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Diagnostic and prognostic utility of systemic inflammation indices in cervical dysplasia

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MAIN POINTS

- In a cohort with chronic cervicitis, LSIL, and HSIL, CBC-derived indices (SII, NLR, PLR) showed no significant differences across grades, limiting their diagnostic/grading utility.
- Multivariable logistic regression indicated modest inverse associations: each unit increase in lymphocyte count and PLR reduced HSIL odds by 0.2% and 2.5%, respectively.
- High-risk HPV genotypes (16/18) were significantly more frequent in HSIL than in LSIL/chronic cervicitis.
- These findings suggest that systemic inflammation indices alone have limited prognostic value, whereas HPV genotyping remains more clinically informative.

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ABSTRACT

Aim: This study investigated the diagnostic and prognostic potential of the Systemic Immune-Inflammation Index (SII), Neutrophil-Lymphocyte Ratio (NLR), and Platelet-Lymphocyte Ratio (PLR) in cervical dysplasia, evaluating their correlation with disease presence and severity for potential clinical applications in risk assessment and patient management.

Materials and Methods: In this retrospective study, the SII, NLR, and PLR values were analyzed using parameters obtained from the routine complete blood count of 215 patients whose cervical dysplasia grades were evaluated through colposcopic biopsy.

Results: HPV DNA types 16 and 18 were detected in 114 (53.0%) of 215 patients, while 101 (47.0%) tested positive for non-16/18 hr-HPV DNA types. No statistically significant differences were observed in WBC, neutrophil, platelet, lymphocyte, SII, NLR, and PLR values across the chronic cervicitis, LSIL (low-grade squamous intraepithelial lesion), and HSIL (high-grade squamous intraepithelial lesion) groups ($p < 0.05$). However, logistic regression analysis for HSIL risk identified lymphocyte count (OR = 0.998) and PLR (OR = 0.975) as significant predictors, where a one-unit increase in each was associated with a 0.2% and 2.5% decrease in the odds of HSIL, respectively.

Conclusion: SII, NLR, and PLR values in diagnosing or grading the presence or severity of cervical dysplasia, indicating that these systemic inflammatory markers alone may have limited value as diagnostic or prognostic tools. Further validation through larger prospective studies is warranted to more comprehensively elucidate the role of these markers.

Keywords: Systemic immune-inflammation index (SII), Platelet-lymphocyte ratio, Neutrophil-lymphocyte ratio, Complete blood count, Cervical intraepithelial neoplasia

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INTRODUCTION

Cervical cancer is the fourth most common cancer among women worldwide [1]. Globally, it remains a significant cause of mortality, accounting for over 300,000 female deaths annually [2]. Infection with Human Papilloma Virus (HPV) is implicated in approximately 99% of cervical cancer cases [3]. The development of most of these cancers is attributed to persistent infection with high-risk HPV genotypes, including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 [4]. HPV types 16 and 18 are responsible for over 70% of cervical cancer diagnoses [4]. While the majority (approximately 90%) of HPV infections undergo spontaneous regression within 1-3 years [3], persistent infection, facilitated by viral integration into the host cell genome and mechanisms that evade immune surveillance, can lead to the progression of cervical lesions from preneoplastic conditions (CIN2-3) to invasive cervical carcinoma. Approximately 10% of women with HPV infection exhibit signs of oncogenic transformation of the cervix [5].

The crucial role of the local immune response to HPV infection in the pathogenesis of cervical intraepithelial neoplasia

(CIN) lesions has long been recognized [6]. The binding of the major L1 capsid protein to heparan sulfate proteoglycans on the keratinocyte surface initiates HPV entry into host cells [7]. The early viral genes, particularly E6 and E7, are expressed following cellular entry. These oncoproteins target and inactivate the tumor suppressor proteins p53 and pRb [8], leading to cell cycle dysregulation. In hr-HPV infections, viral DNA often integrates into the host genome, disrupting the E2 gene and overexpressing E6 and E7 oncoproteins [9]. This genomic instability contributes to the accumulation of cellular abnormalities that progress through stages of precancerous lesions: CIN1 (mild dysplasia), CIN2 (moderate dysplasia), and CIN3 (severe dysplasia/carcinoma in situ). According to the Lower Anogenital Squamous Terminology (LAST) classification, CIN1 is categorized as a low-grade squamous intraepithelial lesion (LSIL), whereas CIN2 and CIN3 are classified as high-grade squamous intraepithelial lesions (HSIL) [10,11]. Despite extensive research into the dynamics of CIN regression, persistence, and progression, morphologic assessment alone cannot reliably predict the clinical outcome of these lesions.

Emerging evidence strongly suggests that systemic inflammation may also play a significant role in CIN pathogenesis and progression [12]. Systemic inflammation is increasingly recognized as a key factor in various chronic diseases, including the development of precancerous lesions and their progression to cancer. The potential of chronic inflammation to drive carcinogenesis is a widely accepted concept; however, sustained inflammatory processes may be critical in malignant transformation and tumor development [13].

The number of inflammatory cells and platelets in the systemic circulation and indices derived from their ratios are considered important indicators of the systemic immune response to cancer [14]. Studies have indicated that the Systemic Immune-Inflammation Index (SII), Neutrophil-to-Lymphocyte Ratio (NLR), and Platelet-to-Lymphocyte Ratio (PLR) are associated with poor prognosis in various solid tumors and correlate with tumor size, stage, and lymph node metastasis [15].

However, the current data regarding the association between systemic inflammation and CIN lesions are inconsistent, necessitating further investigation. This study was based on the hypothesis that changes in systemic inflammatory markers—specifically the SII, NLR, and PLR—reflect the progression of CIN; therefore, these indices could serve as accessible and cost-effective tools for distinguishing between grades of cervical dysplasia.

MATERIALS AND METHODS

This retrospective, observational, cross-sectional study enrolled 215 patients who underwent colposcopic biopsy at Cengiz Gokçek Obstetrics and Gynecology Hospital and Kırıkkale Yuksek Ihtisas Hospital between February 2022 and October 2024. The study protocol received ethical approval from the Ethics Committee of Kırıkkale University (decision date: 2025.03.12, decision number: 2025.03.07). This study was conducted and reported in accordance with the STROBE guidelines for cross-sectional studies.

The study included women aged 30–65 years who had an indication for colposcopic examination based on abnormal PAP smear (Thin-prep) screening results or positive high-risk HPV DNA (HC2; Qiagen, Hilden, Germany) test results. Colposcopy-guided biopsies were classified as either HSIL or LSIL according to the LAST criteria [10]. The study groups were established based on the pathological findings: patients with chronic cervicitis (n = 98), patients with CIN 1 biopsy results (LSIL, n = 63), and patients with CIN 2 and 3 biopsy results (HSIL, n = 54). Routine blood samples were collected on the biopsy day. Participants were managed according to the American Society for Colposcopy and Cervical Pathology guidelines [16], with follow-up or surgical intervention determined by the colposcopic biopsy results. All accessible and eligible patient records within the study period were analyzed.

Exclusion criteria encompassed patients with acute and chronic inflammatory diseases, hematologic disorders, a history of cancer, prior radiotherapy or chemotherapy, the use of anti-inflammatory, immunosuppressive, or anticoagulant agents, and other sexually transmitted infections .

Hematological indices were calculated from complete blood count data. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. The SII was calculated using the following formula: (platelet count × neutrophil count) / lymphocyte count.

Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics, Version 27.0 (IBM Corp., Armonk, NY, USA) package program. Descriptive statistics were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution. The normality of distribution was assessed using visual inspection and the Shapiro–Wilk test.

For normally distributed continuous variables with homogeneity of variance (tested by Levene's test), one-way analysis of variance (ANOVA) was applied to compare the differences among the three groups. For nonnormally distributed variables or in case of unequal variances, the Kruskal–Wallis H test was used. The categorical variables were compared using Pearson's chi-square test. To evaluate the relationship between hematological parameters and the risk of HSIL and LSIL, we performed binary logistic regression analysis (Backward LR method). Assumptions for logistic regression, including log-odds linearity and multicollinearity, were tested and met.

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Table 1. Association between HPV genotypes and the severity of cervical dysplasia.

Variables	LSIL (n=63)		HSIL (n=54)		Chronic cervicitis (n = 98)		Statistical analysis*
	n	%	n	%	n	%	
HPV types							
HPV 16-18	31	49.2	39	72.2	44	44.9	x^2=10.957
Types other than HPV16-18	32	50.8	15	27.8	54	55.1	**p=0.004**

*Pearson-x^2 crosstabs.

Table 2. Comparative analysis of quantitative findings across study groups.

Parameters	LSIL (n=63) X±S.S	HSIL (n=54) X±S.S	Chronic cervicitis (n = 98) X±S.S	Statistical analysis*
Age (years)	45.59±10.17	43.89±8.78	44.94±9.98	x^2=0.668 p=0.716
Hemoglobin(g/dL)	12.76±1.47	12.76±1.62	13.07±1.36	x^2=2.231 p=0.328
WBC(mcL)	7410.48±2016.32	7589.44±2026.98	7545.71±1811.63	F=0.145 p=0.865
Neutrophil(mcL)	4519.68±1476.55	4714.07±1740.86	4554.08±1341.01	x^2=0.187 p=0.911
Platelet (103/μL)	284904.76±71273.38	284925.93±82030.79	295948.98±56656.38	F=0.700 p=0.498
Lymphocyte(mcL)	2171.75±722.12	2170.56±565.95	2317.45±691.34	F=1.264 p=0.285
NLR	2.28±0.98	2.26±0.96	2.13±0.93	x^2=1.846 p=0.397
PLR	141.90±48.21	137.75±47.36	140.85±53.94	x^2=0.286 p=0.867
SII	644273.69±319708.65	640145.43±322440.51	632410.59±306284.63	x^2=0.010 p=0.995

WBC: White blood cell, NLR: Neutrophil-Lymphocyte Ratio, PLR: Platelet-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index. *For data exhibiting a normal distribution, the statistics of the "ANOVA" test (F-statistic) was employed for the comparison of measurement values across three or more independent groups. For data not conforming to a normal distribution, the statistics of the "Kruskal-Wallis H" test (x^2-statistic) were used for the comparison of measurement values among three or more independent groups.

Table 3. Analysis of factors influencing the LSIL probability using binary logistic regression.

Parameters	B	S.H.	Wald	s	p	OR	95 percent confidence interval (OR) Lower	Upper
Age (years)	0.013	0.016	0.691	1	0.406	1.013	0.982	1.046
Hemoglobin(g/dL)	-0.094	0.108	0.756	1	0.384	0.911	0.738	1.124
WBC(mcL)	0.001	0.000	0.762	1	0.383	1.000	1.000	1.001
Neutrophil(mcL)	-0.001	0.000	2.457	1	0.117	0.999	0.998	1.000
Platelet(10^3/μL)	0.000	0.000	0.214	1	0.644	1.001	1.000	1.000
Lymphocyte(mcL)	0.000	0.001	0.239	1	0.625	1.001	0.998	1.001
NLR	0.759	0.807	0.884	1	0.347	2.135	0.439	10.381
PLR	-0.014	0.013	1.230	1	0.267	0.986	0.962	1.011
SII	0.001	0.001	0.071	1	0.790	1.001	1.000	1.000
Constant	0.871	2.815	0.096	1	0.757	2.389		

CCR: 70.7% [Hosmer-Lemeshow Test x^2=3.771; p=0.877]. WBC: White blood cell, NLR: Neutrophil-Lymphocyte Ratio, PLR: Platelet-Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index.

Table 4. Analysis of factors influencing the HSIL probability using binary logistic regression.

Parameters	B	S.H.	Wald	s	p	OR	95 percent confidence interval (OR) Lower	Upper
Lymphocyte(mcL)	-0.002	0.001	5.441	1	**0.020**	0.998	0.997	0.999
PLR	-0.026	0.012	4.892	1	**0.027**	0.975	0.953	0.997
Constant	3.440	1.872	3.377	1	**0.046**	31.196		

CCR: 74.9% [Hosmer-Lemeshow Test x^2=97.90; p=0.280]. PLR: platelet-to-lymphocyte ratio.

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RESULTS

Analysis of the age distribution across the study groups revealed mean ages of 44.94±9.98 years in the chronic cervicitis group, 45.59±10.17 years in the LSIL group, and 43.89±8.78 years in the HSIL group. No significant difference in age was observed between the groups (p = 0.716). Regarding HPV DNA typing, 114 cases tested positive for HPV types 16 and 18, whereas 101 cases tested positive for high-risk HPV types other than 16/18. Specifically, 32 (50.9%) patients with LSIL and 54 (55.1%) patients with chronic cervicitis tested positive for high-risk HPV types other than 16/18, whereas 39 (72.2%) patients with HSIL tested positive for HPV 16-18. A statistically significant association was found between the study groups and HPV types (p < 0.05) (Table 1).

Comparison of the chronic cervicitis, LSIL, and HSIL groups revealed no statistically significant differences in age, hemoglobin, white blood cell count (WBC), neutrophil count, platelet count, lymphocyte count, NLR, PLR, and SII values (p > 0.05) (Table 2).

Logistic regression analysis to assess the risk of LSIL indicated that none of the included parameters had a significant effect on LSIL status (p > 0.05) (Table 3). In contrast, logistic regression analysis for HSIL risk identified lymphocyte count and PLR as significant parameters (p < 0.05). A one-unit increase in lymphocyte count was associated with a 0.2% decrease in the odds of HSIL (OR = 0.998). Similarly, a one-unit increase in PLR was associated with a 2.5% decrease in the odds of HSIL (OR = 0.975) (Table 4).

DISCUSSION

Given the growing interest in inflammation-related biomarkers for cervical disease assessment, this study examined the utility of systemic immune-inflammation indices—namely SII, NLR, and PLR—in differentiating histopathological grades of cervical dysplasia in HPV-positive patients. Despite analyzing a well-defined cohort using colposcopic biopsy data, we observed no significant differences in routine inflammatory parameters across chronic cervicitis, LSIL, and HSIL groups. However, logistic regression analysis revealed that higher lymphocyte count and PLR were inversely associated with HSIL risk, suggesting a possible protective role or immune response modulation.

The increasingly acknowledged role of chronic inflammation in cervical carcinogenesis warrants attention [12]. Immune inflammation indices offer potential clinical utility as readily accessible parameters that reflect the systemic inflammatory milieu. A body of evidence suggests a possible correlation between these indices and the severity and prognosis of cervical lesions [17,18].

The significant role of inflammatory indices in the pathogenesis and clinical trajectory of cervical cancer and advanced-stage dysplasia has been substantiated in the existing literature. Afsar et al. reported significantly elevated inflammatory indices in individuals diagnosed with cervical cancer, proposing their potential as diagnostic adjuncts for distinguishing malignant status [19]. Similarly, Lima et al. demonstrated an association between elevated NLR levels and diminished overall and disease-free survival in invasive cervical neoplasia, concluding that NLR could serve as an independent adverse prognosticator [20]. Moreover, studies [21-23] have identified NLR and WBC count as potential prognostic markers for predicting recurrence risk following excisional procedures in patients with CIN, highlighting the central role of systemic inflammation in CIN recurrence post-LEEP and the utility of preoperative NLR levels as a robust independent prognostic factor for recurrence after surgical excision of CIN. These cumulative findings underscore the importance of the inflammatory response in the clinical management of cervical cancer and its precursor lesions, and highlight the potential clinical applications of inflammatory indices. No significant association in low-grade dysplasia (LSIL) within our cohort supports the hypothesis that inflammatory markers may play a more prominent role in disease progression or in more advanced stages.

Mantoani et al. evaluated data from 51 patients with low- and high-grade squamous intraepithelial lesions, employing colposcopic image analysis to quantify lesion areas and examine corresponding laboratory parameters. Their analysis revealed an inverse correlation between lesion area and NLR (r = -0.446, P = 0.001), PLR (r = -0.438, P = 0.001), and absolute leukocyte count (r = -0.351, P = 0.011) across the entire CIN patient cohort. Furthermore, they established an optimal lesion area cutoff of 21.019 pixels squared (58.87 mm squared) for predicting the absence of residual lesions in patients with CIN 2/3 undergoing excisional surgery [24]. Although our study did not identify significant intergroup differences in inflammatory indices, the findings of Mantoani et al. lend credence to the notion that CIN represents a systemic perturbation potentially manifesting as alterations in NLR, PLR, and leukocyte counts. Conversely, Tas et al. suggested that while NLR and PLR may aid in differentiating precancerous cervical pathologies from overt cervical cancer, their utility in predicting LSIL and HSIL appears limited [25]. Consistent with this, Küçükyurt and Çetin reported no significant variations in inflammatory indices such as NLR and PLR among the CIN I, CIN II, and CIN III groups [26]. The lack of significant differences in SII, NLR, and PLR values across the groups in our study suggests that when considered in isolation, these markers may not possess sufficient discriminatory power for the diagnosis of cervical dysplasia.

The results of our logistic regression analysis regarding HSIL risk indicated a significant influence of both lymphocyte count and PLR (p < 0.05). Specifically, a 0.2% reduction in the odds of HSIL was associated with each unit increment in lymphocyte count (OR = 0.998). Similarly, each unit increase in PLR value correlated with a 2.5% reduction in HSIL odds (OR = 0.975). These observations imply that the systemic inflammatory response plays a complex role in the develop-

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ment of advanced cervical intraepithelial neoplasia. A study assessing the prognostic value of preoperative PLR levels and HR-HPV infection in predicting HSIL recurrence following LEEP at 3- and 5-year intervals demonstrated that elevated PLR levels and HR-HPV infection were associated with an increased risk of HSIL recurrence/residual disease, suggesting their potential as markers for clinical management [27]. Conventionally, a low lymphocyte count and elevated PLR are associated with an unfavorable prognosis in certain malignancies [28,29]. However, the inverse relationship observed in our study warrants further investigation to elucidate the underlying mechanisms contributing to these unexpected findings. This counterintuitive association may be attributed to a complex immune response, where a higher lymphocyte count could reflect an effective antiviral or antitumoral activity. Similarly, an elevated PLR within a certain physiological range might signal a reactive thrombopoietic state rather than a protumorigenic process. These hypotheses warrant further experimental validation.

The significant association between HPV type and lesion grade in our study reinforces the well-established understanding that more severe lesions are associated with high-risk HPV types, particularly HPV 16/18. The interplay between HPV infection and inflammation is multifaceted. Bilir et al demonstrated significantly higher hematological inflammatory markers, such as SIRI and NLR, in women with persistent HPV infection, suggesting their potential utility in predicting persistent HPV infection [30]. Hammes et al. showed a positive correlation between macrophage infiltration in the cervical epithelium and the progression and transformation of CIN lesions to cancer, with inflammation intensity correlated with lesion grade [31]. Kemp et al. reported elevated systemic pro-inflammatory cytokine levels in women with persistent HPV infection [32]. Trinchieri posits that HPV infection may initiate inflammatory pathways in later stages, thereby facilitating tumor progression [33]. This observation provides a readily available parameter for enhanced surveillance of patients with persistent HPV infection for cervical cancer prevention. No significant association was found between SII, NLR, PLR, and varying CIN grades in our study, suggesting that these markers may not be sufficiently reliable as standalone diagnostic tools for low-grade cervical dysplasia. This implies a potential limitation in the utility of these indices for routine screening or primary diagnostic purposes in clinical practice. However, the observed inverse relationship between lymphocyte count and PLR with HSIL risk in logistic regression warrants continued scrutiny. The significant association between HPV type and lesion grade, coupled with the higher prevalence of HPV 16/18 positivity in the HSIL group, aligns with existing literatüre. Typing in risk stratification emphasizes the necessity of implementing HPV type-specific follow-up and management algorithms in clinical practice [34]. This study has certain limitations, including its retrospective design, which may impact the generalizability of the findings. Additionally, the sample size for some subgroup analyses may be limited. Future studies should adopt prospective, longitudinal designs, include larger and more diverse populations, and consider incorporating molecular or immunological biomarkers alongside hematological indices to enhance diagnostic precision.

CONCLUSION

Future studies should adopt a prospective and multidimensional design to better elucidate the clinical utility of hematological inflammatory markers in cervical dysplasia. Therefore, multimodal approaches, integrating inflammatory indices with other clinical and pathological factors, may provide a more holistic perspective in the management of cervical dysplasia.

Ethics Committee Approval: The study protocol received ethical approval from the Ethics Committee of Kırıkkale University (decision date: 2025.03.12, decision number: 2025.03.07).

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Informed Consent: As the study was conducted retrospectively, informed consent from the patients was not required.

Peer-review: Externally peer-reviewed.

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

Author Contributions: YS: Conceptualization, Design, Data curation, Formal analysis, Methodology, Project administration, Writing-original draft, Writing-review and editing, Investigation, Software, Supervision; AE: Data curation, Validation, Visualization, Writing-original draft, Writing-review and editing; CMA: Data curation, Validation, Visualization, Writing-original draft, Writing-review and editing.

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