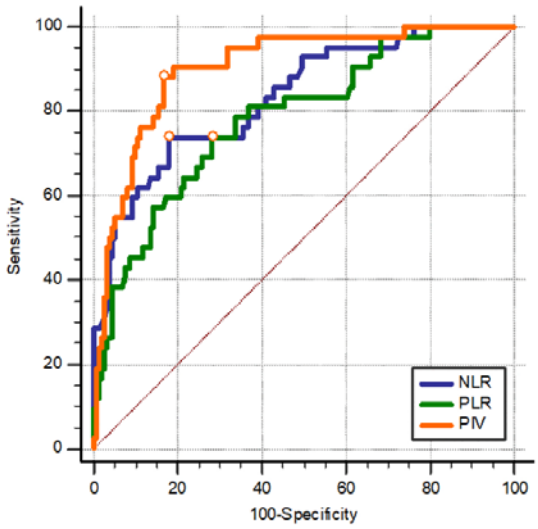

Figure 2. Receiver operating characteristic curves of the diagnostic performance of NLR, PLR, and PIV

DISCUSSION

The 5-year survival rate of patients with rectal cancer varies between 25 and 53% according to the disease stage[13]. Rectal cancer may respond to nCRT to varying degrees, including pCR [14]. An increased inflammatory response causes a poor prognosis in cancer. Their relationship with pCR has been studied before, but they are still not used in clinical practice. pCR is associated with a good clinical prognosis, so it is important to identify biomarkers that can predict patients who will achieve pCR. We investigated the inflammatory markers NLR, PLR, LMR, and PIV in patients with locally advanced rectal cancer who received nCRT and subsequently underwent surgery, followed by chemotherapy.

In our study, pCR was obtained in 20.5% of the 205 patients, which is consistent with the range reported by the NSABP R-04 study (16-22%) [5]. In patients with rectal cancer (n=188) who underwent nCRT and surgery, the NLR and PLR were found to be lower in the pCR (+) group than in the pCR (-) group. The authors stated that the systemic immune-inflammation index (neutrophil x platelet/lymphocyte) might be an independent predictive factor for pCR [15]. Similar to our study, Karakaya et al. determined that low NLR and PLR levels were associated with high pCR among 227 patients with rectal cancer who received nCRT. NLR and PLR were independent predictive markers for pCR [12]. In a retrospective study for rectal cancer (n=176), NLR < 2.0 and PLR < 133.4 were significantly associated with a good tumor response, and patients with NLR < 2.0 had a significantly better five-year DFS and overall survival (OS) rate compared to those with NLR ⩾2.0 [16]. In another study, Ergen et al. found NLR and PLR to be significant prognostic factors for OS and PLR for DFS, according to the ROC analysis. The five-year OS and DFS were found to be worse in the high PLR group [17]. Shen et al. reported that the baseline NLR significantly predicted prognosis in terms of OS in 199 locally advanced RC patients. The multivariate analysis of the same study revealed a cut-off value of NLR ≥ 2.8 as an independent factor of decreased OS. The authors also noted that an increased baseline NLR was a valuable and readily available prognostic factor for OS, as was tumor response after neoadjuvant therapy [18]. On completion of our study, we determined that the neutrophil, platelet, NLR, and PLR of the pCR group were significantly lower than those of the non-pCR group. NLR and PLR were identified as inflammatory biomarkers that could be used to predict pCR in these patients.

In a systematic review investigating the prognostic significance of LMR and PLR in patients with rectal cancer who received nCRT and curative surgery, a lower LMR value was associated with worse DFS and OS; however, PLR did not significantly predict DFS or OS. The authors also noted that a low LMR was inversely correlated with pCR, while no such correlation was found in the analysis of a high PLR [19]. Yamamoto showed the clinical significance of pretreatment LMR in 111 rectal cancer patients who received nCRT. The authors found that a low LMR value indicated a poor prognosis in terms of both OS, and DFS being determined as an independent prognostic factor of OS and DFS in the multivariate analysis [20]. In contrast, no correlation was found between LMR and OS and DFS in the univariate or multivariate analysis in rectal cancer patients (n=543). As a result, the authors concluded that LMR could not predict the prognosis of rectal cancer without metastasis [21]. In the current study, we could not find any difference between the pCR and non-pCR groups in terms of lymphocytes, monocytes and LMR values. We consider that the narrow range of the monocyte value may have led to non-significant results in terms of LMR.

In the literature, PIV has been evaluated in patients with CRC, breast cancer, and melanoma. In 130 patients with metastatic CRC, PIV was evaluated before first-line standard chemotherapy. The univariate and multivariate analyses showed that a high baseline pan-immune inflammation value was associated with poor overall survival and DFS [22]. In an evaluation of six studies, an initially high PIV in CRC was reported to result in poor OS and progression-free survival [23]. In another study, PIV was significantly associated with treatment response in breast cancer patients. The patients in the low PIV group had better OS and DFS than those in the high PIV group. It was concluded that pretreatment PIV appeared to be a marker for pCR and survival, outperforming NLR, LMR, and PLR in the prediction of pCR among women with breast cancer receiving neoadjuvant chemotherapy [24]. In our study, unlike previous studies on rectal cancer, we also evaluated PIV. Our results revealed that PIV was significantly lower in the pCR group than in the non-

pCR group ($p < 0.001$). Diagnostic test performances of NLR, PLR, and PIV in ROC analysis, PIV had the best diagnostic test performance with an AUC value of 90.4% at a cut-off value of ≤331.2.

A single-centered, retrospective design and not being performed in patients receiving total neoadjuvant therapy are our study's limitations. The number of patients receiving total neoadjuvant therapy in our hospital was insufficient for the study. A similar study may be planned in the future for patients receiving total neoadjuvant therapy.

In conclusion, in this study, NLR, PLR, and PIV were determined as inflammatory parameters that could be used to predict pCR in rectal cancer. PIV had the best diagnostic test performance in the ROC analysis. Subject to further studies, inflammatory parameters can be introduced into clinical practice, and their use in predicting pCR can replace guidelines. This study also had certain advantages, such as the evaluation of four inflammatory parameters based on real-life data obtained from a sizable sample of patients.

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REFERENCES

1. Mazidimoradi A, Tiznobaik A, Salehiniya H. Impact of the covid-19 pandemic on colorectal cancer screening: a systematic review. J Gastrointest Cancer. 2022;53:730-44.
2. Oronsky B, Reid T, Larson C, Knox SJ. Locally advanced rectal cancer: the past, present, and future. Semin Oncol. 2020;47:85-92.
3. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22:29-42.
4. Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22:702-15.
5. Allegra CJ, Yothers G, O'Connell MJ, Beart RW, Wozniak TF, Pitot HC et al. Neoadjuvant 5-FU or capecitabine plus radiation with or without oxaliplatin in rectal cancer patients: a phase III randomized clinical trial. J Natl Cancer Inst. 2015;107:djv248.
6. 6-Tang M, Gao X, Sun H, Tian S, Dong J, Liu Z et al. Neutrophil-lymphocyte ratio as a prognostic parameter in NSCLC patients receiving EGFR-TKIs: a systematic review and meta-analysis. J Oncol. 2021;2021:6688346.
7. Li Q, Yu L, Yang P, Hu Q. Prognostic value of inflammatory markers in nasopharyngeal carcinoma patients in the intensity-modulated radiotherapy era. Cancer Manag Res. 2021;13:6799-6810.
8. Timudom K, Akaraviputh T, Chinswangwatanakul V, Pongpaibul A, Korpraphong P, Petsuksiri J et al. Predictive significance of cancer related-inflammatory markers in locally advanced rectal cancer. World J Gastrointest Surg. 2020;12:390-396.
9. Morrison L, Laukkanen JA, Ronkainen K, Kurl S, Kauhanen J, Toriola AT. Inflammatory biomarker score and cancer: a population-based prospective cohort study. BMC Cancer. 2016;16:80.
10. Mandaliya H, Jones M, Oldmeadow C, Nordman II. Prognostic biomarkers in stage IV non-small cell lung cancer (NSCLC): neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR) and advanced lung cancer inflammation index (ALI). Transl Lung Cancer Res. 2019;8:886-94.
11. Guven DC, Sahin TK, Erul E, Kilickap S, Gambichler T, Aksoy S. The association between the pan-immune-inflammation value and cancer prognosis: a systematic review and meta-analysis. Cancers (Basel). 2022;14:2675.
12. Karakaya S, Karadağ İ, Yılmaz ME, Çakmak Öksüzoğlu ÖB. High neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and low lymphocyte levels are correlated with worse pathological complete response rates. Cureus. 2022;14:e22972.
13. Khalfallah M, Dougaz W, Jerraya H, Nouira R, Bouasker I, Dziri C. Prognostic factors in rectal cancer: where is the evidence? Tunis Med. 2017;95:79-86.
14. Garcia-Aguilar J, Chen Z, Smith DD, Li W, Madoff RD, Cataldo P et al. Identification of a biomarker profile associated with resistance to neoadjuvant chemoradiation therapy in rectal cancer. Ann Surg. 2011;254:486-92; discussion 492-3.
15. Eraslan E, Adas YG, Yildiz F, Gulesen AI, Karacin C, Arslan UY. Systemic immune-inflammation index (SII) predicts pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer. J Coll Physicians Surg Pak. 2021;30:399-404.

16. Kim TG, Park W, Kim H, Choi DH, Park HC, Kim SH et al. Baseline neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in rectal cancer patients following neoadjuvant chemoradiotherapy. Tumori. 2019;105:434-40.
17. Ergen ŞA, Barlas C, Yıldırım C, Öksüz DÇ. Prognostic role of peripheral neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy. J Gastrointest Cancer. 2022;53:151-60.
18. Shen L, Zhang H, Liang L, Li G, Fan M, Wu Y et al. Baseline neutrophil-lymphocyte ratio (≥2.8) as a prognostic factor for patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation. Radiat Oncol. 2014;9:295.
19. Hamid HKS, Emile SH, Davis GN. Prognostic significance of lymphocyte-to-monocyte and platelet-to-lymphocyte ratio in rectal cancer: a systematic review, meta-analysis, and meta-regression. Dis Colon Rectum. 2022;65:178-87.
20. Yamamoto A, Toiyama Y, Okugawa Y, Oki S, Ide S, Saigusa S et al. Clinical implications of pretreatment: lymphocyte-to-monocyte ratio in patients with rectal cancer receiving preoperative chemoradiotherapy. Dis Colon Rectum. 2019;62:171-80.
21. Wu QB, Wang M, Hu T, He WB, Wang ZQ. Prognostic role of the lymphocyte-to-monocyte ratio in patients undergoing resection for nonmetastatic rectal cancer. Medicine (Baltimore). 2016;95:e4945.
22. Pérez-Martelo M, González-García A, Vidal-Ínsua Y, Blanco-Freire C, Brozos-Vázquez EM, Abdulkader-Nallib I et al. Clinical significance of baseline pan-immune-inflammation value and its dynamics in metastatic colorectal cancer patients under first-line chemotherapy. Sci Rep. 2022;12:6893.
23. Yang XC, Liu H, Liu DC, Tong C, Liang XW, Chen RH. Prognostic value of pan-immune-inflammation value in colorectal cancer patients: a systematic review and meta-analysis. Front Oncol. 2022;12:1036890.
24. Şahin AB, Cubukcu E, Ocak B, Deligonul A, Oyucu Orhan S, Tolunay S et al. Low pan-immune-inflammation-value predicts better chemotherapy response and survival in breast cancer patients treated with neoadjuvant chemotherapy. Sci Rep. 2021;11:14662.