ORIGINAL ARTICLE

Prediction of CIN3+ in LEEP Specimen by Preoperative Inflammatory Markers

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Objective: To identify preoperative inflammatory markers for predicting lesion of CIN3+ in individuals who underwent loop electrosurgical excision procedure (LEEP).

Materials and Methods: The present study was a retrospective study conducted at the Gynecologic Oncology unit, Thammasat University Hospital (TUH), Thailand. The study period was between 2018 and 2023. Participants were subjects who underwent LEEP at TUH. Preoperative complete blood count (CBC) was obtained for calculation of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammatory response index (SIRI). The data were collected from digital records and analyzed.

Results: Ninety-eight subjects were recruited. Mean age of participants was approximately 43 years old. Two-thirds (62 out of 98) of the subjects were diagnosed with CIN3 or cervical cancer from LEEP histopathology. The combination of the inflammatory markers, including NLR, PLR, and SIRI provided prediction of CIN3+ lesions with sensitivity and positive predictive value of 93.5% and 63.7%, respectively.

Conclusion: The combination of NLR, PLR, and SIRI could predict CIN3+ lesions in patients who underwent LEEP.

Keywords: Cervical cancer; CIN; LEEP; Inflammatory markers

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Gynecologic malignancy is a common and significant health issue for women worldwide. The most prevalent gynecologic malignancy is cervical cancer, ranking as the fourth most common cancer in women globally[1]. Cervical cancer screening is the most effective method for cervical cancer prevention as evidenced by reduced incidence and mortality in cervical cancer patients. The reason behind the substantial decrease is premalignant lesions can be detected and treated before progressing to cancerous status. However, a study from Thailand reported an under-screening rate as high as 33% among female hospital employees[2]. Premalignant cervical lesions are classified as cervical intraepithelial neoplasia (CIN) 1, CIN2, and CIN3 based on the severity of the lesion. CIN1 can be managed through close observation, given its high spontaneous cure rate. CIN2 and CIN3 should be treated with either ablative treatment or excision due to the risk of malignant progression[3].

The loop electrosurgical excision procedure (LEEP) is performed by using a wire loop to remove precancerous lesions of the cervix following a cone shaped path. The mechanism of LEEP is penetration using high radiofrequency provided by the wire loop. Since CIN2 and CIN3 are categorized as high-grade intraepithelial lesions (HSIL) on the progression of malignancy, LEEP is commonly performed in these patient groups. Although LEEP is recognized as an effective outpatient procedure, some patients may experience complications such as local vaginal trauma, abortion, and preterm labor.

Considering the epidemiology, a correlation exists between the inflammatory process and the occurrence of cancer as well as its progression and metastasis. The inflammatory response can alter white blood cell counts. Some inflammatory markers

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derived from preoperative complete blood count (CBC) evaluation have been chosen as prognostic factors in several types of cancer. For example, the neutrophil-to-lymphocyte ratio (NLR) has been used as an indicator to assess the progression of cancer patients, including those with colon cancer, gastric cancer, and breast cancer[4,5]. Additionally, NLR has been associated with disease recurrence in patients with HSIL after LEEP[6-8]. Furthermore, there is a study that reported the efficacy of NLR levels for predicting CIN[9]. Other markers, such as the platelet-to-lymphocyte ratio (PLR), have also been recently investigated as a prognostic factor for recurrence and residual disease in HSIL patients after LEEP[10]. Moreover, there are some inflammatory markers derived from preoperative CBC evaluation, such as monocyte-to-lymphocyte ratio (MLR) and systemic inflammatory response index (SIRI) that is calculated by NLR multiplied by monocyte count. However, there are only a few studies to demonstrate the correlation between those inflammatory markers and the degree of cervical histopathology. According to the American Society for Colposcopy and Cervical Pathology (ASCCP) 2019 guidelines[11], the focus is the detection of CIN3 or greater lesions. The aim of the present study was to identify preoperative inflammatory markers for predicting CIN3 or greater lesion in individuals who have undergone LEEP.

Materials and Methods

The present study was a retrospective study conducted at the Gynecologic Oncology Unit, Thammasat University Hospital (TUH). Data from patients underwent LEEP for abnormal cervical histopathology between 2018 and 2023 was analyzed. Ethical approval was obtained from The Human Research Ethics Committee of Thammasat University (Medicine) MTU-EC-OB-0-241/66 in year 2023. Patients with abnormal cervical cancer screening results which require colposcopy according to ASCCP 2019 guideline[11] were appointed to the colposcopy clinic at TUH. Excisional procedure was done for therapeutic, diagnostic purposes or both. In addition, it was also performed for therapeutic purposes for lesions that were not suitable for ablative procedures. Inclusion criteria included patients who underwent LEEP at TUH with complete digital medical records, including pre-procedural CBC results and follow-up data. CBC in the present study was performed by standard automative machine of TUH. LEEP procedure was performed at one-day surgery unit. Pre-operative laboratory was no more than three days. Exclusion occurred with patients with incomplete data, no preoperative laboratory investigations, or missing follow-up records and conditions affecting CBC namely infection or inflammation. Preoperative CBC data was used to calculate four inflammatory markers: NLR, PLR, MLR, and SIRI. According to ASCCP 2019 guidelines, CIN3 or greater, risk was chosen as the best benchmark for cancer risk. Accordingly, participants were divided into two groups according to their LEEP histopathology results of less than CIN3 and CIN3 and greater.

The sample size of the present study was calculated based on a two-sample comparison of means. According to Tas et al's study in 2019[12], a cut-off value of 2.02 was a cervical cancer predictor with a sensitivity of 71% and specificity of 60%. The ratio of less than CIN3 to CIN3 and greater and group were 1:1 with alpha and beta errors at 0.05 and 0.2, respectively. The calculated minimum sample size per group was 76 for statistically significant results. Thirty percent compensation for data losing was added. The total sample size in the present study was 100 cases.

The present study collected demographic and clinical characteristics of participants, including age range of 20 to 65 years, weight, height, body mass index (BMI), pre/post-procedure cervical histopathology results and Pap smear results at the 6-month follow-up. The inflammatory markers were calculated from pre-procedure blood tests such as NLR, PLR, MLR, and SIRI, using standard formulas.

Data were analyzed using IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics for continuous data were presented as mean ± standard deviation (SD). Chi-square or Fisher's exact tests were used for categorical data, and receiver operating characteristic (ROC) curves were generated to determine appropriate cut-off values. Statistical significance was set at p-value less than 0.05.

Results

The present study enrolled 98 patients who underwent LEEP at TUH during the study period (Figure 1). Both groups, the less than CIN3 and CIN3 and greater had comparable baseline and clinical characteristics. Mean age and BMI of participants were 43 years old and 23.7 kg/m^2, respectively. Nine-tenths (89 out of 98) of participants had atypical or high-grade cervical cytologic results from cervical cancer screenings. Two-thirds (62 out of 98) of participants were diagnosed with CIN3 or cervical

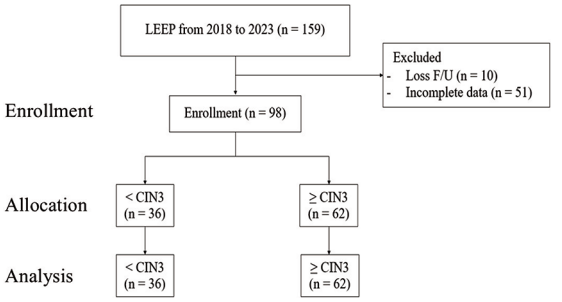
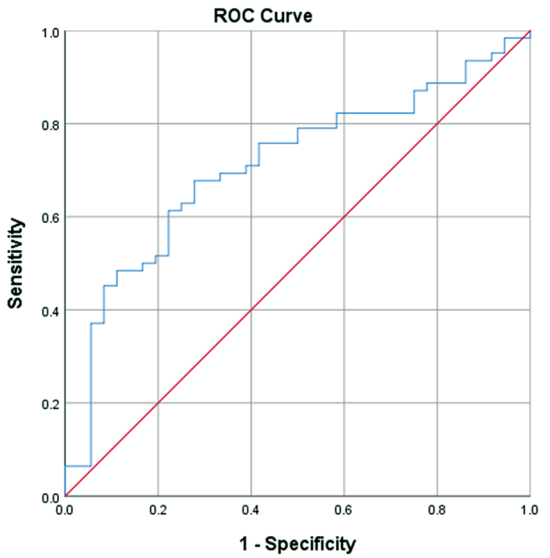


Figure 1. Study flow of CIN 3 recurrent at 6 months after LEEP

LEEP: loop electrosurgical excision procedure, F/U: follow up, CIN: cervical intraepithelial neoplasia



$$p = \frac{\exp(0.292 - 0.815(SIRI) - 0.015(PLR) + 1.375(NLR))}{1 + \exp(0.292 - 0.815(SIRI) - 0.015(PLR) + 1.375(NLR))}$$

Figure 2. Receiver operating characteristic curve (ROC) for prediction of ≥CIN3. Combined test, NLR, PLR and SIRI showed area under curve (AUC) at 0.709.

CIN: cervical intraepithelial neoplasia, ROC: receiver operating characteristic curve, NLR: neutrophil-to-lymphocyte ratio, PLR: platelets to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, SIRI: systemic inflammatory response index, p: propability of event, exp: exponential function

cancer from LEEP's histopathology reports. Almost 90% (85 out of 98) of the participants had normal Pap smears at the 6-month follow-up. Baseline and clinical characteristics are presented in Table 1.

The Hosmer-Lemeshow goodness-of-fit test was performed (p>0.05), indicating acceptability for explaining the correlation with CIN3 and greater lesion in the logistic regression. The inflammatory markers, including NLR, PLR, and SIRI had shown association with the equation as shown in Figure 2.

Table 1. Baseline and clinical characteristic

	<CIN3 (n=36)	≥CIN3 (n=62)	p-value
Age (years); mean±SD	43.7±10.4	43.1±12.1	0.789
BMI (kg/m^2); mean±SD	24.8±4.8	23.2±4.1	0.102
Cytology prior LEEP; n (%)			0.379
NILM/LSIL	5 (13.9)	4 (6.4)	
Atypical smear	10 (27.8)	12 (19.4)	
HSIL/SCC	21 (58.3)	46 (74.2)	
NED at 6 mo. F/U; n (%)	31 (86.1)	54 (87.1)	0.890
Positive HPV prior LEEP; n (%)	13 (36.1)	16 (25.8)	0.226
WBC (10^3 cell/cu.mm); mean±SD	7.61±2.38	8.21±2.28	0.221
Neutrophil	4.26±1.89	5.12±1.92	0.036
Lymphocyte	2.30±0.69	2.18±0.66	0.403
Monocyte	0.38±0.04	0.42±0.02	0.368
Platelets (10^5 cell/cu.mm); mean±SD	2.88±0.71	2.72±0.64	0.245
Inflammatory marker; mean±SD			
NLR	2.09±0.23	2.50±0.16	0.135
PLR	136.44±56.06	135.22±55.19	0.917
MLR	0.18±0.03	0.20±0.01	0.442
SIRI	1.01±0.32	1.10±0.10	0.721

CIN=cervical intraepithelial neoplasia; BMI=body mass index; LEEP=loop electrosurgical excision procedure; NILM=negative for intraepithelial lesion or malignancy; LSIL=low grade squamous intraepithelial lesion; HSIL=high grade squamous intraepithelial lesion; SCC=squamous cell carcinoma; HPV=human papillomavirus; NED at 6 mo F/U=no evidence of disease at 6 month follow up; WBC=white blood count; NLR=neutrophil-to-lymphocyte ratio; PLR=platelets-to-lymphocyte ratio; MLR=monocyte-to-lymphocyte ratio; SIRI=systemic inflammatory response index

A ROC curve was generated, showing area under curve (AUC) of 0.709. Selecting an optimal cut-off value of 0.416, the sensitivity, positive predictive value, negative predictive value, and specificity were determined as 93.5% (58 out of 62), 63.7% (58 out of 91), 42.8% (3 out of 7), and 8.3% (3 out of 36), respectively.

Discussion

Several literature reviews suggested a complex interplay between the inflammatory response and various aspects of cancer including its occurrence, progression, and metastasis. The inflammatory response can alter white blood count (WBC) levels. From a physiological perspective, the mechanism involves alterations in WBC levels triggered by the inflammatory response. Different WBC types play distinct roles in immune function. Lymphocytes, for instance, act as critical anti-tumor defenders by secreting cytokines that inhibit tumor cell proliferation and exerting direct cytotoxic effects. In contrast, neutrophils had immunomodulatory effects that suppressed lymphocyte activity, potentially promoting tumor progression and metastasis[13]. Additionally, activated platelets have been shown to

Table 2. Comparison study of CIN and cervical cancer

	Chun[6]	Farzaneh[7]	Tas[12]	Xu[9]	Origoni[8]	Huang[10]	Present study
Year	2017	2019	2019	2021	2022	2023	2024
Country	Korea	Iran	Turkey	China	Italy	China	Thailand
Cases (n)	230	307	140	212	428	335	98
Age (years)	45.4	40.3	38	44.5	38.4	37	43.3
BMI (kg/m^2)	22.5	NM	NM	NM	NM	NM	23.7
Marker							
NLR	>2.1	≥1.9	≥2.02	>2.3	≥2		Com
PLR			≥126.7			>176.1	Com
SIRI							Com
Outcome							
RFS	DC	DC					
RR					IC		
5-year RR						IC	
Prediction							
• CIN				OC			
• ≥CIN3							OC
• CC			OC				
HR	7.66	4.55				2.16	
Sensitivity (%)			71, 83	73.5			93.5
OR					2.09	2.29	
PPV (%)							63.7

CIN=cervical intraepithelial neoplasia; BMI=body mass index; NLR=neutrophil-to-lymphocyte ratio; PLR=platelets to lymphocyte ratio; SIRI=systemic inflammatory response index; RFS=recurrent free survival; RR=recurrent rate; CC=cervical cancer; HR=hazard ratio; OR=odds ratio; PPV=positive predictive value; NM=not mentioned; DC=decrease; IC=increase; OC=study's outcomes; Com=combination of markers

contribute to tumor cell growth and survival through paracrine signaling[14].

From the previous study, Chun et al. and Farzaneh et al. reported from Korea and Iran that NLR results greater than 2.1 and 1.9, respectively could predict the recurrence free survival of CIN in the subjects who underwent LEEP[6,7]. Origoni et al. reported from Italy in 2022 that NLR greater than 2 could predict recurrent rate of CIN after LEEP with OR 2.09[8]. Xu & Song reported from China in the year 2021 that NLR greater than 2.3 could predict CIN1 or more with sensitivity at 73.5%[9]. Moreover, not only NLR could be associated with abnormal cervical lesions, data from China showed that PLR more than 176.1 also could predict 5-year recurrence rate of CIN in the subject who underwent LEEP with hazard ratio (HR) 2.16[10]. Tas et al. from Türkiye reported in 2019 that both NLR of 2.02 or greater and PLR of 126.7 or greater could predict cervical cancer in LEEP specimens with sensitivity of 71% and 83%, respectively[12].

From the current study, the authors reported the combination of NLR, PLR, and SIRI for prediction of CIN3 or greater lesion in LEEP specimen. The present study provided evidence that a combined inflammatory marker score incorporating NLR, PLR, and SIRI effectively discriminated between less than CIN3, and CIN3 or greater lesions. The model utilized in the study, with a cut-off value at 0.416 demonstrated promising sensitivity of 93.5% and positive predictive value of 63.7% for predicting CIN3 or greater lesions. This finding resonates with study by Xu & Song on the predictive value of NLR for CIN[9]. Nevertheless, certain limitations persisted in this study. The short follow-up period prevented this study from replicating findings on recurrent rates, as reported in studies by Chun et al., Farzaneh et al., and Origoni et al[6-8]. Comparison of the current to the previous study are summarized and presented in Table 2.

According to ASCCP 2019 guideline, CIN3 or greater lesions risk was the topic of interest in colposcopic referral threshold[11]. The threshold of treatment was CIN2[13]. Ablation treatment was more conservative than excisional treatment but had a higher recurrent rate[13]. The high sensitivity of 93.5% of the current study for prediction of CIN3 or greater lesions risk could be used for assisting clinicians to select which patients to perform treatment by LEEP or by conservative measures such as ablation treatments

or follow up, for lesions below CIN3. High sensitivity with low specificity of these markers alerted the physician to select the treatment and follow up plan.

However, bias from retrospective nature, single-center design, limited number of sample size and short follow-up duration were the limitations of study. Larger, multi-center studies with extended follow-up periods, different population conduction, and addition of any other markers were essential to validate the potential of inflammatory markers for predicting CIN3 or greater lesions after LEEP robustly in clinical practice. This approach will help mitigate issues such as recall bias and enhance the generalizability of the findings.

Conclusion

The combination of NLR, PLR, and SIRI was statistically significant in prediction of CIN3 or greater lesions in patients who underwent LEEP. High sensitivity with low specificity of these markers needed the addition test. Colposcopy was still required for another test.

What is already known about this topic?

Some inflammatory markers have also been recently investigated as a prognostic factor for recurrence and residual disease in HSIL patients after LEEP. However, there are only a few studies to demonstrate the correlation between those inflammatory markers and the degree of cervical histopathology.

What does this study add?

The combination of NLR, PLR, and SIRI was statistically significant in prediction of CIN3 or greater lesions in patients who underwent LEEP.

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Conflicts of interest

The authors declare no conflict of interest.

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