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ORIGINAL ARTICLE/ORİJİNAL MAKALE

Cervical intraepithelial neoplasia (cin) and the importance of leukocytes, platelets, mean platelet volume, platelet distribution width, red cell distribution width, plateletcrit, neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte ratios in diagnosis

Servikal intraepitelyal neoplazilerde lökosit,trombosit, ortalama trombosit hacmi,trombosit dağılım genişliği, eritrosit dağılım genişliği , plateletcrit, nötrofil/lenfosit,trombosit/lenfosit, lenfosit/monosit oranı ve tanıda önemi

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ABSTRACT

Aim: Cervical intraepithelial neoplasia (CIN) is the abnormal growth of cells on the surface of the cervix that could potentially lead to cervical cancer. In this study, we investigated whether hematological parameters, such as White Blood Cell Count (WBC), Platelet Count (PLT), Mean Platelet Volume (MPV), Platelet Distribution Width (PDW), Red Blood Cell Distribution Width (RDW), Plateletcrit (PCT), Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR), and Lymphocyte/Monocyte Ratio (LMR), which are useful in predicting the risk of developing cervical lesions.

Materials and Methods: The study is retrospective. The hematological parameters (WBC, PLT, MPV, PDW, RDW, PCT, NLR, PLR, and LMR) of female patients aged 18-65, who visited the Istanbul Training and Research Hospital Gynecology and Obstetrics Clinic between 01/01/2012 and 31/12/2023, and were histologically confirmed to have CIN I, CIN II, or CIN III based on colposcopy results, were compared. These inflammatory indices were calculated based on complete blood counts taken at diagnosis.

Results: When examining the comparisons made in our study, there was no significant difference in the age of patients among the CIN I, CIN II, and CIN III groups because of LEEP/Conization (p>0.05). There were no significant differences in hematological parameters; WBC, PLT, MPV, PDW, RDW, PCT values, and Neutrophil/Lymphocyte, Platelet/Lymphocyte, and Lymphocyte/Monocyte Ratios among the CIN I, CIN II, and CIN III groups (p>0.05).

Conclusion: In this study, we compared hematological parameters among CIN I, CIN II, and CIN III patients to prevent overtreatment of CIN1, CIN2, and CIN3 patients and to predict the onset of invasive cervical cancer at an early stage. We did not find a significant difference. However, large-scale, multicenter studies and long-term validation are required for clinical practice.

Keywords: Cervical Intraepithelial Neoplasia, Lymphocyte/Monocyte, Neutrophil/Lymphocyte, Platelet/Lymphocyte

ÖZET

Amaç: Bu çalışmanın amacı, hematolojik parametrelerin—beyaz kan hücresi sayısı (WBC), trombosit sayısı (PLT), ortalama trombosit hacmi (MPV), trombosit dağılım genişliği (PDW), kırmızı kan hücresi dağılım genişliği (RDW), trombosit krit (PCT), nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR) ve lenfosit/monosit oranı (LMR)—servikal intraepitelyal neoplazi (CIN) riski ve CIN'in evreleri arasındaki farkları tahmin etmedeki geçerliliğini araştırmaktır.

Materyal ve Yöntem: Bu retrospektif çalışmada, 1 Ocak 2012 ile 31 Aralık 2023 tarihleri arasında İstanbul Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'ne başvuran, yaşları 18-65 arasında değişen ve kolposkopi sonuçlarına göre histolojik olarak CIN I, CIN II veya CIN III olarak tanı konmuş kadın hastaların hematolojik parametreleri incelenmiştir. Hematolojik indeksler, tanı anında alınan tam kan sayımı sonuçlarına dayandırılmıştır.

Bulgular: Çalışmamızda, CIN I, CIN II ve CIN III grupları arasında yaş açısından anlamlı bir fark bulunmamıştır (p>0,05). Ayrıca, WBC, PLT, MPV, PDW, RDW, PCT, NLR, PLR ve LMR değerleri açısından CIN I, CIN II ve CIN III grupları arasında anlamlı bir farklılık tespit edilmemiştir (p>0,05).

Sonuç: Bu çalışmada, CIN I, CIN II ve CIN III evreleri arasındaki hematolojik parametrelerin anlamlı farklılıklar göstermediği bulunmuştur. Bu durum, bu parametrelerin CIN'in ilerleyişini veya invaziv servikal kanser riskini tahmin etmede güvenilir göstergeler olmayabileceğini düşündürmektedir. Gelecek araştırmalar için büyük ölçekli, çok merkezli ve uzun vadeli çalışmalar yapılması gerekmektedir.

Anahtar Kelimeler: Servikal İntraepitelyal Neoplazi, Lenfosit/Monosit Oranı, Nötrofil/Lenfosit Oranı, Trombosit/Lenfosit Oranı

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INTRODUCTION

Cervical intraepithelial neoplasia (CIN) is a pre-invasive condition that precedes cervical cancer and is equivalent to the term cervical dysplasia. This condition was first introduced by Richart, who also highlighted the high risk of cervical dysplasia leading to cervical malignancies (1). Cervical cancer is one of the most common causes of cancer deaths among women worldwide (2). CIN often occurs in the metaplastic area of the transformation zone at the squamocolumnar junction (SCJ). The pathological features for CIN diagnosis include cellular immaturity, irregularity, nuclear abnormalities, and increased mitotic activity. The degree of mitotic activity, immature cellular proliferation, and nuclear atypia define the grade of neoplasia. If mitoses and immature cells are confined to the lower third of the epithelium, it is classified as CIN I, and involvement of the middle and upper thirds is classified as CIN II and CIN III, respectively (3). CIN I and some CIN II lesions regress spontaneously. CIN III, which includes severe dysplasia and carcinoma in situ, should be treated due to its high likelihood of progressing to invasive cancer (4). The loop electrosurgical excision procedure (LEEP), laser conization, and cold knife conization (CKC) are the most frequently used excisional procedures in the diagnosis and treatment of CIN (5). Since 1950, literature on the natural history of CIN has been reviewed, especially regarding regression, persistence, and progression, and morphology alone cannot predict which lesions will progress or regress (6). Thus, future efforts should seek factors beyond morphology to predict prognosis in individual patients (7). Cancer-related inflammation plays a central role in the development and progression of malignancies. Increasing evidence suggests that systemic inflammation induced by cancer cells, by promoting proliferation and metastasis or angiogenesis, predicts tumor progression (8). Hematological parameters are easily accessible, routinely measured, and inexpensive inflammatory biomarkers (9). Studies have shown that hematological parameters, particularly RDW and MPV, are valuable in predicting the prognosis of various cancers (10,11,12). Inflammatory cells, platelet counts, and ratios are the best indicators of immune responses to cancer. Studies have shown that high platelet counts are associated with poor prognosis in various cancers, including pancreatic, gastric, colorectal, endometrial, and ovarian cancers (13,14). While the role of neutrophils in cancer is unclear, a high neutrophil-lymphocyte ratio is noted as a prognostic indicator in various cancers (15,16). In gastric cancer patients, LMR, NLR, PLR, and ICPI (Inflammation-combined-prognostic-index) are associated with tumor size, histological differentiation, and pathological tumor-node-metastasis (17). MLR, LMR, PLR, and other biomarkers have been used as prognostic markers in several cancers, including head and neck, gastric, colorectal, and brain metastases (18,19). Identifying reliable and cost-effective biomarkers to determine which patients are at high risk of developing cervical cancer and should receive treatment remains challenging (20). Therefore, there is a need for more objective, easier, and simpler tests. This study aimed to determine whether hematological parameters are useful in predicting the risk of developing pre-cancerous cervical lesions and early detection of invasive cervical cancer.

MATERIALS AND METHODS

The study design is retrospective. The sample of this study consists of patients who applied to the the Health Sciences Universty Istanbul Training and Research Hospital, Gynecology

and Obstetrics Clinic, between 01/01/2012 and 31/12/2023, who aged between 18 and 65 years. A total of 9097 women who applied to the gynecology outpatient clinic had their smear, colposcopy, and LEEP/conization results screened. Based on the screening, 808 patients met the criteria, and 361 patients were excluded due to incomplete colposcopy and LEEP/conization results. The remaining 447 women, who were only primiparous, were included. The exclusion criteria were the presence of additional diseases, being outside the age range, and being multiparous women. For this study, approval was obtained from the Health Sciences University Istanbul Training and Research Hospital Clinical Research Ethics Committee with decision number 283 dated 27.10.2023.

The demographic characteristics, ages, and hematological parameters (WBC, PLT, MPV, PDW, RDW, PCT, NLR, PLR, LMR) of patients histologically confirmed to have CIN 1, CIN 2, and CIN 3 based on colposcopy, LEEP/conization results were compared. The inflammatory indices listed above were calculated based on complete blood counts taken at the time of diagnosis. The blood samples were analyzed using the BC-6800 Plus Hematology Analyzer (Mindray, Shenzhen, China) on EDTA-K2 anticoagulant whole blood samples (21).

Statistical Methods

Descriptive statistics of the data included mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The distribution of the variables was measured using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Kruskal-Wallis test was used for the analysis of quantitative independent data. The analyses were performed using the SPSS 27.0 software.

RESULTS

A total of 447 patients, histologically confirmed by colposcopy, were included in the study: 75 patients (16.8%) with CIN1, 138 patients (30.9%) with CIN2, and 234 patients (52.3%) with CIN3. The ages of the cases ranged from 23 to 65 years, with a mean age of 42.5 ± 8.1 years. (Table 1)

Tablo 1. Comparison of specific parameters of CIN I, CIN II, and CIN III resulting from LEEP/Conization

		Min-Max	Median	Mean ± SD/n-%
Age		23.0 - 65.0	42.0	42.5 ± 8.1
WBC		2.10 - 21.00	7.46	7.79 ± 2.29
PLT		1.9 - 556.0	266.0	268.8 ± 67.7
MPV		1.50 - 13.70	10.10	10.07 ± 1.35
PDW		6.50 - 62.10	13.60	15.39 ± 8.65
RDW		10.7 - 26.5	13.4	13.9 ± 1.9
PCT		0.12 - 484.00	0.27	2.63 ± 28.50
NLR		0.09 - 38.33	2.04	2.37 ± 2.37
PLR		1.0 - 1565.4	118.0	130.4 ± 91.8
LMR		0.20 - 13.48	4.45	4.62 ± 1.65
Colposcopy results	CIN 1			75 16.8%
	CIN 2			138 30.9%
	CIN 3			234 52.3%

CIN: Cervical intraepithelial neoplasia, WBC: White Blood Cell Count, PLT: Platelet Count, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, RDW: Red Blood Cell Distribution Width, PCT: Plateletcrit, NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, LMR: Lymphocyte/Monocyte Ratio

The mean age of the cases with colposcopy results of CIN1, CIN2, and CIN3 were 44.1 ± 8.2; 41.9 ± 7.9, and 42.4 ± 8.1 years, respectively. The hematological parameters of the patients with colposcopy results of CIN1, CIN2, and CIN3 were as follows: WBC: [(7.46 ± 2.12); (7.67 ± 2.03); (7.95 ± 2.47)], PLT: [(265.9 ± 74.5); (269.1 ± 70.3); (269.5 ± 63.9)], MPV: [(10.1 ± 1.3); (10.0 ± 1.4); (10.1 ± 1.4)], PDW: [(15.7 ± 8.6); (15.6 ± 8.9); (15.2 ± 8.5)], RDW: [(14.0 ± 1.9); (13.8 ± 1.7); (13.9 ± 2.0)], PCT: [(0.30 ± 0.28); (3.99 ± 41.22); (2.57 ± 23.48)], NLR: [(2.42 ± 1.42); (2.45 ± 3.25); (2.31 ± 1.96)], PLR: [(131.6 ± 47.7); (134.0 ± 86.2); (127.9 ± 105.1)], LMR: [(4.57 ± 1.72); (4.5 ± 1.51); (4.70 ± 1.71)]. (Table 2)

Table 2. Comparison of certain parameters between CIN I, CIN II, and CIN III

	LEEP/Colonization results										p	
	CIN I				CIN II				CIN III			
	Mean ± SD/n-%			Median	Mean ± SD/n-%			Median	Mean ± SD/n-%			Median		
Age	44.1	±	8.2	44.0	41.9	±	7.9	41.0	42.4	±	8.1	42.0	0.084	K
WBC	7.46	±	2.12	7.19	7.67	±	2.03	7.38	7.95	±	2.47	7.64	0.149	K
PLT	265.9	±	74.5	261.0	269.1	±	70.3	254.5	269.5	±	63.9	269.0	0.621	K
MPV	10.1	±	1.3	10.1	10.0	±	1.4	10.1	10.1	±	1.4	10.0	0.972	K
PDW	15.7	±	8.6	14.3	15.6	±	8.9	13.5	15.2	±	8.5	13.6	0.730	K
RDW	14.0	±	1.9	13.7	13.8	±	1.7	13.3	13.9	±	2.0	13.4	0.453	K
PCT	0.30	±	0.28	0.27	3.99	±	41.22	0.27	2.57	±	23.48	0.27	0.512	K
NLR	2.42	±	1.42	2.12	2.45	±	3.25	2.01	2.31	±	1.96	2.03	0.815	K
PLR	131.6	±	47.4	123.3	134.0	±	86.2	125.2	127.9	±	105.1	113.5	0.108	K
LMR	4.57	±	1.72	4.06	4.50	±	1.51	4.39	4.70	±	1.71	4.59	0.259	K

[K] Kruskal-wallis (Mann-Whitney u test)

CIN: Cervical intraepithelial neoplasia, WBC: White Blood Cell Count, PLT: Platelet Count, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, RDW: Red Blood Cell Distribution Width, PCT: Plateletcrit, NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, LMR: Lymphocyte/Monocyte Ratio

DISCUSSION

In our study, no significant differences were found in WBC, PLT, MPV, PDW, RDW, PCT, NLR, PLR, and LMR values between the groups diagnosed with CIN1, CIN2, and CIN3 confirmed by colposcopy.

Chun et al., in a study conducted in South Korea in 2017 on the relationship between NLR and CIN, reported that individuals with high NLR levels have a high risk of disease recurrence (22). Xu L et al. (2021) examined NLR in 106 patients with histologically confirmed CIN1-3 treated with LEEP/cold knife conization. They found a significant difference between the CIN1 and CIN2, and CIN2 and CIN3 groups, and reported that NLR predicts the stage of CIN (4). In a study conducted by Lima PSV et al. (2021), platelet count, NLR, PLR, RDW, and fasting glucose (FPG) values were compared in patients with CIN and invasive cervical cancer. They found high NLR, PLR, RDW, and FPG values in patients with invasive cervical cancer. In our study, we compared WBC, PLT, MPV, PDW, RDW, PCT, NLR, PLR, and LMR values among CIN1, CIN2, and CIN3 patients(23). Mantoani PTS et al. (2022) reported an inverse correlation between lesion area and NLR, PLR, and leukocyte count in 51 patients with CIN (24). No significant differences were found between CIN1, CIN2, and CIN3 in our study. Additionally, our study has a larger number of patients and more comprehensive parameters were compared. Origoni M et al. (2022) examined

NLR in evaluating CIN recurrences and found that NLR increased with the recurrence rate (25). Farzaneh F et al. studied high NLR and hematological parameters associated with CIN recurrence and linked high NLR values with increased recurrence. In our study, we compared CIN1, CIN2, and CIN3 patients and found no difference in NLR values (26). Afsar S et al. (2023) reported significantly higher NLR, MLR, and PLR values in a cross-sectional study in CIN I to CIN II-III and CIN II-III to cervical cancer. Contrary to these studies, we examined WBC, PLT, MPV, PDW, RDW, PCT, NLR, PLR, and LMR values and found no differences among CIN1, CIN2, and CIN3 patients (27). Qin L (2024) found high NLR, PLR, and MLR values in patients with endometrial malignant tumors (28). In another study, Rajakumar et al. (2024) examined NLR, PLR, and triglyceride-glucose index (TyG) to differentiate between benign and malignant breast tumors. They found a moderate positive correlation between PLR and BI-RADS score and found NLR associated with the cancer stage (29). Karateke A. et al. (2015) found that MPV, PDW, and PCT values were correlated with the severity of endometrial pathology with the highest values in endometrial cancer (30). Staniewska E et al. (2024) evaluated the relationship between pre-treatment RDW, systemic immune inflammation index (SII), and overall survival (OS) in patients treated with radiotherapy for cervical cancer. They found longer OS in patients with low RDW and SII (31).

CONCLUSION

Our study is one of the rare studies comparing hematological parameters in patients with CIN 1, CIN 2, and CIN 3. In our literature review, we did not find sufficient and comprehensive studies investigating whether inexpensive, easily accessible, objective, and routinely examined hematological parameters are useful in predicting the risk of developing pre-cancerous lesions of cervical cancer. In our study, conducted to prevent overtreatment of patients and to predict the onset of invasive cervical cancer at an early stage, we did not find significant differences in hematological parameters among CIN1, CIN2, and CIN3. However, large-scale, multicenter studies and long-term validation are required for clinical practice.

Ethics Committee Approval

Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Istanbul Training and Research Hospital with decision number 283 dated 27.10.2023.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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Authorship Contributions

Conception and design: AKK, AÇ Acquisition of data: AKK, AÇ Analysis and interpretation of data: AKK, AÇ Drafting of the manuscript: AKK, AÇ Critical revision of the manuscript: AKK, AÇ Statistical analysis: AKK, AÇ Administrative technical or material support: : AKK, AÇ Supervision: AKK, AÇ.

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