Journal of Inflammation Research Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Associations Between Preoperative Inflammatory Indices and Residual or Recurrent Cervical Intraepithelial Neoplasia Post Loop Electrosurgical Excision Procedure

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Background: High-grade cervical intraepithelial neoplasia (CIN2/3) is a precursor to invasive cervical cancer, necessitating effective management. While the Loop Electrosurgical Excision Procedure (LEEP) is a successful treatment, recurrence remains a significant concern. This study evaluates the predictive value of preoperative immune-inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII), in assessing the risk of residual or recurrent CIN post-LEEP.

Methods: A retrospective analysis was performed on 423 women who underwent LEEP for CIN2/3 at Cangzhou Central Hospital between 2016 and 2020. Cox proportional hazards regression models with restricted cubic splines were used to evaluate linear and non-linear associations between immune-inflammatory indices and recurrence risk. Multivariate models were adjusted for confounding factors, and subgroup analyses were conducted to test the robustness of the associations. Threshold non-linear fitting and saturation effect analyses were also performed to identify inflection points influencing residual or recurrent disease risk.

Results: Significant differences in age, menopausal status, TCT results, HPV status, degrees of CIN and margin status were observed between recurrence and non-recurrence groups. NLR demonstrated a U-shaped relationship with recurrence risk, with a threshold effect. NLR values below 3.15 were associated with a reduced recurrence risk, while higher values increased the risk. PLR and SII showed a modest protective effect below their respective thresholds.

Conclusion: Systemic inflammation plays a key role in CIN recurrence following LEEP. NLR serves as a valuable prognostic marker, highlighting the potential for personalised follow-up strategies. Further research is needed to confirm these findings and elucidate the underlying mechanisms.

Keywords: cervical intraepithelial neoplasia, loop electrosurgical excision procedure, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, residual disease/recurrence

Introduction

Cervical cancer remains a major global health concern, ranking as the fourth most common cancer in women worldwide. According to 2020 data from the Global Cancer Observatory (GLOBOCAN), approximately 600,000 new cases and 350,000 death occur annually.[1] High-grade cervical intraepithelial neoplasia (CIN2/3) is a recognised precursor to invasive cervical cancer, highlighting the critical importance of effective management to prevent disease progression.[2] The Loop Electrosurgical Excision Procedure (LEEP) is a common treatment for CIN2/3, known for its high success rates and low morbidity.[3] Besides surgical procedures, medical treatments such as imiquimod and 5-fluorouracil cream are also considered acceptable alternatives for CIN2/3.[4] However, despite these various treatment options, the potential for residual or recurrent disease post-LEEP, with reported rates ranging from 5% to 25%, remains a significant clinical challenge.[5] Studies indicate that most CIN recurrences occur within the first two years post-treatment, with

Received: 5 July 2024
Accepted: 6 November 2024
Published: 13 November 2024

approximately 80% detected within the first 18 months.[6] Identifying risk factors for recurrences is essential to improve patient care and improve follow-up protocols.

Several high-risk factors for cervical intraepithelial neoplasia (CIN) recurrence have been identified, including age, menopausal status, positive surgical margins, histologic CIN grade, pretreatment or persistent high-risk human papillomavirus (HR-HPV) infection post-surgery, glandular involvement and immunosuppression.[7–10] Given the potential for recurrence following surgical treatment, continued research into these factors is critical. Recent studies have increasingly recognised the role of systemic inflammation in the development and progression of various cancers, including cervical cancer.[11,12] Immune-inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII), have gained attention for their prognostic value in cervical cancer. NLR reflects the balance between pro-inflammatory neutrophils and immune-surveillance lymphocytes; PLR accounts for platelet counts, which promote angiogenesis and tumour growth; and SII is a composite indicator of inflammatory and immune status. These markers have shown potential as predictors of cervical cancer survival.[13–15] However, the relationship between these pre-LEEP inflammatory markers and the risk of residual or recurrent CIN post-LEEP remains insufficiently explored.

Previous studies investigating the association between inflammatory markers and residual or recurrent CIN have yielded inconsistent results.[16–18] The prognostic value of PLR and SII, in particular, has been less explored compared to NLR, and the potential non-linear relationships between these markers and CIN risk are not well understood. This study aims to address this gap by examining the association between preoperative immune-inflammatory indices, including NLR, PLR and SII, and the risk of residual or recurrent disease following LEEP in patients with high-grade CIN. By assessing the predictive value of these biomarkers, we seek to improve post-treatment risk assessment and patient management.

Methods

Study Population

This study analysed the clinical and pathological data of women diagnosed with CIN2/3 who were treated at Cangzhou Central Hospital between January 2016 and December 2020. All participants underwent LEEP and were followed until December 2021, with a maximum follow-up period of 5 years. The study was approved by the hospital's Ethics Committee (approval no. 2021-054-02). Data collected included demographic information, reproductive history, menopausal status, ThinPrep cytologic test (TCT) results, HPV classification (HPV testing was conducted using a polymerase chain reaction (PCR)-based method to detect high-risk HPV types), degrees of CIN, glandular involvement and initial LEEP margin status.

Eligibility Criteria

Inclusion criteria were: women with a CIN2/3 diagnosis confirmed by colposcopic multi-site cervical biopsy, who underwent LEEP and agreed to follow-up. Exclusion criteria included: individuals with concurrent reproductive tract illnesses, severe respiratory or circulatory conditions, liver or kidney dysfunction, those who had undergone total hysterectomy, post-operative diagnosis of invasive cervical cancer (ICC), a history of cervical pathologies, current hormone replacement therapy, acute infectious diseases, or pregnancy.

Critical Definitions

Experienced gynaecologists performed LEEP by excising a cone-shaped section from the transformation zone, the primary site of CIN. The excision depth and edges were tailored to ensure complete removal of the lesion while preserving cervical integrity, confirmed via colposcopy. Histopathological examination determined the presence of residual disease (identified within one year post-LEEP) or recurrent disease (detected after one year). Due to their similar clinical implications, residual and recurrent lesions were analysed together.

Follow-Up Protocol

Patients were followed semi-annually for two years, then annually thereafter. At each follow-up visit, patients underwent both TCT and HPV testing. In cases of positive HPV findings, further colposcopy and biopsy were performed. Histological assessments during follow-up visits identified the most severe abnormalities. All procedures were supervised by experienced gynaecologists and confirmed by pathologists, continuing until detection of residual/recurrent CIN, dropout or death.

Indices

Complete blood counts were performed using an automated hematology analyzer (Sysmex XN-3000, Japan) following standard operating procedures. NLR and PLR were calculated by dividing the absolute neutrophil and platelet counts, respectively, by the absolute lymphocyte count. SII was calculated as: SII = platelet count × neutrophil count / lymphocyte count. All indices were based on routine blood tests conducted prior to the LEEP procedure.

Statistical Methods

Continuous variables were reported as mean ± standard deviation or median (interquartile range), while categorical variables were expressed as frequencies or percentages. To compare means and proportions between groups, we used Student's *t*-test for normally distributed continuous variables, Mann–Whitney *U*-test for non-normally distributed continuous variables, and Chi-square test for categorical variables.

A Cox proportional hazards model with restricted cubic splines was initially employed to explore the relationship between inflammatory indices and the risk of residual or recurrent disease.[19] If a linear association was observed, univariate and multivariate linear regression models were applied to further assess the relationship. Both unadjusted and fully adjusted models were developed following the STROBE guidelines. The fully adjusted model included covariates that altered the matched odds ratio by at least 10%, accounting for potential non-linear relationships between the variables and the risk of recurrence or residual disease. In cases of non-linear correlation, a two-piecewise Cox regression model was used to assess the threshold effect of the inflammatory indices, based on a smoothing plot.[20] The recursive method automatically identified the inflection point that maximised model likelihood when the relationship between inflammatory indices and disease risk was depicted as a smooth curve. Subsequently, Subgroup analyses were conducted using stratified binary Cox regression models. The likelihood ratio test was applied to assess modifications and interactions within subgroups to identify effect-modifying factors. Confounding factors or modifiers were excluded to isolate the independent impact of inflammatory indices on the risk of residual or recurrent disease. Hierarchical interaction analyses were performed to ensure the robustness of results across subgroups.

All statistical analyses were performed using R software (version 4.2.0, http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA). The analysis utilized several R packages including "rms" for restricted cubic splines and smoothing plots, "survival" for Cox regression analysis, and "segmented" for threshold effect analysis. P-values below 0.05 (two-sided) were considered statistically significant.

Results

Patient Characteristics Analysis

The baseline characteristics of the study population are summarised in Table 1. The mean age of patients without residual or recurrent CIN was 41.5 years, compared to 43.4 years in those with residual or recurrent CIN, but this difference was not statistically significant (P = 0.161). Pregnancy, parity and glandular involvement did not show significant differences between the two groups (P > 0.05). However, menopause was significantly more prevalent in the residual/recurrent CIN group (P = 0.020). Significant differences were observed in TCT results, HPV status, degrees of CIN and margin status between the two groups (P < 0.001 for all). NLR and SII were significantly lower in the residual/recurrent CIN group (P = 0.016 and P = 0.003, respectively), while PLR did not show a significant difference (P = 0.081).

Table 1 Baseline Characteristics of the Population

Patient Characteristic	No Residual/Recurrent CIN (n=345)	Residual/Recurrent CIN (n=78)	*P-value*
Age (years)	41.54 ± 9.81	43.44 ± 10.99	0.161
Pregnancy, n (%)			0.604
<3	179 (51.88%)	43 (55.13%)	
≥3	166 (48.12%)	35 (44.87%)	
Parity, n (%)			0.829
<2	115 (33.33%)	27 (34.62%)	
≥2	230 (66.67%)	51 (65.38%)	
Menopause, n (%)			0.020
No	265 (76.81%)	50 (64.10%)	
Yes	80 (23.19%)	28 (35.90%)	
TCT, n (%)			<0.001
<ASC-H	221 (64.06%)	27 (34.62%)	
≥ASC-H	124 (35.94%)	51 (65.38%)	
HPV, n (%)			<0.001
No HR-HPV	9 (2.61%)	3 (3.85%)	
HPV16/18	179 (51.88%)	64 (82.05%)	
Other HR HPV	157 (45.51%)	11 (14.10%)	
Degrees of CIN, n (%)			<0.001
CIN2	251 (72.75%)	16 (20.51%)	
CIN3	94 (27.25%)	62 (79.49%)	
Glandular involvement, n (%)			0.181
No	231 (66.96%)	46 (58.97%)	
Yes	114 (33.04%)	32 (41.03%)	
Margin status, n (%)			<0.001
Negative	264 (76.52%)	17 (21.79%)	
Positive	81 (23.48%)	61 (78.21%)	
PLR	246.34 (59.24)	234.58 (53.11)	0.081
NLR	1.73 (1.34–2.26)	1.52 (1.25–1.93)	0.016
SII	402.70 (302.86–548.21)	341.84 (261.81–463.38)	0.003

Note: Data are shown as mean ± standard deviation or median (interquartile range) or percentage. P value< 0.05 was considered significant.

Abbreviations: CIN, cervical intraepithelial neoplasia; TCT, ThinPrep cytological test; ASC-H, atypical squamous cells cannot exclude high grade squamous intraepithelial lesion; HR-HPV, high-risk human papilloma virus; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammation index=platelet×neutrophil/lymphocyte.

The median follow-up time was 25 months (6–60 months), with 75% of patients being followed for more than 18 months. The overall rate of residual or recurrent high-grade CIN (CIN2 or worse) followed for five years after LEEP was 18.4%. The median time to patient residual/recurrent disease was 21 months (6–51 months).

Associations Between the Immune-Inflammatory Index and Residual or Recurrent Disease Following LEEP Conization for High-Grade CIN

Multivariable Cox regression analysis results are presented in Table S1. Hazard ratios (HRs) for systemic haemato-immunological indices (NLR, PLR and SII) were calculated. For NLR, the unadjusted HR was 0.92 (95% CI: 0.72–1.19, P = 0.537) and the adjusted HR was 1.11 (95% CI: 0.88–1.40, P = 0.390). For PLR, the unadjusted HR was 0.99 (95% CI: 0.99–1.00, P = 0.055) and the adjusted HR was 1.00 (95% CI: 0.99–1.00, P = 0.340). For SII, the unadjusted HR was 1.00 (95% CI: 1.00–1.00, P = 0.177) and the adjusted HR was 1.00 (95% CI: 1.00–1.00, P = 0.906). None of the associations between these indices and residual or recurrent disease were statistically significant in the multivariable Cox regression models, suggesting a potential non-linear relationship.

Using the Cox model with restricted cubic splines, we identified an approximate U-shaped relationship between systemic haemato-immunological indices and the risk of residual or recurrent CIN for both NLR and SII, as observed in unadjusted (Figure 1A and C) and adjusted models (Figure 1D and F). For PLR, the risk decreased with increasing values up to a certain point, after which the risk plateaued (Figure 1B and E).

We then applied a piecewise binary Cox regression model to capture different slopes across inflection points, selecting the best-fit model using the log-likelihood ratio test. The inflection points for NLR, PLR and SII were determined using a recursive algorithm, and we calculated the effect sizes and confidence intervals on both sides of these points (Table 2). The results indicated a threshold effect for NLR and SII, consistent with the smoothing curve fit (Figure 1), although the unadjusted and adjusted

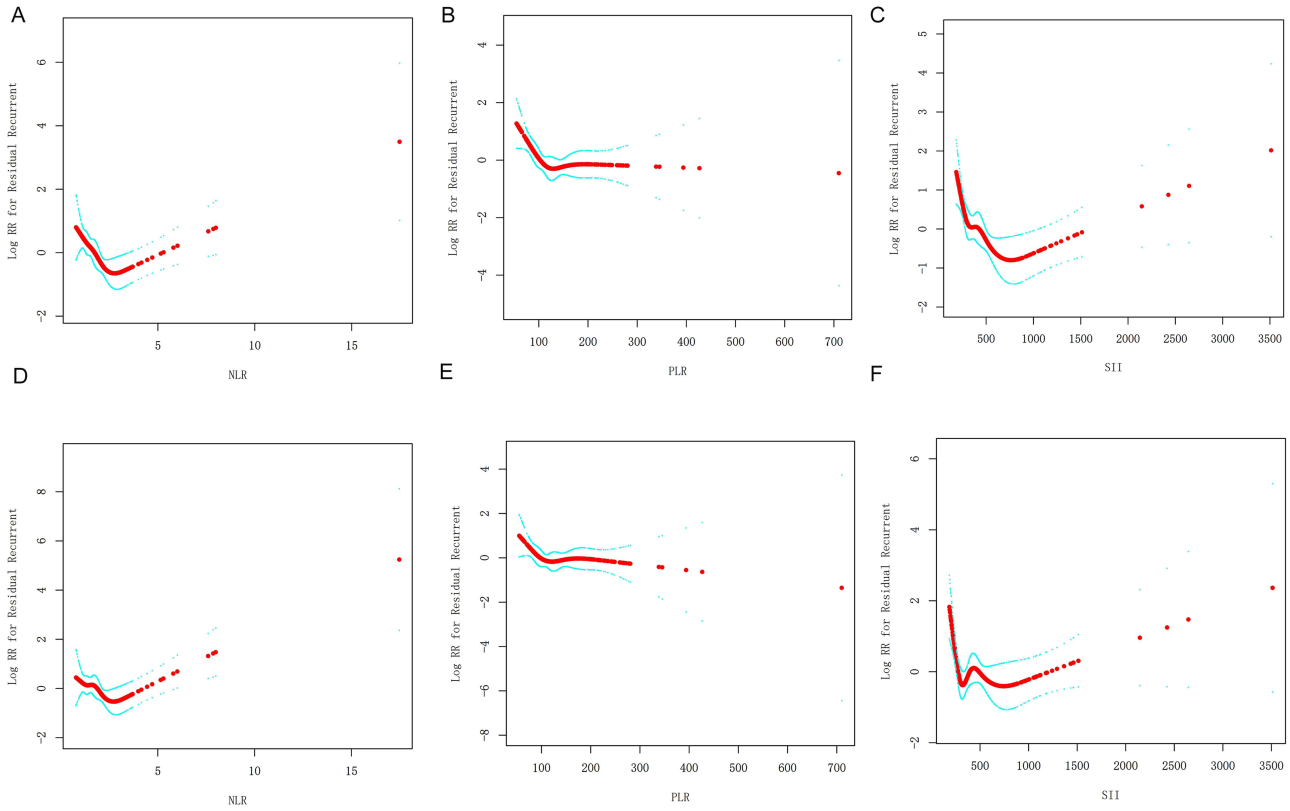

Figure 1 Non-linear associations between preoperative inflammatory indices and the risk of residual/recurrent Cervical Intraepithelial Neoplasia (CIN) post-LEEP: Neutrophil-to-Lymphocyte Ratio (NLR) with unadjusted (**A**) and adjusted (**D**) models. Platelet-to-Lymphocyte Ratio (PLR) with unadjusted (**B**) and adjusted (**E**) models. Systemic Immune-Inflammation Index (SII) with unadjusted (**C**) and adjusted (**F**) models. The red lines represent the fitted curves for each index, while the blue shaded areas indicate the 95% confidence intervals.

Table 2 Threshold Effect Analysis of Systemic Hemato-Immunological Indices to Recurrence/Residual CIN Using the Two-Piecewise Linear Regression Model

Incident	Crude (HR, 95% CI, *P*)	Adjusted (HR, 95% CI, *P*)
Exposure NLR		
Fitting model by standard linear regression	0.92 (0.72, 1.19) 0.537	1.11 (0.88, 1.40) 0.390
Fitting model by two-piecewise linear regression		
Inflection point of NLR (n below/above = 383/40)	2.95	3.15
< Inflection point	0.49 (0.32, 0.75) 0.001	0.65 (0.43, 1.00) 0.049
> Inflection point	1.36 (1.15, 1.63) 0.001	1.53 (1.24, 1.89) <0.000
Log likelihood ratio	<0.001	0.003
Exposure PLR		
Fitting model by standard linear regression	0.99 (0.99, 1.00) 0.055	1.00 (0.99, 1.00) 0.340
Fitting model by two-piecewise linear regression		
Inflection point of PLR (n below/above = 133/290)	102.06	101.78
< Inflection point	0.97 (0.95, 0.99) 0.001	0.98 (0.96, 1.00) 0.023
> Inflection point	1.00 (0.99, 1.00) 0.861	1.00 (0.99, 1.00) 0.891
Log likelihood ratio	0.006	0.052
Exposure SII		
Fitting model by standard linear regression	1.00 (1.00, 1.00) 0.177	1.00 (1.00, 1.00) 0.906
Fitting model by two-piecewise linear regression		
Inflection point of SII (n below/above = 71/352)	579.79	266.07
< Inflection point	1.00 (0.99, 1.00) <0.000	0.97 (0.96, 0.98) <0.000
> Inflection point	1.00 (1.00, 1.00) 0.036	1.00 (1.00, 1.00) 0.278
Log likelihood ratio	<0.001	<0.001

Notes: Crude model was adjust for: None. Adjusted model was adjust for: Age; Pregnancy; Menopause; TCT; HPV; Degrees of CIN; Glandular involvement; Margin status.

Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; CIN, Cervical Intraepithelial Neoplasia; HR, Hazard Ratio; CI, Confidence Interval; OR, Odds Ratio; TCT, ThinPrep Cytologic Test; HPV, Human Papillomavirus.

models yielded differing results. Table 2 presents the threshold effect analysis of systemic haemato-immunological indices on recurrence or residual CIN using the two-piecewise Cox regression model. For NLR, in the unadjusted model, the HR was 0.49 (95% CI: 0.32–0.75, P = 0.001) below the inflection point of 2.95 and 1.36 (95% CI: 1.15–1.63, P = 0.001) above it. After adjustment, the HR was 0.65 (95% CI: 0.43–1.00, P = 0.049) below the inflection point of 3.15 and 1.53 (95% CI: 1.24–1.89, P < 0.0001) above it. For PLR, the unadjusted HR was 0.97 (95% CI: 0.95–0.99, P = 0.001) below the inflection points of 102.06 and 1.00 (95% CI: 0.99–1.00, P = 0.861) above it. After adjustment, the HR was 0.98 (95% CI: 0.96–1.00, P = 0.023) below the inflection point of 101.78 and 1.00 (95% CI: 0.99–1.00, P = 0.891) above it. For SII, the unadjusted model showed an HR of 1.00 (95% CI: 0.99–1.00, P < 0.000) below the inflection point of 579.79 and 1.00 (95% CI: 1.00–1.00, P = 0.036) above it. In the adjusted model, the HR was 0.97 (95% CI: 0.96–0.98, P < 0.000) below the inflection point of 266.07, while the risk above the inflection point remained unchanged (HR: 1.00, 95% CI: 1.00–1.00, P = 0.278).

These analyses highlight that NLR, PLR and SII exhibit distinct threshold effects on the risk of recurrence or residual CIN. Adjustments generally attenuated or slightly altered the risk estimates. NLR demonstrated a clear threshold effect, with protective effects at lower levels and increased risk at higher levels, particularly after adjustment. PLR exhibited a modest protective effect below its inflection point, which remained stable post-adjustment. SII showed a neutral effect in the unadjusted model, but after adjustment, a protective effect was observed below the inflection point, while the risk above the inflection point remained stable.

Associations of Immune-Inflammatory Index with Residual/Recurrent Lesions Post-LEEP for High-Grade Cervical Intraepithelial Neoplasia Across Stratified Subgroups

Given the pronounced threshold effect of NLR, with protective effects at lower levels and increased risk at higher levels, especially after adjustment, we further investigated whether the non-linear relationship between the immune-

inflammatory index and residual/recurrent disease post-LEEP conization for high-grade CIN was consistent across different subgroups. We performed hierarchical and interactive analyses using all covariates as stratifying variables to examine trends in effect sizes.

Subgroup analysis of NLR using a two-piecewise Cox regression model revealed significant U-shaped relationships and threshold effects in several patient subgroups, with both sides of the inflection points showing statistical significance. Specifically, in older patients (≥50 years, inflection point at 1.86), the HR was 0.16 (95% CI: 0.05–0.56, P = 0.004) below the inflection point and 1.35 (95% CI: 1.14–1.58, P = 0.0003) above it (Figure 2A and Table S2). In menopausal patients, the inflection point was 3.04, with an HR of 0.41 (95% CI: 0.18–0.90, P = 0.0255) below the inflection point and 1.61 (95% CI: 1.25–2.07, P = 0.0002) above it (Figure 2D and Table S2). Patients with CIN3 had an inflection point at 3.47, with an HR of 0.56 (95% CI: 0.35–0.88, P = 0.0133) below and 1.73 (95% CI: 1.35–2.21, P < 0.0001) above it

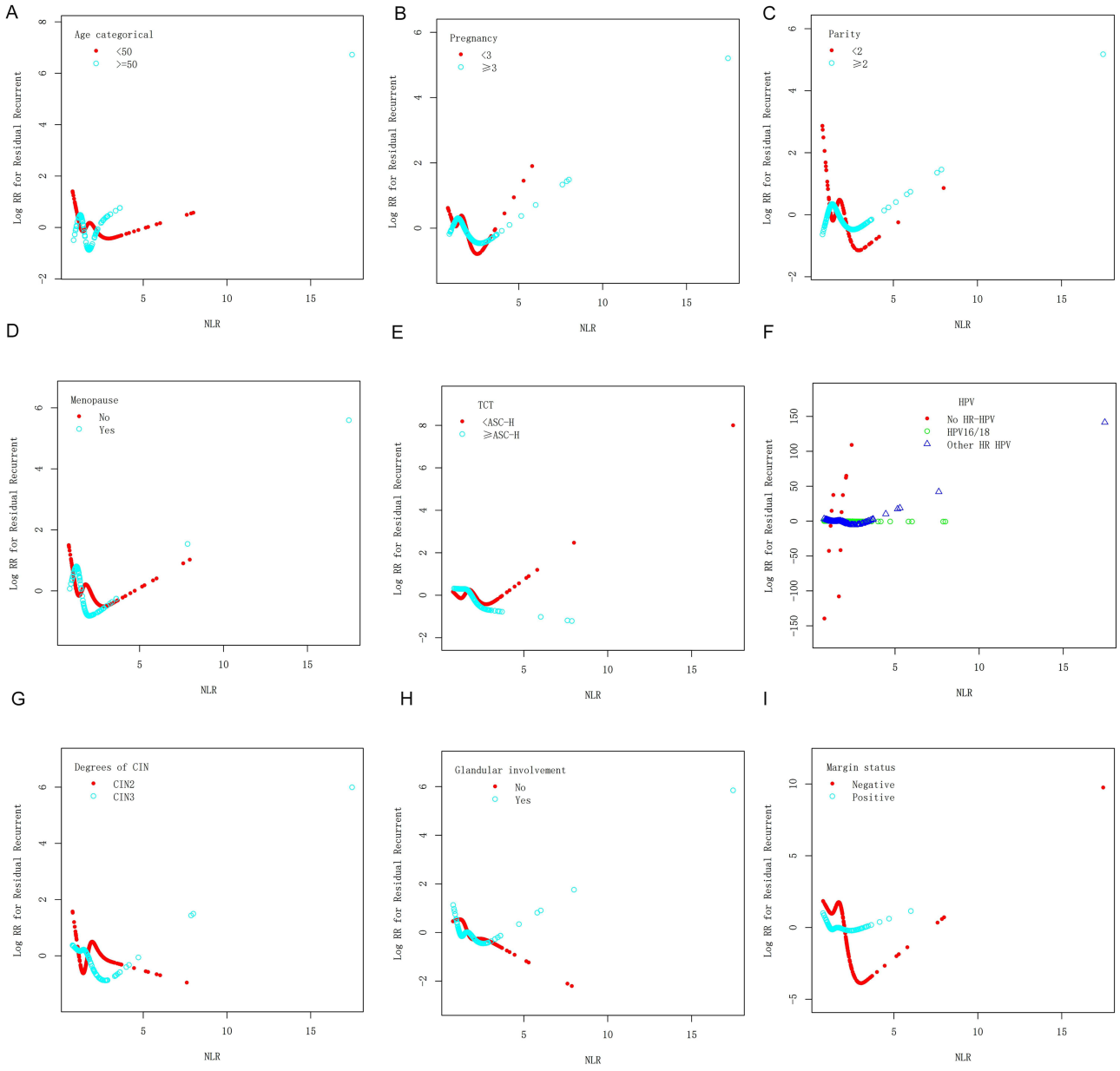

Figure 2 Associations between Neutrophil-to-Lymphocyte Ratio (NLR) and the risk of residual/recurrent Cervical Intraepithelial Neoplasia (CIN) across stratified subgroups: (**A**) Age; (**B**) Pregnancy; (**C**) Parity; (**D**) Menopause; (**E**) ThinPrep Cytologic Test (TCT); (**F**) Human Papillomavirus (HPV) status; (**G**) CIN grade; (**H**) Glandular involvement; (**I**) Margin status. The red lines and dashed blue lines represent the fitted curves for each subgroup.

(Figure 2G and Table S2). In patients with negative margin status, the inflection point was 3.36, with an HR of 0.16 (95% CI: 0.04–0.61, P = 0.007) below and 2.24 (95% CI: 1.42–3.53, P = 0.0005) above it (Figure 2I and Table S2). These U-shaped relationships and threshold effects were statistically significant on both sides of the inflection points. In other subgroups (Figure 2B, C, E, F and H), while U-shaped relationships and threshold effects were observed, they did not reach statistical significance on both sides of the inflection points (Table S2). Despite the presence of significant U-shaped relationships and threshold effects in several subgroups, no significant interactions were observed between subgroups in the overall threshold effects analysis.

Discussion

This study investigates the correlation between systemic immune-inflammatory markers and the risk of residual or recurrent CIN following LEEP. The results indicate distinct threshold effects of NLR, PLR and SII on the likelihood of CIN recurrence or residual disease. Notably, a significant U-shaped association was observed for NLR, with lower levels conferring a protective effect and higher levels corresponding to an increased risk. PLR and SII also exhibited minor protective effects below their respective threshold.

The link between SII and the persistence or recurrence of lesions after conization for high-grade CIN is becoming increasingly evident. Chronic inflammation may impair anti-tumour immunity by affecting immune cell function and altering cytokine production.[21] Factors such as IL-6 and TNF-α, which are associated with persistent inflammation in the tumour microenvironment, can promote lesion growth, support HPV survival and exacerbate lesion progression.[22,23] Systemic inflammation could also impede healing processes and trigger local inflammatory responses, facilitating lesion persistence or reinfection.[24] Additionally, genetic variations in inflammatory pathways may influence disease susceptibility and outcomes.[25] Understanding the role of immune-inflammatory markers is critical for identifying predictive biomarkers that can help assess prognosis in patients undergoing conization for high-grade CIN. Blood markers, such as neutrophils and lymphocytes, and their ratios (NLR and PLR), are indicators of systemic inflammation and provide valuable insights into immune responses.[26]

Recent studies have highlighted NLR's potential as a prognostic marker for CIN recurrence post-conization.[27,28] Several researchers have demonstrated a significant association between elevated NLR levels and an increased risk of CIN recurrence after conization.[29,30] These studies consistently report higher recurrence rates in patients whose NLR levels exceed specific thresholds, typically ranging from 1.9 to 2.[16,31] Additional research by Prabawa et al[32] and Huang et al[33] further supports NLR's importance in cervical cancer staging and its correlation with various clinical parameters. Our study revealed a notable U-shaped relationship between NLR and CIN recurrence/residual disease, especially after adjusting for confounding factors. Specifically, NLR showed a protective effect below the threshold of 3.15 (adjusted HR: 0.65, 95% CI: 0.43–1.00), while an increased risk was observed above this threshold (adjusted HR: 1.53, 95% CI: 1.24–1.89). This suggests that both very low and very high NLR values may be associated with an elevated risk of CIN recurrence/residual disease, with an optimal range between these extremes. These findings align with the dual role of inflammation in cancer progression and suppression.[34] Low NLR values may reflect an insufficient immune response, potentially leading to HPV persistence and lesion recurrence. Conversely, high NLR values could indicate chronic inflammation, which has been linked to cancer progression. The optimal NLR range identified in our study likely represents a balanced immune state capable of effectively managing HPV infection and CIN progression.

While most studies focus on the role of NLR in CIN recurrence, Huang et al[35] explored the prognostic significance of PLR in high-grade CIN after LEEP. Their findings revealed that elevated PLR levels were associated with an increased likelihood of recurrence or residual disease at 3- and 5-year follow-ups, indicating a higher cumulative risk. These results suggest that preoperative PLR levels could be a valuable predictor of recurrence or residual disease in patients with high-grade squamous intraepithelial lesions (HSIL) following LEEP. Interestingly, our study observed a different trend, with PLR showing a slight protective effect below the threshold of 101.78 (adjusted HR: 0.98, 95% CI: 0.96–1.00), but no significant effect above this level. This subtle influence indicates that, within our cohort, PLR may not be as strong a predictor of recurrence or residual disease as NLR and SII.

The SII, a novel marker combining platelet, neutrophil and lymphocyte counts, has shown promise as a biomarker for predicting CIN progression to cancer. A cross-sectional study by Afsar et al[17] demonstrated that SII levels were

significantly higher in patients with cervical cancer, with good predictive accuracy for the disease. Our study identified a protective effect for SII below the threshold of 266.07 (adjusted HR: 0.97, 95% CI: 0.96–0.98), with no significant impact above this level. This suggests that lower SII values, reflecting a more favourable balance of platelets, neutrophils and lymphocytes, may offer protection against CIN recurrence or residual disease. These findings align with previous research showing an association between lower SII levels and improved cancer outcomes.[36]

Subgroup analyses revealed a significant U-shaped relationship for NLR, particularly in older patients (≥50 years), menopausal women, patients with CIN3 and those with negative margin status. These results indicate that NLR may have greater prognostic value in these high-risk subgroups. The stronger correlation in older and menopausal women could be due to age-related changes in immune function and hormonal status, which may affect both NLR levels and CIN progression.[37] The more pronounced association in patients with CIN3 compared to those with CIN2 suggests that NLR might be a more effective prognostic indicator in advanced precancerous lesions, given the heightened inflammatory response associated with severe dysplasia.[38,39] Notably, the U-shaped relationship was particularly evident in patients with negative margin status, suggesting that in cases where complete excision is achieved, systemic inflammatory status, as indicated by NLR, may play a significant role in recurrence risk.[40] Conversely, in cases with positive margins, the local factors associated with incomplete excision may overshadow the influence of systemic inflammation on recurrence risk.

Our study distinguishes itself from previous research by identifying a U-shaped relationship between NLR and CIN recurrence or residual risk, as well as non-linear threshold effects for PLR and SII. These findings may result from our use of advanced statistical methods, such as non-linear regression and threshold effect analysis, alongside differences in study populations, follow-up periods and potential confounding factors. These results highlight the need for further research to validate these non-linear associations and explore their underlying biological mechanisms.

The strengths of this study include the comprehensive analysis of non-linear relationships and threshold effects, as well as the examination of subgroup interactions. However, several limitations should be acknowledged. First, the retrospective design may introduce biases related to selection and information. Second, the relatively small sample size may limit the detection of significant associations within certain subgroups. Lastly, the absence of data on other potential confounders, such as smoking status and immunosuppression, could affect the observed relationship between inflammatory markers and the risk of residual or recurrent CIN.

Looking forward, to translate these findings into clinical practice, our data suggest a preliminary risk stratification framework with NLR values: a reference range (2.0–3.15) showing optimal outcomes, and higher risk categories (NLR < 2.0 or > 3.15) potentially indicating increased recurrence risk. However, recognizing the limitations of single-marker assessment, future studies should focus on developing an integrated predictive model incorporating multiple inflammatory indices. Such a model, combining NLR, PLR, and SII with established risk factors, could provide more precise guidance for personalized follow-up strategies and improve the clinical applicability of our findings.

Conclusions

Our study demonstrates that pre-LEEP inflammatory markers—NLR, PLR and SII—exhibit a non-linear association with the risk of residual or recurrent CIN in women with CIN2/3. The U-shaped pattern observed for NLR and the threshold effect suggest an optimal range that may help mitigate this risk. These findings are significant for risk assessment and individualised follow-up strategies. However, further validation through larger, prospective studies is necessary to confirm these results and to explore the underlying biological mechanisms in greater depth.

Data Sharing Statement

Some or all of the datasets generated and/or analyzed in the current study are not publicly available, but are available on reasonable request by the relevant authors.

Ethics

This study was conducted in strict accordance with the ethical standards set forth in the Declaration of Helsinki and approved by the Ethics Committee of Cangzhou Central Hospital (Approval No. 2021-054-02). Since this study involved

retrospective data analysis, patient consent for reviewing medical records was not required. All patient data were anonymized and handled with strict confidentiality to protect patient privacy.

Consent to Participate

Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Consent for Publication

All of the authors approved the publication of the article.

Funding

This study was supported by the Key Research project, Hebei Medical Science Research Project (20220350).

Disclosure

The authors declare no competing interests in this work.

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