RESEARCH ARTICLE

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# Inflammatory Markers in Prior Loop Electrosurgical Excision Procedure (LEEP) as a Prognosis Factor in the Recurrence of Cervical Intraepithelial Neoplasia

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## Abstract

**Objectives:** To investigate the relationship between preoperative inflammatory markers and recurrence of CIN after loop electrosurgical excision procedure (LEEP). **Methods:** A retrospective historical cohort study was conducted at gynecologic oncology unit, Bhumibol Adulyadej Hospital, Royal Thai Air Force, Thailand. Data was collected from medical records of CIN cases from year 2016 to 2021. Inclusion criteria were subjects who were diagnosed of CIN and underwent LEEP with pathologic confirmation and followed up for two years (at 6 months, 1 year, and 2 years). Preoperative complete blood count (CBC) was obtained within one month for calculation as systemic inflammatory values. **Results:** One hundred and ten cases of CIN were enrolled. Mean age of participants was 48.1 years old. Three-fourths (83/110) of the participants had histological confirmation as CIN2/3. Sixteen (18/110) and twenty (22/110) percentage of cases had recurrence of disease at 1 and 2 years, respectively. Monocytes /lymphocytes ratio (MLR) and systemic inflammation response index (SIRI) could predict recurrence of CIN within 2 years. MLR more than 0.16 and SIRI more than 0.57 gave the sensitivity and negative predictive value (NPV) at percentage of 77.3/ 81.8 and 91.8/ 90.2, respectively. Combination of MLR and SIRI had sensitivity and NPV at 90.5 and 95.4 percent, respectively. MLR and SIRI could not predict marginal involvement, glandular involvement, and LEEP confirmed CIN 2/3. **Conclusion:** Pretreatment MLR and SIRI were statistically significant in predicting the recurrence in CIN after post LEEP procedure within 2 years follow up.

**Keywords:** CIN- recurrent- MLR- SIRI

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## Introduction

Cervical cancer is the fourth most common cancer in women globally. It is commonly caused by human papillomavirus (HPV) infection. Incidence rate of cervical cancer in Thailand was reported as 9.4% as in year 2020 [1]. Cervical intraepithelial neoplasia (CIN) is the precancerous lesion of the cervix. Untreated CIN ultimately leads to development of cervical cancer. CIN is categorized into three groups namely CIN 1, CIN 2 and CIN 3. According to ASCCP guideline, It is recommended for patients who were 25 years or older and had consecutive histologic diagnosed as CIN 1 for at least 2 years. Observation is preferred but treatment is acceptable [2, 3]. CIN 2 and 3 are treated with either ablation or excision (loop electrosurgical excision procedure: LEEP) [2, 3]. Risk factors for recurrent or residual CIN were HPV infection, immunosuppression, positive margin of CIN, CIN grading, glandular involvement, and higher systemic inflammatory markers [4, 5].

There are various studies demonstrating the relationship between inflammation and development of various solid cancers, including gynecological cancer. It is believed that oncological outcomes can be predicted through this concept [4-6]. Chronic inflammation leads to tumor angiogenesis, growth, and advanced stage of cancer [5]. The inflammatory parameters are quantified through the use of complete blood count (CBC) which is a routine blood test with low cost, easy accessibility and practically reflects inflammatory response. Pre-treatment inflammatory markers derived from CBC compose of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte

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ratio (PLR), monocyte/lymphocyte ratio (MLR), systemic immune-inflammatory index (SII), systemic inflammation response index (SIRI), aggregate inflammation response index (AISI). High inflammatory response in cervical cancer and CIN in some studies had both statistically significant and insignificant prognosis outcomes. In precancerous lesion of cervix, inflammatory parameters predict prognosis of diagnosis of CIN, grading high CIN and CIN recurrence [4, 7-9]. However these high inflammatory markers have varying cut-off value and prognostic relationships. Thereby, this study was conducted to investigate the relationship between preoperative inflammatory markers as a prognosis factor in CIN recurrent for all types after LEEP procedure.

## Materials and Methods

A retrospective historical cohort study was carried out in the Obstetrics and Gynecology Department at Bhumibol Adulyadej Hospital, Royal Thai Air Force, Thailand. The study was approved by the Institutional Review Board (IRB No.95/66) and registered in Thai clinical trials (TCTR: https://www.thaiclinicaltrials.org/show/TCTR20231120002). Data was collected from medical records of patients from year 2016 to 2021. Inclusion criteria were patients who underwent LEEP of all CIN types with pathologic confirmation with followed up visits up to two years (at 6 months, 1 and 2 years). Preoperative hematological values were obtained within one month prior of LEEP procedure including complete blood count (CBC) to calculate as systemic inflammatory values. NLR, PLR and MLR were calculated by neutrophils, platelets, and monocytes count divided by lymphocytes count. SIRI was calculated by number of multiplied neutrophils and monocytes count, divided by number of lymphocytes count. SII was calculated by number of multiplied neutrophils, and platelets divided by number of lymphocytes counts. AISI was calculated by number of multiplied platelets, neutrophils and monocytes count, divided by number of lymphocytes count. The exclusion criteria were incomplete data collection, loss or incomplete follow-up, underwent hysterectomy due to no free margin and cervical cancer followed by LEEP procedure. Sample size calculation was made by proportion difference of case control with 80 percentage of power. The ratio of study and control was one by one. Alpha and beta errors were set at level of 0.05 and 0.2, respectively. According to Farzaneh (2019) study, recurrence CIN was 28.6 and 4.8 percent among NLR cut-off value more and less than 1.9, respectively [10]. At least 46 cases in each side by continuity correction were needed for statistical significant. Twenty percent compensation was added to both groups. There were 110 cases required in this study.

Demographic and clinical characters included age, parity, cervical histopathology, glandular involvement, marginal involvement, and recurrence. Preoperative routine CBC values were obtained within one month prior of LEEP procedure to calculate systemic inflammatory markers (NLR, PLR, MLR, SII, SIRI, and AISI). Collected data were analyzed using Statistical Pack-age for Social Sciences version version 26.0 software (SPSS Inc, Chicago, IL, USA). Statistical analyses included descriptive statistics continuous data was presented as mean ± standard deviation (SD). Chi-square test and Fisher's exact test were used for categorical data as appropriate application. Receiver operating characteristic curve (ROC) was generated for an appropriate cut off value. A p-value less than 0.05 was considered as statistically significant.

## Results

A total of 110 CIN cases who underwent LEEP were enrolled as in Figure 1. The demographic characteristics were middle aged multiparous women who all had cervical pathology CIN2/3 prior LEEP. Three-fourths (83/110) of the participants had histological confirmation as CIN2/3 after LEEP. CIN recurrence occurred at 1 and 2 years by sixteen (18/110) and twenty (22/110) percentage of cases respectively. Among the recurring subjects, two-third

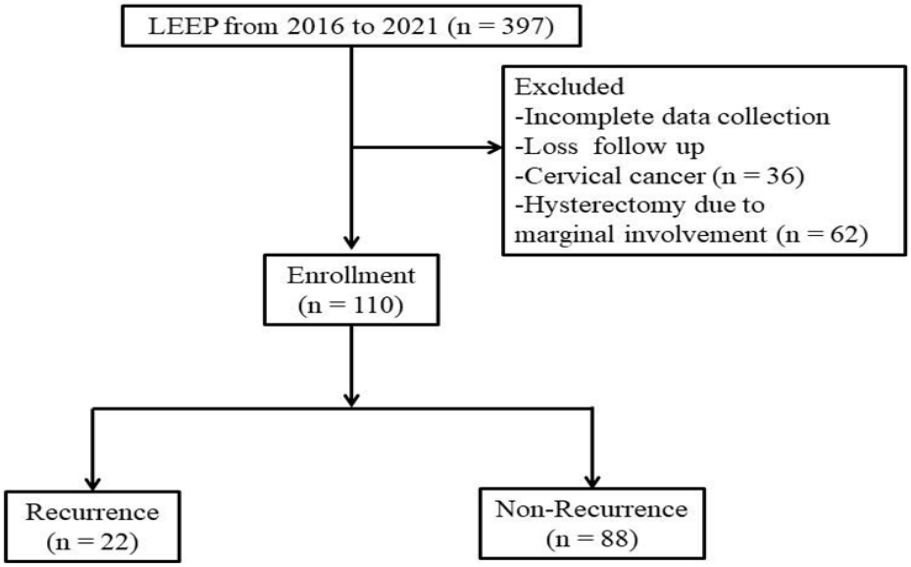


Figure 1. Flow of Study of CIN Recurrence

Table 1. Baseline Characteristic of CIN who Underwent LEEP among Recurrent (n=22) and Non-Recurrence (n=88)

| | Total | Univariated analysis | | | | Multivariated analysis | |
|---|---|---|---|---|---|---|---|
| | | Recurrence | Non-recurrence | MeD (95%CI) | p-value | Adj OR (95%CI) | p-value |
| Hb (g/%) | 12.6 ± 4.7 | 12.8 ± 3.5 | 12.6 ± 4.9 | 0.6 (-1.7, 2.8) | 0.62 | | |
| Age (yrs) | 48.1 ±10.9 | 52.9 ±15.4 | 46.9 ± 9.2 | 6.1 (-1.0, 13.1) | 0.09 | | |
| Multiparity** | 87 (79.1) | 18 (81.8) | 69 (78.4) | | 0.73 | | |
| HIV infection** | 5 (4.5) | 3 (13.6) | 2 (2.3) | | 0.02 | | |
| HPV Vaccination** | 8 (7.3) | 0 (0) | 8 (9.1) | | 0.14 | | |
| Inflammatory markers | | | | | | | |
| ANC (x $10^3$/$mm^3$) | 4.79 ± 4.39 | 4.30 ± 1.67 | 4.92 ±4.83 | -0.61 (-2.69, 1.46) | 0.56 | | |
| ALC (x $10^3$/$mm^3$) | 2.31 ± 0.71 | 2.18 ± 0.73 | 2.34 ± 0.71 | -0.17 (-0.50, 0.17) | 0.33 | | |
| AMC (x $10^3$/$mm^3$) | 0.35 ± 0.09 | 0.39 ± 0.11 | 0.33 ±0.76 | 0.05 (0.01, 0.09) | 0.01 | | |
| PLT (x $10^3$/$mm^3$) | 302.4 ±71.8 | 307.8 ± 64.6 | 301.9 ± 73.8 | 6.8 (-27.3, 40.8) | 0.69 | | |
| NLR | 2.0 ±0.9 | 2.2 ± 1.1 | 2.0 ± 0.8 | 0.2 (-0.2, 0.6) | 0.36 | | |
| PLR | 141.1 ± 55.2 | 157.9 ±69.5 | 136.9 ± 50.6 | 20.9 (-4.9, 46.9) | 0.11 | | |
| MLR | 0.2 ± 0.1 | 0.2 ± 0.1 | 0.2 ± 0.1 | 0.03 (0.01, 0.06) | 0.01 | $0.05x10^6$ ($7.74, 302.83x10^6$) | 0.02 |
| SIRI | 0.7 ± 0.3 | 0.8 ± 0.3 | 0.7 ± 0.3 | 0.1 (0.01, 0.3) | 0.03 | 5.96 (1.19, 29.82) | 0.03 |
| SII | 631.4 ±351.1 | 701.9 ± 421.8 | 613.8 ± 331.5 | 88.1 (-77.7, 253.9) | 0.29 | | |
| AISI | 207.9 ± 109.8 | 249.4 ± 130.9 | 197.5 ±102.0 | 51.9 (0.8, 103.1) | 0.05 | | |
| LEEP CIN 2/3** | 83 (75.5) | 16 (72.7) | 67 (76.1) | | 0.74 | | |
| GI * | 46 (41.8) | 8 (36.4) | 38 (43.2) | | 0.56 | | |
| MI ** | 34 (30.9) | 5 (22.7) | 29 (33) | | 0.35 | | |
| Recurrence** | | | | | | | |
| Within 1 year | 18 (16.3) | 18 (81.8) | | | | | |
| Within 2 years | 22 (20.0) | 22 (100.0) | | | | | |
| Recurrence CIN 2/3 | 13 (11.8) | 13 (59.1) | | | | | |

CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision; Hb, hemoglobin; ANC, absolute neutrophils count; ALC, absolute lymphocytes count; AMC, absolute monocytes count; PLT, platelets count; HPV, human papillomavirus; Co-testing, conventional cytology and HPV DNA test; NLR, neutrophils to lymphocytes ratio; PLR, platelets to lymphocytes ratio; MLR, monocytes to lymphocytes ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammation response index; AISI, aggregate inflammation response index; GI, Glandular involvement; MI, marginal involvement; *Mean ± SD; **Number (%); MeD (95%CI), Mean difference (95% confidential interval; CI); Adj OR (95%CI), Adjusted odd ratio (95% confidential interval; CI).

cases (13/22) had CIN2/3 in recurrence. All participants had never received HPV vaccination before colposcopy and LEEP. Only eight cases obtained HPV vaccination after LEEP and shown no CIN recurrence (Table 1). Hematological parameters of AMC, MLR, SIRI and AISI in recurrent group were higher than non-recurrent group (p-value=0.01, 0.01, 0.03, 0.05, respectively.). While other inflammatory markers (ANC, ALC, NLR, PLR and SII) were not significance in both groups. One-third (33/110) of the participants who underwent LEEP performed co-testing, meanwhile the others followed up by conventional cytology every 6 months according to The Thai Minister of Public Health protocol. After adjusted of HIV infection cases, only MLR and SIRI were still significant factors. Table 2 and Figure 2 showed ROC curve generating the relationship between preoperative inflammatory values and CIN recurrence in post LEEP within 2 years. MLR (≥ 0.16) and SIRI (≥0.57) could predict recurrence within

Table 2. Inflammatory Markers to Predict Prognostic Outcomes in Recurrent CIN within 2 Years

| | Cut-off | AUC | Sensitivity | Specificity | NPV | PPV | Accuracy | p-value |
|---|---|---|---|---|---|---|---|---|
| NLR | 0.99 | 0.54 | 81.8 | 4.5 | 50 | 17.6 | 20 | 0.565 |
| PLR | 120.56 | 0.59 | 72.7 | 51.1 | 88.2 | 55.5 | 55.5 | 0.194 |
| MLR | 0.16 | 0.69 | 77.3 | 63.6 | 91.8 | 34.7 | 66.4 | 0.007 |
| SIRI | 0.57 | 0.64 | 81.8 | 42 | 90.2 | 26.1 | 50 | 0.048 |
| SII | 653.1 | 0.56 | 54.5 | 68.2 | 85.7 | 30 | 65.5 | 0.415 |
| AISI | 221.3 | 0.62 | 54.5 | 69.3 | 85.9 | 30.8 | 66.4 | 0.096 |
| Combined | | 0.69 | 90.5 | 70 | 95.4 | 51.9 | 87.9 | 0.007 |

NLR, neutrophils to lymphocytes ratio; PLR, platelets to lymphocytes ratio; MLR, monocytes to lymphocytes ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammation response index; AISI, aggregate inflammation response index; AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value; Combined test; combination of MLR ≥ 0.16 and SIRI ≥ 0.57.

Table 3. Comparison study of inflammatory makers in CIN and cervical cancer.

| Author (Year) | | Inflammatory markers with Cut-off Value | | | | | | Outcome | Result |
|---|---|---|---|---|---|---|---|---|---|
| | | NLR | PLR | MLR | SIRI | SII | AISI | | |
| CIN | | | | | | | | | |
| | Chun (2017) | 2.1* | | | | | | Recur | Sense 57.1%, |
| | Farzaheh (2019) | 1.9* | 135.9 | | | | | Recur | Sense 73.7% |
| | Xu (2020) | 2.3 | | | | | | Diag | NS |
| | Origoni (2022) | 2.0* | | | | | | Recur | Sense 52.4%, |
| | Bilir F (2022) | 2.1* | 133* | 0.28* | 0.9* | | | HPV | SIRI: Sense 95% |
| | Kyung (2023) | 2 | | | | | | Diag | NS |
| | Huang (2023) | | 176.1* | | | | | Recur | HR 2.082 |
| Cervical cancer | | | | | | | | | |
| | Huang (2019) | 2.4 | 118 | 0.26 | | 475* | | OS | HR 2.53 |
| | Chao (2020) | 2.8 | 135 | 0.29 | 1.25* | | | OS | HR 1.82 |
| | Li YX (2021) | 2.49* | 154.1 | 0.26* | 1.02 | | | OS | HR 1.721/ 1.446 |
| | Kajima (2022) | | | | 2.147* | | | PFS | HR 2.204 |
| | Guo (2023) | 1.72 | 111.96 | 0.24 | 1.38 | 566.2 | | OS | NS |
| | Li N (2023) | 2.85 | 164.2* | 0.25 | 1.07 | | 301.3 | OS | HR 1.385 |
| This study | | 0.99 | 120.56 | 0.16* | 0.57* | 653.1 | 221.3 | CIN recur | Sense 77.3/ 81.8% |

NLR, neutrophils to lymphocytes ratio; PLR, platelets to lymphocytes ratio; MLR, monocytes to lymphocytes ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammation response index; AISI, aggregate inflammation response index; Recur, recurrence; Diag, diagnosis; Sense, sensitivity; HR, hazard ratio; OS, overall survival; PFS, progression free survival; p, p-value; *, significant in statistic; NS, not significant in statistic

2 years, (sensitivity 77.3 %, NPV 91.80% and sensitivity 81.8 %, NPV 90.2 %, respectively). Combination of MLR and SIRI in predicting recurrence within 2 years had a sensitivity of 90.5 % and NPV of 95.4 % (Figure

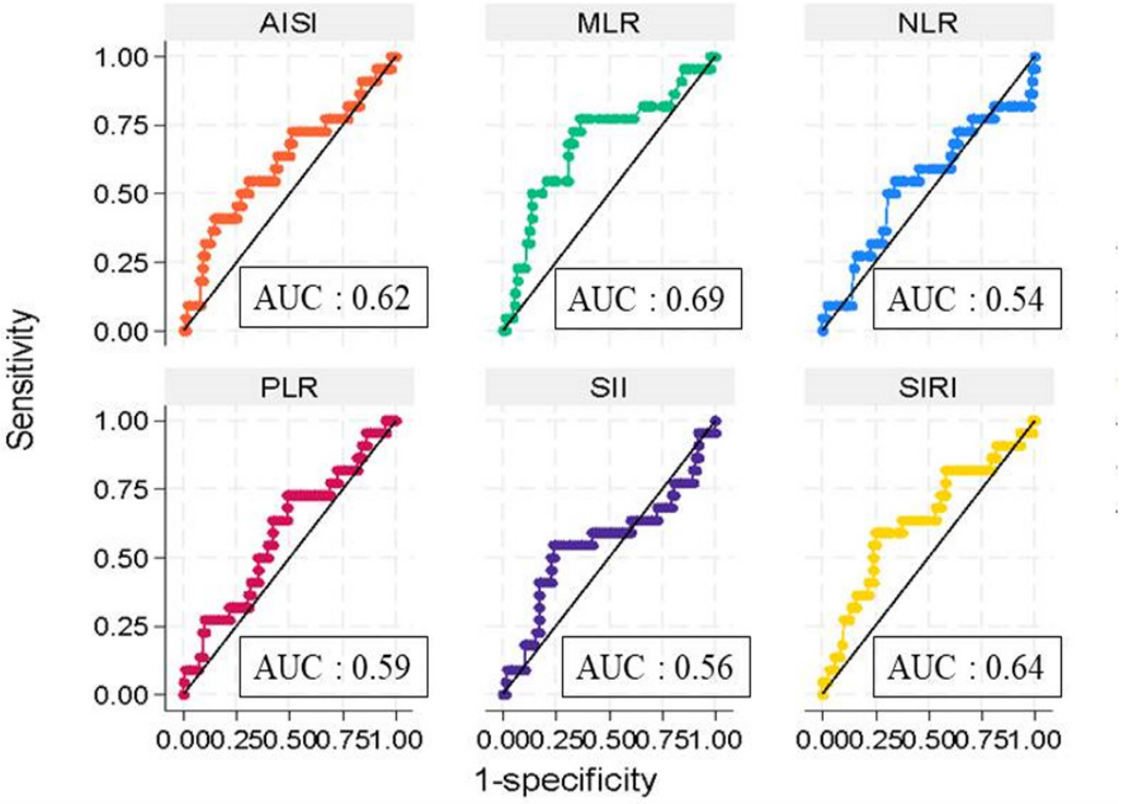


Figure 2. Receiver Operating Characteristic Curve (ROC) for Prediction of CIN Recurrence within 2 Years. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammation response index; AISI, aggregate inflammation response index; AUC, area under curve.

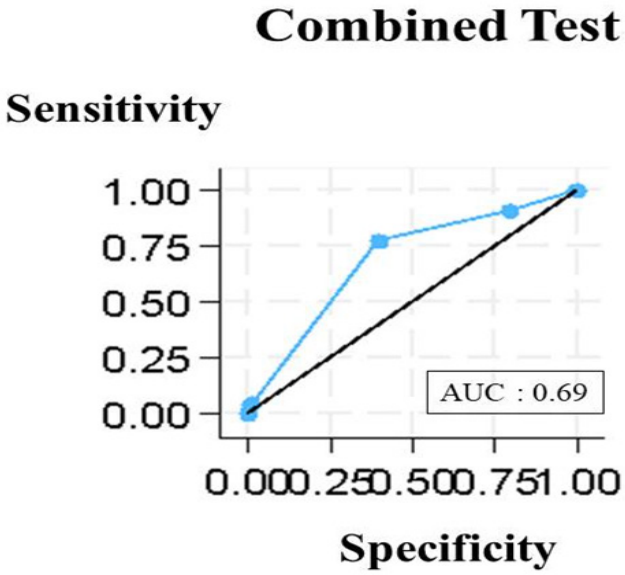


Figure 3. Receiver Operating Characteristic Curve (ROC) for Prediction of CIN Recurrence within 2 Years. Combined test, MLR ≥ 0.16 and SIRI ≥ 0.57; AUC, area under curve.

3). Variables as marginal involvement, glandular involvement, and LEEP confirmed CIN 2/3 were equally in both recurrence and non-recurrence groups (Table 1).

## Discussion

It has been widely confirmed that high hematologic markers can be used for predicting of worsening outcome in various solid tumor such as small cell lung, colorectal, pancreatic, breast, and gynecological cancer (ovarian, endometrial, and cervical cancer) [6]. Table 3 showed the comparison study in inflammatory values of CIN and cervical cancer. The high pre-treatment inflammatory markers in CIN significantly predicted recurrent, persistent and grading of disease [4-5, 10-14]. Previous studies by Chun, Farzaneh and Origoni reported the efficacy of NLR for predicting of CIN recurrence. NLR cut-off value ranging from 1.9 to 2.1 was shown. Sensitivity and negative predictive value (NPV) ranging from 52.4 to 73.7 and 87.3 percent respectively were reported [4-5, 10]. However, NLR from the current study did not predict recurrence of CIN. Huang demonstrated that PLR could predict recurrence/residual HSIL at 3-5 year follow up, while Farzaneh displayed no benefit of PLR in recurrent CIN [10, 14]. The present study reported PLR could not predict the recurrence of CIN. This supported Farzaneh's report.

MLR could predict persistent of HPV infection and overall survival (OS) of cervical cancer. Bilir and Li reported that MLR at 0.28 and 0.26 could predict persistence in HPV infection and OS of cervical cancer, respectively [12, 15]. Conversely, Huang, Chao, Li and Guo stated the unpredictability of MLR in OS of cervical cancer [7-9, 16]. MLR at level of 0.16 from the present study could predict recurrent CIN within 2 years. It might be only the possible predicting factor for inflammatory processes resulted from either precancerous or cervical cancer. Bilir reported that SIRI (0.9) could predict persistence of HPV infection [12]. Moreover, SIRI (from 1.25 to 2.15) could predict OS and progression free survival (PFS) of cervical cancer [7, 17]. While previous studies from Li, Guo and Li, SIRI could not predict the OS of cervical cancer [8-9, 15]. The present study supported the previous studies that SIRI (0.57) could predict recurrence CIN within 2 years [8-9, 15]. SIRI might be an interesting inflammatory marker. It composed of neutrophils, monocytes and lymphocytes for calculation. From the current study, combination of SIRI and MLR gave the predicting value in recurrent CIN within 2 years with sensitivity and NPV at level of 90.5 and 95.4 percent, respectively.This supported our suggestion that using a combination of SIRI and MLR could better in predicting recurrence of CIN. Both SIRI and MLR were composed of all leukocytes parameters (neutrophils, monocytes and lymphocytes), which had better prediction than using in some markers.

Neutrophils play a role in inhibiting lymphocytes function, resulting in tumor progression. Lymphocytes determine a critical part of immune response to tumor defense mechanisms. Platelets release cytokine, growth factors and vascular endothelial growth factor (VEGF) which promoting vascularization and progression of tumor. Monocytes differentiate tumor-associated macrophages that promoting tumor growth and immune response [7-8, 15]. Combination of three leucocytes could predict an outcome according to the inflammatory markers. Using pretreatment inflammatory markers as a combined test creates awareness to physicians for counseling to post LEEP participants who had high inflammatory marker related high chance to recurrence CIN within 2 years. Moreover, there were also no benefits in any parameters to predict cases with positive margin, glandular involvement, LEEP confirmed CIN 2/3 and recurrence confirmed CIN2/3 in that needed further study.

There were few studies investigating in the combination of inflammatory cells in precancerous condition [4-5,

10-14], meanwhile mostly focusing on cervical cancer [6-8, 15-17]. This present study investigated many inflammatory markers as NLR, PLR, MLR, SIRI, SII and AISI for predicting in the various prognosis outcomes. Participants who were diagnosed and confirmed of CIN 2/3 from colposcopy-directed biopsy were enrolled. Expedited LEEP treatment was not performed as primary management in the study institute. Cervical specimens obtaining for HPV based testing which relevant to ASCCP guideline [2]. ASCCP guideline advised using HPV based testing at six months, repeated testing annually for three years consecutive and then every three years for at least 25 years [2].

However, there was limitation of application according to high cost of HPV based testing especially in low resource country. We recommend using pretreatment MLR and SIRI combining test which was effectively predicting the recurrent CIN after LEEP within 2 years significantly with high sensitivity and NPV for helping to discriminate the patients who should perform strictly follow up with co-testing.

Regarding the limitations of this study, it was a retrospective cohort, single-center study which has recall bias and information bias in data collection. This study also had a relatively small sample size. The study design included inhomogeneity as all CIN categories were included in the study, despite CIN 2/3 having a higher risk of progression than CIN 1. Sixty percent of this study had CIN2/3 in diagnosed by LEEP, which is not reflective of the whole population. The cut off value of each inflammatory marker was varied, and combining inflammatory cells were most studied in cervical cancer, which might not dedicate to use in precancerous lesion of cervix. Using combination of inflammatory markers could be more accurate as chronic inflammation in cancer that affected in all inflammatory cells. Future studies were suggested to be conducted prospectively with long-term follow-up for recurrences. It should be considered to the limited studies on CIN 2/3 using MLR and SIRI as inflammatory markers. Larger studies are adviced in order to expand knowledge of hematological values in CIN. Finally, we suggest combining many factors, not only inflammatory response to the best evaluate prognosis outcome in CIN and cervix cancer.

In conclusion, pretreatment MLR and SIRI were statistically significant in predicting the recurrence of cervical intraepithelial neoplasia after LEEP procedure within 2 years follow up.

*Abbreviations*

CIN: cervical intraepithelial neoplasia, LEEP: Loop electrosurgical excision procedure, HPV: human papillomavirus, Co-testing: conventional cytology and HPV DNA test, CBC: complete blood count, NLR: neutrophils/lymphocytes ratio, PLR: platelets/lymphocytes ratio, MLR: monocytes/lymphocytes ratio, SII: systemic immune-inflammatory index, SIRI: systemic inflammation response index, AISI, aggregate inflammation response index.

## Author Contribution Statement

All authors contributed equally in this study.

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*Conflict of interest*

The authors declares that there is no conflict of interest.

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