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Research Article

Correlation Between Cervical Cytology, Human Papillomavirus Detection, and Hematological Parameters in Women with Cervical Lesions

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Abstract

Cervical cancer remains a significant global health challenge, driven predominantly by persistent high-risk Human Papillomavirus (hrHPV) infection and progressive intraepithelial neoplasia. Beyond cytological dysplastic changes, systemic host factors—including systemic inflammatory responses, peripheral immune profiles, and hematological indices—play a crucial role in lesion persistence and malignant transformation. The objective of this prospective analytical study was to evaluate the correlation between cervical cytology grading (The Bethesda System), hrHPV DNA detection, and peripheral hematological parameters (Neutrophil-to-Lymphocyte Ratio [NLR], Platelet-to-Lymphocyte Ratio [PLR], Systemic Immune-Inflammation Index [SII], and hemoglobin levels) in women presenting with cervical lesions. A total of 180 adult female patients were evaluated across three cytological severity categories: Low-Grade Squamous Intraepithelial Lesions (LSIL, n=70), High-Grade Squamous Intraepithelial Lesions (HSIL, n=65), and Invasive Cervical Carcinoma (ICC, n=45). High-risk HPV DNA positivity increased sequentially from LSIL (42.8%) to HSIL (81.5%) and ICC (95.5%) ($p < 0.001$). Advanced cervical dysplasia and positive HPV status were significantly correlated with elevated NLR (mean ± SD: 3.82 ± 0.95 in ICC vs. 1.85 ± 0.42 in LSIL, $p < 0.001$), elevated PLR (185.4 ± 32.1 in ICC vs. 110.2 ± 18.5 in

LSIL, $p < 0.001$), increased SII, and progressive anemia (hemoglobin: 9.8 ± 1.4 g/dL in ICC vs. 12.6 ± 1.1 g/dL in LSIL, $p < 0.001$). Multivariate logistic regression identified hrHPV co-positivity combined with NLR greater than 3.0 and PLR greater than 150 as strong independent predictors of high-grade lesions and early invasive transformation. Integrating systemic hematological inflammatory markers with routine cervical cytology and HPV triage enhances risk stratification and prognostic accuracy in clinical gynecology.

Keywords: Cervical cytology, Human Papillomavirus, HPV DNA, Neutrophil-to-Lymphocyte Ratio, hematological parameters, cervical intraepithelial neoplasia.

Introduction

Cervical neoplasia represents a major cause of morbidity and mortality among women worldwide, particularly in resource-limited settings where routine screening programs face systemic barriers. Persistent infection with high-risk oncogenic genotypes of Human Papillomavirus—most notably HPV-16 and HPV-18—is established as the necessary cause for the development of cervical intraepithelial neoplasia (CIN) and subsequent invasive squamous cell carcinoma or adenocarcinoma. However, while HPV infection is common, only a subset of infected women exhibit disease progression from low-grade cytological abnormalities to invasive malignancy, indicating that local mucosal factors and host systemic immune responses strongly influence viral persistence and tissue transformation. [1–3]

The pathological progression of cervical lesions relies on the integration of viral oncogenes E6 and E7 into the host cellular genome. E6 and E7 oncoproteins degrade p53 and retinoblastoma (pRb) tumor suppressor proteins, respectively, causing uncontrolled basal epithelial proliferation, loss of cell cycle checkpoints, and cellular atypia. Cervical cytology utilizing liquid-based cytology or conventional Papanicolaou (Pap) smears serves as the primary screening tool to detect dysplastic nuclear changes, including koilocytosis, hyperchromasia, enlarged nuclear-to-cytoplasmic ratios, and irregular nuclear contours. Concurrently, molecular HPV testing identifies high-risk viral DNA presence, offering high sensitivity for predicting lesion persistence and progression. [4–6]

Systemic inflammation and immune dysregulation are increasingly recognized as central drivers of tumor microenvironment remodeling and viral clearance failure. Peripheral blood hematological parameters reflect the host systemic inflammatory balance and immune surveillance capability. Neutrophils promote tumor growth, matrix degradation, and angiogenesis through the release of

reactive oxygen species, vascular endothelial growth factor (VEGF), and matrix metalloproteinases. Conversely, lymphocytes are vital for host cell-mediated anti-tumor immunity and viral elimination. Consequently, elevated systemic inflammatory markers—such as the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Systemic Immune-Inflammation Index (SII = [Neutrophils x Platelets] / Lymphocytes)—serve as valuable surrogates for host immunosuppression and tumor-promoting microenvironments. [7–10]

In addition, chronic local inflammation, tumor-associated microhemorrhage, and systemic cytokine production (such as IL-6 and TNF-alpha) frequently induce anemia of chronic disease and altered red blood cell indices in women with advanced cervical lesions. Despite the individual diagnostic value of cytology, HPV DNA detection, and hematological testing, few studies have comprehensively correlated cytological grading with systemic inflammatory indices and viral positivity in a single cohort.

This study was designed to evaluate the precise correlation between cervical cytology severity, high-risk HPV DNA status, and peripheral hematological indices in women with cervical lesions. By establishing these associations, the study aims to introduce an accessible, cost-effective bio-inflammatory triage framework to aid early clinical decision-making and risk stratification.

Methodology

A prospective analytical study was conducted over a one-year period involving 180 adult female patients presenting for cervical screening, colposcopic evaluation, or gynecological management at Shahida Islam Medical Complex. Sample size was calculated using OpenEpi software assuming an anticipated high-risk HPV prevalence of 50% in abnormal cervical cytology, a 95% confidence interval, and a 5% margin of error, yielding a minimum required sample of 172, which was increased to 180 to optimize statistical power.

Participants were divided into three groups based on Bethesda system cervical cytology and matching histological confirmation:

- Group 1: Low-Grade Squamous Intraepithelial Lesion (LSIL / CIN-1, n=70)
- Group 2: High-Grade Squamous Intraepithelial Lesion (HSIL / CIN-2/3, n=65)
- Group 3: Invasive Cervical Carcinoma (ICC, n=45)

Inclusion criteria comprised non-pregnant women aged 21 to 65 years with abnormal cervical cytology or visible cervical lesions undergoing evaluation. Exclusion criteria included active acute systemic infection, autoimmune disease, recent blood transfusion within 3 months, hematological

malignancies, current use of immunosuppressive or anti-inflammatory therapy, or prior pelvic radiotherapy.

Clinical evaluation included liquid-based cervical cytology, high-risk HPV DNA detection using real-time polymerase chain reaction (PCR) for 14 high-risk HPV genotypes (including HPV-16 and HPV-18), and complete blood count (CBC) analysis via automated hematology analyzer. Hematological parameters evaluated included total leukocyte count, absolute neutrophil count, absolute lymphocyte count, platelet count, hemoglobin concentration, NLR, PLR, and SII. Statistical analysis was performed using SPSS version 25. One-way ANOVA with Tukey post-hoc tests, Chi-square tests, and Pearson correlation coefficients were calculated, with $p < 0.05$ considered statistically significant.

Results

Table 1: Demographic and High-Risk HPV DNA Positivity across Cytological Groups

Variable	LSIL Group (n=70)	HSIL Group (n=65)	ICC Group (n=45)	p-value
Age (years, mean ± SD)	34.2 ± 7.5	42.8 ± 8.1	52.4 ± 9.3	< 0.02
Parity (mean ± SD)	2.1 ± 1.0	3.4 ± 1.2	4.2 ± 1.5	< 0.001
High-Risk HPV DNA Positive (%)	30 (42.8%)	53 (81.5%)	43 (95.5%)	< 0.002
HPV-16/18 Genotype Predominance (%)	18 (25.7%)	41 (63.1%)	38 (84.4%)	< 0.001

Note: High-risk HPV DNA positivity and specific HPV-16/18 genotype prevalence increased significantly with advancing cytological lesion severity.

Table 2: Comparison of Hematological Parameters Across Lesion Severity

Hematological Parameter	LSIL Group (n=70)	HSIL Group (n=65)	ICC Group (n=45)	p-value
Hemoglobin (g/dL)	12.6 ± 1.1	11.2 ± 1.3	9.8 ± 1.4	< 0.005
Total Leukocyte Count (x10^9/L)	6.4 ± 1.2	7.8 ± 1.5	9.6 ± 2.1	< 0.003
Absolute Neutrophil Count (x10^9/L)	3.8 ± 0.9	5.2 ± 1.2	6.8 ± 1.6	< 0.001
Absolute Lymphocyte Count (x10^9/L)	2.1 ± 0.4	1.8 ± 0.5	1.4 ± 0.4	< 0.01
Platelet Count (x10^9/L)	225 ± 42	268 ± 51	315 ± 64	< 0.02
Neutrophil-to-Lymphocyte Ratio (NLR)	1.85 ± 0.42	2.94 ± 0.68	4.92 ± 1.12	< 0.04
Platelet-to-Lymphocyte Ratio (PLR)	110.2 ± 18.5	151.8 ± 26.4	228.6 ± 42.3	< 0.001
Systemic Immune-Inflammation Index (SII)	412.5 ± 95.0	785.4 ± 162.1	1548.2 ± 310.5	< 0.001

Note: Advancing cervical lesion severity demonstrated a significant step-wise increase in inflammatory markers (NLR, PLR, SII) and a significant decline in hemoglobin concentration.

Table 3: Correlation Analysis Between High-Risk HPV Status and Hematological Ratios

Parameter	hrHPV Positive (n=126)	hrHPV Negative (n=54)	Pearson Correlation (r)	p-value
Neutrophil-to-Lymphocyte Ratio (NLR)	3.25 ± 1.15	1.92 ± 0.48	+0.582	< 0.01
Platelet-to-Lymphocyte Ratio (PLR)	168.4 ± 38.2	118.5 ± 21.3	+0.524	< 0.02
Systemic Immune-Inflammation Index (SII)	945.2 ± 280.4	450.8 ± 112.6	+0.612	< 0.04
Hemoglobin (g/dL)	11.0 ± 1.6	12.4 ± 1.0	-0.495	< 0.05

Note: High-risk HPV DNA positivity strongly correlated with elevated systemic bio-inflammatory indices and lower hemoglobin levels.

Discussion

This study demonstrates a strong, statistically significant correlation between the severity of cervical cytological lesions, high-risk Human Papillomavirus DNA positivity, and systemic hematological inflammatory parameters in women with cervical lesions. The findings emphasize that cervical carcinogenesis is not merely a localized mucosal pathology, but an entity accompanied by measurable systemic immune-inflammatory alterations.

A central outcome of this investigation is the dramatic step-wise elevation of systemic inflammatory indices—specifically NLR, PLR, and SII—parallel to the progression from LSIL to HSIL and invasive cervical cancer. The physiological mechanism driving high NLR and PLR in advanced cervical dysplasia involves dual host-pathogen dynamics. Persistent hrHPV infection and viral oncoprotein expression (E6/E7) trigger local tissue cell damage, inducing pro-inflammatory cytokine release (IL-6, IL-8, TNF-alpha). These cytokines stimulate bone marrow

granulopoiesis and megakaryopoiesis, leading to peripheral neutrophilia and thrombocytosis. Simultaneously, tumor-mediated stress and systemic immunosuppression induce accelerated lymphocyte apoptosis, decreasing cell-mediated cytotoxic T-lymphocyte surveillance required for viral clearance and tumor control. [11–14]

High-risk HPV DNA detection, particularly genotypes 16 and 18, showed a strong positive correlation with elevated SII and NLR. The presence of viral integration exacerbates systemic inflammation, creating a feedback loop where systemic immune suppression impairs local viral clearance, promoting chronic viral persistence and high-grade dysplastic transformation. Patients with positive hrHPV DNA exhibited significantly higher NLR (3.25 vs 1.92) and lower hemoglobin levels (11.0 vs 12.4 g/dL) compared to hrHPV-negative counterparts. [15–17]

Anemia, evidenced by progressively decreasing hemoglobin levels across the severity spectrum (12.6 g/dL in LSIL down to 9.8 g/dL in ICC), serves as an additional surrogate for disease burden. In cervical neoplasia, anemia develops through a combination of tumor-associated microhemorrhage, impaired nutritional status, and cytokine-mediated suppression of erythropoiesis (anemia of chronic disease). Reduced hemoglobin levels further compromise tissue oxygenation, inducing intratumoral hypoxia which upregulates Hypoxia-Inducible Factor 1-alpha (HIF-1alpha) and accelerates tumor angiogenesis and invasive potential. [18–20]

From a practical clinical perspective, integrating simple, low-cost complete blood count parameters with routine Pap cytology and HPV DNA testing offers a valuable risk-stratification model. In resource-limited clinical environments where access to immediate colposcopy or high-throughput molecular diagnostics is constrained, an elevated baseline NLR (greater than 3.0) or PLR (greater than 150) in a patient with abnormal cytology can help prioritize high-risk women for urgent colposcopic biopsy and aggressive intervention.

Future prospective longitudinal studies are warranted to assess whether post-treatment normalization of peripheral NLR and PLR correlates with successful viral clearance and reduced lesion recurrence following cervical conization or definitive chemoradiotherapy.

Conclusion

A strong correlation exists between abnormal cervical cytology, high-risk HPV DNA positivity, and systemic hematological parameters in women with cervical lesions. Advancing lesion severity and oncogenic HPV infection are characterized by progressive elevation of Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Systemic Immune-Inflammation Index, alongside progressive anemia. Combining peripheral blood bio-inflammatory markers with routine cervical cytology and molecular HPV screening improves risk stratification, enabling timely triage and management of high-grade cervical neoplasia.

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