RESEARCH ARTICLE

Editorial Process: Submission:10/12/2025 Acceptance:03/19/2026 Published:04/07/2026

Prediction Score of Cervical Intraepithelial Neoplasia Grade II or Higher (CIN2+) in Patients with Low-Grade Cytology (ASC-US, LSIL) and HPV- Negative or Non-type 16/18 High-Risk HPV-Positive Results

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Abstract

Objective: The aim of this study was to identify and quantify the risk factors with the greatest impact on the development of CIN2+ in patients with low-grade cytology and either HPV-negative or high-risk HPV-positive (non-16/18) results. The secondary aim was to develop and validate a multiparameter, risk-based prediction system. **Materials and Methods:** This retrospective cohort study was conducted in the Department of Obstetrics and Gynecology at Thammasat University Hospital between January 2021 and December 2024. Women who underwent cervical cancer screening and had a report of low-grade cytological abnormalities (ASC-US or LSIL), with either non-16/18 high-risk HPV infection or a negative HPV test, were included. **Results:** A total of 480 participants were included. The mean age of participants was 40.7 years. The prevalence of CIN2+ was 15.6% (75/480). The predictive model was developed by incorporating six factors: having three or more deliveries, six or more lifetime sexual partners, smoking, no cervical screening within five years, lack of HPV vaccination, and high-risk HPV positivity (non-16/18). Subjects with a score of 5 or more out of 14 points were classified as high-risk and recommended to undergo colposcopy within four weeks. The model demonstrated a sensitivity of 97.3% and a negative predictive value (NPV) of 98.6%. **Conclusion:** The risk factors for CIN2+ included having three or more deliveries, six or more lifetime sexual partners, smoking, no cervical screening within the past five years, lack of HPV vaccination, and high-risk HPV positivity (non-16/18). The predictive model demonstrated a sensitivity of 97.3% and a negative predictive value (NPV) of 98.6%.

Keywords: CIN2+- low-grade cytology- HR-HPV non16,18

Asian Pac J Cancer Prev, **27 (4)**, 1515-1522

Introduction

According to global cancer statistics (GLOBOCAN 2020), the age-standardized incidence rate (ASR) for cervical cancer (CC) in Thailand was approximately 16.4 cases per 100,000 women per year [1]. The incidence and mortality rates of CC are the highest in developing countries due to limitations in cervical cancer screening programs and restricted access to appropriate treatment [2].

Persistent infection with high-risk human papillomavirus (HPV) was a major risk factor for CC. Early screening and detection of precancerous lesions are therefore essential, as CC can be cured if diagnosed at an early stage and treated promptly [3]. Fourteen high-risk HPV genotypes have been identified (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68), of which HPV 16 and HPV 18 are strongly associated with CC [4].

Currently, there were three primary methods for CC screening, including cervical cytology, primary HPV testing, combined HPV testing and cervical cytology (co-testing). Among these, co-testing had shown to have a very high sensitivity (up to 99%) for detecting precancerous lesions and an exceptionally high negative predictive value (NPV) of nearly 100% [5]. Recent data from north-eastern Thailand indicated that, although conventional pap smear and physician-collected HPV provided acceptable reliability, self-collected HPV was limited by poor follow-up. Furthermore, overall CIN2+/CIN3+ detection remained very low (0.1–0.5%), underscoring the need for improved risk-stratification approaches [6].

Previous studies had identified several factors associated with the development of CC, including HR-HPV infection, a greater number of lifetime sexual partners, early age of coitarche, smoking, high parity, immunosuppression, and long-term oral-contraceptive

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use [4]. Based on current knowledge, a risk factor–based prediction score for CIN2+ in cases of low-grade cytology with HPV-negative or non-16/18 high-risk HPV (LG w/o 16,18) has not been formally developed or evaluated. The current study focused on this group because HPV16/18-positive women are already referred for colposcopy, while the LG w/o 16,18 group is still large and clinically important and needs further investigations.

Therefore, the objective aimed to quantify the associations between individual risk factors and histologically confirmed CIN2+. Predictive model from a pragmatic point-based screening score was generated to stratify risk and thereby prioritize timely access to more precise treatment.

Materials and Methods

Study design

This retrospective cohort study was conducted at Thammasat University Hospital, Pathum Thani, Thailand. The study was approved by the Ethics Committee, Faculty of Medicine (MTU-EC-OB-0-032/68).

Data source and study population

The participants were women who underwent cervical cancer screening with cotesting between 2021 and 2024, and were found to have low-grade cytological abnormalities (ASC-US, LSIL) in combination with either HPV-negative or HR-HPV positive non16,18 were recruited. The inclusion criteria comprised women who subsequently underwent colposcopic examination with histopathological confirmation. Participants were classified into a control group (pathology report ≤ CIN1) and a study group (pathology report CIN2+, including CIN2, CIN3, AIS, or cervical cancer). Exclusion criteria were incomplete medical records (e.g., missing HPV data, missing questionnaire information), unavailable histopathological results from colposcopic biopsy, or a history of prior radiotherapy, chemotherapy, or hysterectomy. As the current study was a retrospective review, withdrawal or termination criteria were not applicable.

All women who underwent colposcopic examination were requested to complete a questionnaire regarding demographic, reproductive, and gynecologic history, including age group, body mass index (BMI), marital status, age at first sexual intercourse, lifetime number of sexual partners, number of deliveries, and history of cervical screening. These questionnaires were collected and used as a part of the study data.

Each cervical specimen was collected from the corresponding patient, and cytology slides were prepared and diagnosed by cytopathologists according to the 2014 Bethesda System. Residual liquid-based cytology samples were then processed following the manufacturer's instructions. HPV testing, either DNA-based or RNA-based, was performed, and results were reported in three categories. The categories inlcuded HPV16, HPV18/45, and 11 other high-risk HPV types (31, 33, 35, 39, 51, 52, 56, 58, 59, 66, and 68). For histological examination, cervical biopsies were placed in screw-capped labeled bottles containing 20 ml of 10% formal-saline fixative and transported to the pathology laboratory of the university hospital, where they were processed by an academic pathologist. Microscopic evaluation of slides was categorized as normal histology, cervicitis, CIN1, CIN2, CIN3, AIS, cancer, or other malignant findings.

Sample size

The sample size was calculated using Stata version 18 (StataCorp, College Station, TX, USA). Based on seven candidate predictors, an anticipated AUC of 0.80, and a CIN2+ prevalence of 15%. Previous studies have reported that women with ASC-US and HR-HPV positivity non 16,18 progressed to CIN2+ at a rate of 8.4% [7], whereas those with LSIL and HR-HPV positivity non 16,18 progressed at 6.8% [8]. The calculation indicated a minimum of 57 outcome events, requiring a total sample size of at least 380. A stepwise multivariable logistic regression model was applied to identify factors associated with CIN2+, with a p-value threshold <0.05. Logistic coefficients were transformed into risk-based system. Internal validation was performed by boostrapping precedure.

Results

This study initially included 495 participants, of whom 480 were confirmed eligible for analysis. The mean age was 40.7 years. Two-thirds (296/480) of participants were multiparous. Overall, 340 of 480 women (70%) had ASC-US cytology and 140 (30%) had LSIL. CIN2+ was detected in ASC-US 48/340 (14%) and LSIL 27/140 (19%). Regarding HPV status, 90 women (19%) were HPV-negative and 390 (81%) were positive for non-16/18 high-risk HPV genotypes. The prevalence of CIN2+ was 2.2% (2/90) in the HPV-negative group and 18.7% (73/390) among women with non-16/18 high-risk HPV infection.

Participants were divided into two groups including the control group (405/480, 85%) with pathology reports of ≤ CIN1, and the study group (75/480, 15%) with pathology-confirmed CIN2+ as shown in Figure 1. There were no between-group differences in BMI, education level, or occupational status. However, the proportions with multiple lifetime sexual partners (≥6), multiparity (≥3), early coitarche (<18), HR-HPV positive non16,18, smoking and anal intercourse were substantially higher in the study group than in the control group, as shown in Table 1. In contrast, recent cervical screening (within 5 years) and prior HPV vaccination were more prevalent in the control group compared with the study group (63% vs 31% and 20% vs 1%; both p<0.001)

Model development

After including seven candidate predictors in the multivariable logistic regression model, anal intercourse was found not to be statistically significant, as shown in Table 2. Following backward elimination, six independent predictors remained in the final model including parity of three or more deliveries, having six or more lifetime sexual partners, current smoking, absence of cervical screening

Table 1. Demographic Data of Subject in among ≤CIN 1(n=405) and CIN2+(n=75)

	≤CIN 1*	CIN 2+*	p-value
Age (yr)**	41±11	39±10	0.07
Couple	277 (68)	56 (74)	0.34
BMI (kg/m^2)**	23.5±4.4	22.8±4.0	0.18
Parity (≥3 births)	6 (1)	5 (7)	0.02
Lifetime Sexual partners ≥ 6	12 (3)	28 (37)	<0.001
First SI before age 18	40 (10)	15 (20)	0.05
≥ Bachelor's degree	375 (93)	71 (94)	0.68
Smoking	4 (1)	12 (16)	<0.001
Occupation			0.23
Housewife	50 (12)	4 (5)	
Government	76 (19)	19 (25)	
Business	170 (42)	31(42)	
Other	109 (27)	21 (28)	
No CS within 5 years	151 (37)	52 (69)	<0.001
HR-HPV			<0.001
Negative	88 (22)	2 (3)	
Positive non16, 18	317 (78)	73 (97)	
Cytology			0.17
LSIL	113 (28)	27 (36)	
ASC-US	292 (72)	48 (64)	
AnI	2 (0.5)	9 (12)	<0.001
Vaccine	82 (20)	1 (1)	<0.001
HIV infection	6 (1)	3 (4)	0.15

*, n (%); **, mean ± standard deviation; ≤CIN 1, equal or less than cervical intraepithelial neoplasia grade 1; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; Couple, marital status; BMI, body mass index; Parity, number of child; SI, sexual intercourse; CS, cervical screening; HR-HPV, high-risk human papillomavirus; non16, 18, other genotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68; LSIL, Low-grade squamous intraepithelial lesion; ASC-US, Atypical squamous cells of undetermined significance; AnI, anal intercourse; Vaccine, human papillomavirus vaccine; HIV, human immunodeficiency virus

within the past five years, lack of HPV vaccination, and HR-HPV positive non16,18 infection. These predictors were subsequently used to calculate the regression coefficients, which were then transformed into weight scores to construct the risk prediction model, referred to as the SYN Score (Sarochinee Yutyuenyong Score), as presented in Table 3.

The SYN score was developed by summarizing the weight scores assigned to each of the identified risk factors (parity ≥3, ≥6 lifetime sexual partners, smoking, absence of cervical screening within five years, lack of HPV vaccination, and HR-HPV non 16,18 infection). Each factor contributed a specific weight, and the total SYN score for an individual was calculated by adding the scores of all present risk factors. The receiver operating characteristic (ROC) curve was generated as shown in Figure 2. Area under the curve (AUC) were 0.8465. The appropriate cut-off point of the model was 5 point which provided sensitivity, specificity, PPV, and NPV at 97.3, 32.6, 18.0 and 98.6 percent, respectively. The likelihood ratio analysis demonstrated a LR+ of 1.44 and a LR- of 0.08.

Accuracy of predictive model

Internal validation was performed using bootstrap resampling. Calibration was excellent on the calibration plot as shown in Figure 3, indicating close agreement between predicted and observed risks. Decision-curve analysis demonstrated clinical utility as shown in Figure 4.

To apply the SYN model for predicting CIN2+ in patients with LG w/o 16,18, a total score of 14 was calculated and classified into two categories: low risk (<5) and high risk (≥5). Using a cut-off score of 5, the prediction model achieved sensitivity and a NPV at 97.3 and 98.6 percent, respectively. This supports the use of the model as a screening tool. The enhanced predictive model

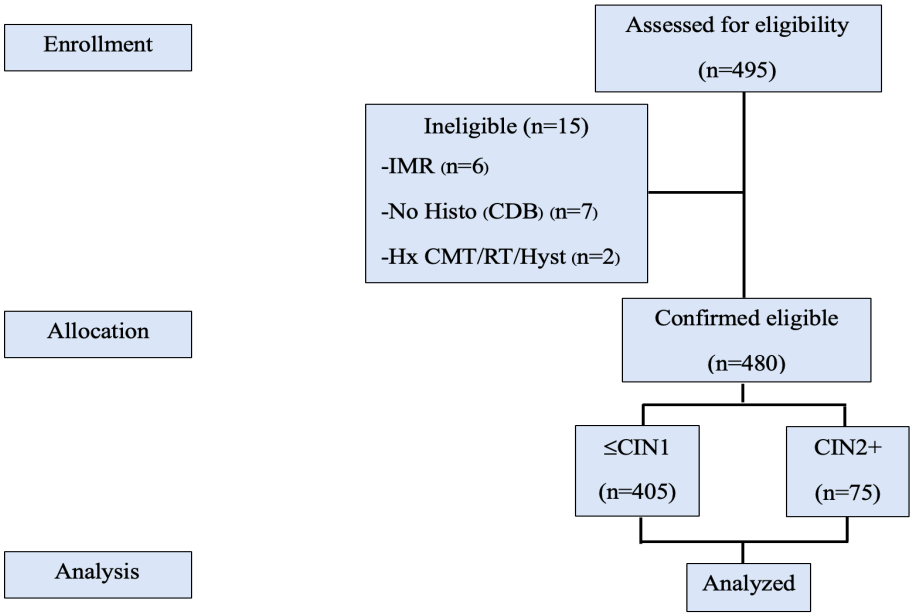

Figure 1. Participants Flow Diagram. IMR, incomplete medical record; Histo, histopathology; CDB, colposcopic-directed biopsy; Hx, history of; CMT, chemotherapy; RT, radiotherapy; Hyst, hysterectomy; ≤CIN 1, equal or less than cervical intraepithelial neoplasia grade 1; CIN2+, cervical intraepithelial neoplasia grade 2 or higher

Table 2. Uni and Multivariable Analysis of Risk Factor for CIN2+ (AuROC 0.85)

	Univariable		Multivariable	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Parity				
<3	Ref	1		
≥3	7.9 (2.67, 23)	<0.001	8.4 (2.0, 35.8)	0.004
Lifetime Sexual partners				
<6	Ref	1		
≥ 6	19.5 (9.3, 40.9)	<0.001	14.3 (5.4, 37)	<0.001
Smoking*	19.1 (6, 61.1)	<0.001	21.4 (3.4, 135)	0.001
CS within 5 years *				
Yes	Ref	1		
No	3.8 (2.2, 6.5)	<0.001	2.6 (1.4, 4.9)	0.003
HR-HPV*				
Negative	Ref	1		
Positive non16,18	10.1 (2.4, 42.1)	0.001	15.2 (2.2, 105)	0.006
AnI*	27.4 (5.8, 130)	<0.001	1.7 (0.2, 14.1)	0.61
Unvaccinated*	18.8 (2.6, 137)	0.004	10.5 (1.3, 83)	0.02
HIV infection	2.8 (0.6, 11.3)	0.16		

OR, odd ratio; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; Parity, number of child; CS, cervical screening; HR-HPV, high-risk human papillomavirus; non16, 18, other genotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68; AnI, anal intercourse; Unvaccinated, no prior human papillomavirus vaccine; HIV, human immunodeficiency virus; AuROC, area under the receiver operating characteristic curve

could be accessed through this website-based platform (https://nadeebcc154.github.io/SYNscore/) or QR code as shown in Figure 4.

Discussion

The 2019 ASCCP risk-based management consensus guidelines recommended direct referral to colposcopy for women who test positive for HPV16 or HPV18, irrespective of cytology [9]. Therefore, individuals with HPV16 or 18 positivity were excluded from the analysis process. Among women with low-grade cytology (ASC-US/LSIL) who are HPV-positive, the immediate risk of CIN3+ exceeds 4%, thereby indicating colposcopic evaluation, although the majority of low-grade abnormalities do not progress to clinically significant disease [9]. In the present study, the prevalence of CIN2+ was 15% (75/480), indicating that 85% (405/480) of women (≤CIN1) could be safely managed with surveillance, while 15% required therapeutic intervention.

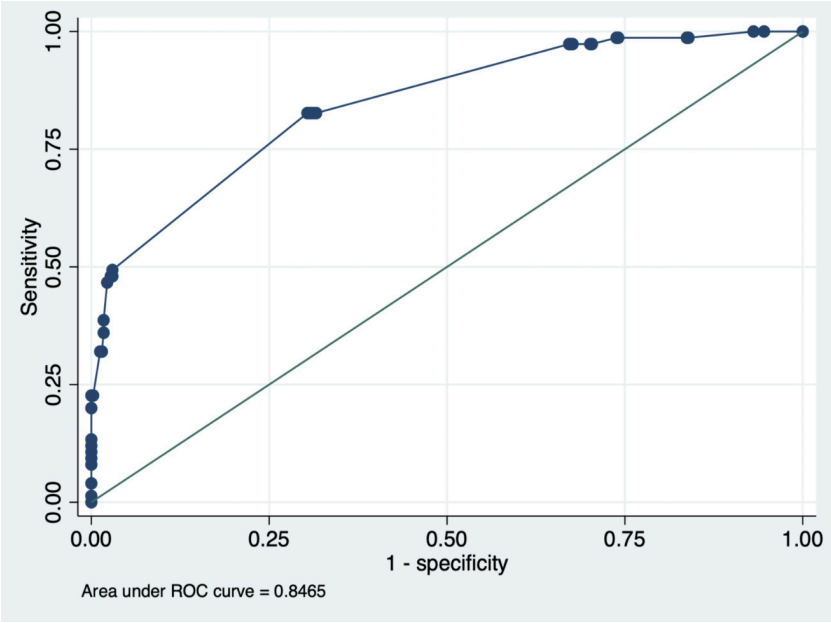

Figure 2. Receiver Operating Curve (ROC) of SYN Score to Predict CIN2+. PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio; SYN Score, Sarochinee Yutyuenyong Score

Table 3. Multivariable Analysis of Risk Factor for CIN2+ after Backward Elimination (AuROC 0.85)

	Multivariable		Co-efficient	Weight score
	OR (95%CI)	p-value		
Parity (≥3 births)	8.5 (2.0, 36)	0.004	2.1	2
Lifetime Sexual partners ≥ 6	15.9 (6.5, 38.9)	<0.001	2.7	3
Smoking*	21.7 (3.4, 136)	0.001	3.1	3
No CS within 5 years *	2.6 (1.4, 4.9)	0.003	1	1
HR-HPV non16,18	15.7 (2.3, 109)	0.005	2.7	3
Unvaccinated*	10.8 (1.3, 87)	0.004	2.3	2

OR, odd ratio; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; Parity, number of child; CS, cervical screening; HR-HPV, high-risk human papillomavirus; non16, 18, other genotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68; Unvaccinated, no prior human papillomavirus vaccine; AuROC, area under the receiver operating characteristic curve

In the current study, for women with NILM and HR-HPV positivity, p16/Ki-67 dual-stain cytology has emerged as a triage method. A positive dual-stain result generally leads to colposcopic evaluation, while a negative result offers reassurance and may reduce unnecessary procedures [10]. Additionally, extended HPV genotyping, which assesses high-risk types beyond HPV16/18, allows for more refined risk stratification by identifying infections with other types (e.g., 33, 52, 58) that are associated with progression to CIN2+ [11]. However, the widespread implementation of dual-stain cytology and extended genotyping remains constrained in many regions due to financial and resource limitations.

Within this framework, the SYN score was developed as a simple, non-invasive, and cost-free prediction tool to estimate the risk of CIN2+ among women with LG w/o 16,18. The SYN score demonstrated high sensitivity with discriminative ability (AUC 0.85). Excellent calibration on internal validation was shown in Figure 3. Thus, it serves as a valuable tool for prioritizing high-risk women for colposcopic evaluation (score ≥5), particularly in resource-limited settings where timely or universal access to colposcopy may not be feasible.

The risk factors included in the model were selected based on previous studies that demonstrated an increased risk for CIN2+ with statistical significance, as shown in Table 4. Prior studies identified the absence of cervical screening within five years as a contributing factor for CIN2+ (OR 2.54–3.0) [12, 13], which was consistent with the present findings (OR 2.6; 95% CI 1.4–4.9). Smoking has also been reported as a contributing factor (OR 1.7–2.2) [14, 15], with an even stronger association observed in our Thai population (OR 21.7; 95% CI 3.4–136). Similarly, multiple lifetime sexual partners (≥6) have been shown to increase the risk of CIN2+ (OR 1.81–2.4) [13, 16], supporting our results as presented in Table 3. Parity has also been implicated as one study reported that multiparity (≥4) increased the risk of CIN2+ by 2.72-fold [13]. However, given the contemporary trend of lower parity, another study [17] found that parity of three or more conferred only a modest increase (OR 1.04). In the recent study, parity ≥3 was significantly associated with CIN2+ (OR 8.5; 95% CI 2.0–36), aligning with the Thai context. In addition, a recent meta-analysis [18] confirmed the protective effect of HPV vaccination (RR 0.06; 95% CI 0.02–0.18), whereas absense of vaccination was associated

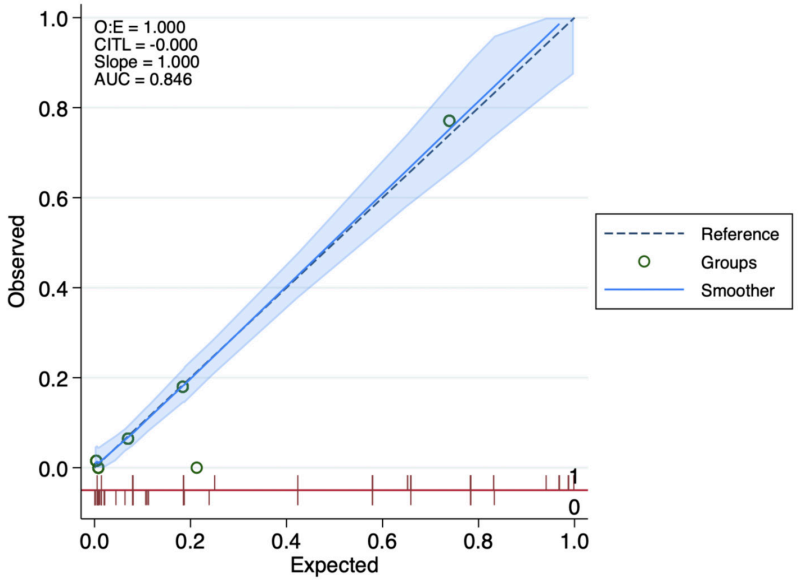

Figure 3. Calibration Plot of Expected and True CIN2+ Prediction. The result of internal validation was used by the Bootstrap method. X axis (Expected) represented the predictive of CIN2+ by model. Y axis (Observed) represented the real CIN2+. The predictive model showed excellent internal validation according the calibration plot.

Table 4. Comparison of Risk Factors of CIN2+ between Our and Previous Studies

	Present	Derbie12	Gonzalez14	Kasamatsu13	Yamagushi16	Belinson17
Year	2025	2022	2022	2019	2021	2008
Country	Thai	Ethiopia	Spain	Paraguay	Japan	China
Designs	Retro	Cross	Obs	Cross	Cross	Cross
Case	480	335	1188	5677	3231	2055
Risk factors						
No CS within 5 years	√	√		√		
Lifetime Sexual partners	≥6			≥6	≥6	≥3
Smoking	√		√			
Parity	≥3			≥4		≥3
Unvaccinated	√					
HR-HPV		√	√			√
Non 16,18	√		√		√	
Cytology	LG		LG			

CIN2+, cervical intraepithelial neoplasia grade 2 or higher; Retro, retrospective cohort study; Cross, cross-sectional study; Obs, observational study; CS, cervical screening; HR-HPV, high-risk human papillomavirus; non16, 18, other genotypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68; Parity, number of child, Partner, number of sexual partner; Unvaccinated, no prior human papillomavirus vaccine; LG, low-grade cytology (ASC-US, LSIL); √, showed a statistically significant association

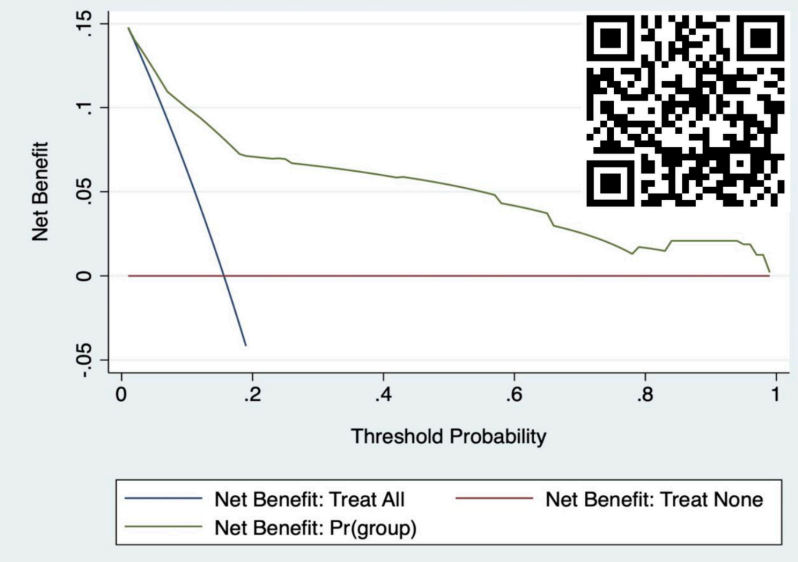

Figure 4. Decision Curve Analysis of the Presenting Model. Decision curve for prediction model from 480 participants in the current study. Blue line represented the condition of treating all participants as CIN2+, Red line represented the condition of treating none. Green line represented the effect of treatment according to the presenting model. The presenting model give the expected net benefit than no model used.

with nearly a tenfold increased risk in the current study. Finally, HR-HPV non16,18 positivity, previously reported with odds ratios ranging from 3.1 to 78.5 [14, 16], was associated with an approximately 15-fold increased risk of CIN2+ in this analysis.

A previous study [19] demonstrated an association between anal intercourse, HR-HPV infection, and the subsequent development of cervical dysplasia. In the present analysis, anal intercourse was significant in univariable testing but did not retain significance in the multivariable model, possibly due to confounding effects and limited sample size. This finding indicates that its role as an independent predictor of CIN2+ remains unclear and requires further investigation. HIV infection is another factor of interest, as it has been reported to substantially increase the risk of CIN2+ [20]. In contrast, no significant association was observed in the current study, which may reflect the impact of modern antiretroviral therapy, effective viral load suppression, and broader access to treatment, thereby reducing the excess risk previously reported.

Differences in study populations may partly explain the variability in results across studies, as shown in Table 4. The cohort in the current study included only women with low-grade cytology (ASC-US/LSIL) and non-16/18 HR-HPV or HPV-negative status, whereas some previous studies enrolled women with a broader range of cytologic abnormalities and HPV genotypes. In addition, variations

in parity, sexual behavior, HPV vaccination status, and other demographic factors between settings may influence the observed strength of association for individual risk factors.

The model was developed as a screening tool to prioritize high-risk cases (score ≥5) for colposcopic evaluation within 4 weeks, while low-risk women could be scheduled within 8-12 weeks. Another potential benefit worth highlighting was that in high-score cases, clinicians can emphasize the importance of timely management to reduce loss to follow-up, which remains a major challenge in Thailand. The web-based platform is easily accessible in Thailand via smartphones, providing a practical resource to support decision-making and facilitate timely referral to gynecologic oncology services.

Strengths and weakness

Our study is the first to develop a predictive model, which has been further implemented into a user-friendly application with a QR code accessible via smartphones. This model is particularly suitable for physicians with limited time and resources, such as restricted access to colposcopy, as it facilitates prioritization of high-risk cases. The model was derived from influential factors previously validated across multiple institutions as being associated with CIN2+. However, this study has several limitations. First, Only women who underwent colposcopic biopsy with histopathologic confirmation were included. Women with low-risk findings on colposcopy (normal appearance) may not have undergone biopsy, and women who had cytology alone without concurrent HPV testing were also excluded. These factors may have introduced selection bias, leading to an underestimation of the true proportion of low-risk cases and limiting the generalizability of our findings to settings where HPV testing is not routinely available. Second, the relatively small sample size and unavoidable confounding remain limitations. In addition, this study is limited by its retrospective, single-centre design and by possible information bias arising from variable screening tests and examiner experience, which may affect the robustness of our conclusions. Future studies are needed to confirm how well this model performs in real-world clinical settings.

In conclusion, the SYN model was developed, incorporating six independent risk factors for predicting CIN2+ in LG w/o 16,18. The model is accessible online via computer or smartphone devices. When stratified into low- and high-risk groups, the predictive model demonstrated a sensitivity of 97.3% and a NPV of 98.6%. Nonetheless, the relatively small sample size and absence of external validation represent limitations of the study. Future research should focus on external validation and integration of the model into clinical practice.

Author Contribution Statement

SY collected the data, prepared the database, and drafted the manuscript. YP contributed to the study conception and protocol development and assisted in drafting and revising the manuscript. KS performed the statistical analysis and contributed to data interpretation. AP supervised the overall project and critically reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgements

This study was funded by the Thammasat University Hospital Research Fund (No. 01/2568). The authors would like to express their sincere thanks to Punnawit Pinitchanon, M.D., for expert consultation and support. This study was approved by the Ethics Committee of the Faculty of Medicine, Thammasat University (MTU-EC-OB-0-032/68). As this was an observational retrospective cohort study using questionnaire data, it was not registered in a clinical trial registry. The authors declare no conflicts of interest relevant to this article. The data that support the findings of this study are available from the corresponding author on reasonable request; the data are not publicly available due to privacy and ethical restrictions.

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