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ORIGINAL RESEARCH

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High performance of human papillomavirus 16/18/58 genotyping combined with cytology in the initial screening of cervical cancer in China

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Abstract

Background: This study evaluated the diagnostic performance of high-risk human papillomavirus (HR-HPV) genotyping combined with cytological triage for detecting histological high-grade squamous intraepithelial lesions or worse (HSIL+) in women without prior screening history. **Methods**: A total of 1081 women with abnormal HPV test results underwent cytology testing and colposcopy-guided biopsy. The proportion and risk of HSIL+ positivity were analyzed based on HPV genotype and cytological findings. **Results**: Among the HR-HPV types, HPV16 was the most prevalent, followed by HPV52 and HPV58. HSIL+ was diagnosed in 286 women (26.5%). HPV16-positive women exhibited the highest incidence of HSIL+ (49.9%), followed by those positive for HPV18 and HPV58. In women with normal cytology (negative for intraepithelial lesion and malignancy (NILM), n = 463), 103 cases of HSIL+ were identified, accounting 36.0% of all HSIL-positive cases. The risk ratios and 95% confidence intervals (CIs) for HSIL+ in women positive for HPV16, HPV18 and HPV58 were 5.84 (95% CI: 2.86–11.92), 2.69 (95% CI: 1.08–6.69), and 3.11 (95% CI: 1.12–8.66), respectively, compared to other HR-HPV types. Multivariate analysis indicated that HPV16/18/58 positivity and cytology atypical squamous cells of undetermined significance or worse (cytology $\geq$ ASC-US (atypical squamous cells of undetermined significance)) were independent predictors of HSIL or worse. The sensitivity of predicting HSIL or worse was over 90%, and the negative predictive value was 92.0%. **Conclusions**: The combination of HPV genotyping and cytology demonstrated high diagnostic performance in women without a screening history. In regions with a high prevalence of HPV58, referral for colposcopy or histological examination is warranted for HPV58-positive women to optimize early detection of HSIL.

Keywords

High-risk human papillomavirus; HPV genotyping; High-grade cervical lesions; Cervical cancer; Initial screening; Diagnostic performance

1. Introduction

Cervical cancer is the fourth most common cancer and the fourth leading cause of cancer-related mortality among women worldwide [1]. Persistent high-risk human papillomavirus (HR-HPV) infection is the primary etiological factor for cervical cancer. Women with low income and no prior screening history are at significantly elevated risk for developing cervical intraepithelial neoplasia and cervical cancer [2]. In 2020, the World Health Organization (WHO) introduced a global strategy to eliminate cervical cancer [3]. Despite the implementation of cervical cancer screening programs in China since 2009, participation in screening and HPV vaccination remains suboptimal, and in 2020, a total of 109,741 new cervical cancer cases and 59,060 deaths attributed to the disease were observed in China [1]. The absence of comprehensive public health databases and follow-up systems has resulted in many women undergoing cervical cancer screening without prior screening records, which has substantially increased the burden on healthcare institutions and society. Therefore, improving screening strategies and management approaches remains imperative to expedite the diagnosis and treatment of cervical cancer and its precancerous lesions [2].

In 2019, the American Society of Colposcopy and Cervical Pathology (ASCCP) introduced risk-based management guidelines for abnormal screening results and precancerous cervical lesions and recommend the Hybrid Capture II test as the preferred method for HPV detection [4]. For women testing positive for HPV16 or HPV18, colposcopy is recommended regardless of the cytological findings. HPV16-positive women with advanced squamous intraepithelial lesions detected on cytology can receive quicker treatment. This approach facilitates

early detection and treatment of precancerous and cancerous cervical lesions.

HPV genotyping has been shown to enhance the detection and management of high-grade cervical lesions [5–7], allowing HPV16/18-positive women to proceed more quickly to diagnostic evaluation and treatment. However, the distribution of HR-HPV genotypes varies significantly across geographical regions. In regions outside East Asia, the most common genotypes are HPV16, HPV18, HPV31, HPV33 and HPV45. In contrast, East Asia has a distinct HR-HPV profile, with HPV58 and HPV52 being prevalent alongside HPV16 and HPV18 [8]. Several studies conducted in China have reported a high incidence of HPV58 and HPV52, both of which are strongly associated with high-grade cervical intraepithelial neoplasia (CIN) [9, 10]. Despite these findings, it remains unclear whether incorporating HPV genotyping for HPV16, 18, 58 and 52 into initial screening can improve the detection of high-grade cervical intraepithelial neoplasia in China.

This study aims to evaluate the efficacy of combining HPV genotyping and cytological testing for the identification of high-grade intraepithelial lesions and cervical cancer in women with no documented screening history.

2. Materials and methods

This cross-sectional study was approved by the institutional ethics committee. Between May 2022 and April 2023, women undergoing cervical cancer screening at the Cervical Disease Centre, Suqian Hospital of Nanjing Drum Tower Hospital Group, were invited to participate. Eligible participants had positive high-risk HPV (HR-HPV) genotyping results and no prior history of standardized cervical cancer screening. Women with a history of cervical intraepithelial lesions, cervical cancer, hysterectomy, or pregnancy were excluded.

All participants underwent cervical cytology combined with HR-HPV genotyping. After obtaining informed consent, they were referred for colposcopy within one week of the initial screening. A trained colposcopist conducted the colposcopies, and cervical biopsies were performed. The biopsies were guided by observed white areas with acetic acid application. If the squamocolumnar junction appeared normal, random biopsies were performed in each of the four quadrants of the cervix. In cases where the squamocolumnar junction was not visible, multi-point cervical biopsies combined with cervical canal scraping were conducted. Histopathological examination was performed by two histopathologists at our institution's pathology department. p16 immunohistochemistry was used to confirm the diagnosis of high-grade lesions in cases with inconclusive results. The primary outcome was histopathological confirmation of high-grade squamous intraepithelial lesions or worse (HSIL+), which included HSIL, adenocarcinoma *in situ*, and invasive carcinoma. The demographic and clinical characteristics of the study population were obtained from the electronic medical record system and the colposcopy register.

The HPV typing assay in this study was conducted using a human papillomavirus nucleic acid test kit (S20040032, Bohui Innovation Biotechnology Co., Beijing, China) based on a biochip method, capable of detecting 14 genotypes: HPVs 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Cervical cytology was performed using a ThinPrep 2000 slide processor (Hologic, Inc., Marlborough, MA, USA) to prepare liquid-based thin-layer cytology slides, which were subsequently stained using Pap stain. The cytology slides were evaluated by a cytotechnologist from the pathology department of the medical institution. The 2001 Bethesda System nomenclature for reporting cervical cytology results was applied. The cytological results were categorized as follows: negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion (ASC-H), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC), and adenocarcinoma *in situ* (AIS).

Statistical analyses were performed using SPSS version 26.0 for Windows (SPSS Inc., Chicago, IL, USA). Age was expressed as mean ± standard deviation, and categorical variables were presented as percentages. Differences in the prevalence of HSIL+ by HPV genotype were assessed using the chi-square test. Stepwise logistic regression was used to identify independent predictors of HSIL+, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs). A significance level of $p < 0.05$ was considered statistically significant.

3. Results

A total of 1809 women with no history of standardized screening were tested positive for high-risk HPV genotyping. Of them, 168 were excluded due to a history of hysterectomy, 56 due to a history of cervical intraepithelial lesions, and 504 cases due to incomplete information or unavailable histopathological findings. The final study cohort consisted of 1081 cases. Table 1 presents the demographic characteristics of the study population, with a mean age of 41.8 ± 10.4 years. Notably, 89.6% of the participants were older than 30 years. Among the high-risk HPV types detected, HPV16 was the most prevalent (31.0%), followed by HPV52 (23.4%), HPV58 (12.2%) and HPV18 (8.1%). The remaining 10 HR-HPV types, including HPVs 31, 33, 35, 39, 45, 51, 56, 59, 66 and 68, accounted for 368 cases (34.0%). The most frequently observed cytological result was NILM (42.8%), followed by ASC-US (38.9%), LSIL (11.2%), and ASC-H or worse (which included ASC-H, HSIL and AGC, 7.0%). Histopathological examination identified HSIL or worse in 286 cases (26.5%), among which 16 cases (1.5%) were diagnosed as cervical cancer or adenocarcinoma *in situ* (Table 1).

Table 2 shows the distribution of histologic HSIL or worse among the different HR-HPV genotypes and cytological categories in the 1081 study participants. Histologic HSIL or worse was most frequent in HPV16-positive individuals, occurring in 49.9% of cases, followed by HPV18-positive cases (30.7%), HPV58-positive cases (24.6%), HPV52-positive cases (15.6%), and those positive for the other 10 high-risk HPV genotypes (12.5%). Among cytological categories, histologic HSIL or worse was identified in 22.2% of cases with NILM, 23.1% of cases with ASC-US or LSIL (125/542), and 74.4% of cases with ASC-H, HSIL, or AGC.

TABLE 1. Characteristics of the study population (N = 1081).

Characteristics	n (%)
Age, yr	
<30	112 (10.4)
≥30	969 (89.6)
Cytology triage	
NILM	463 (42.8)
ASC-US	421 (38.9)
LSIL	121 (11.2)
ASC-H	40 (3.7)
HSIL	28 (2.6)
AGC	8 (0.7)
Histology	
Normal or Cervicitis	570 (52.7)
LSIL	225 (20.8)
HSIL	270 (25.0)
Cervical Cancer	11 (1.0)
AIS	5 (0.5)
HR-HPV genotype results	
HPV16+	335 (31.0)
HPV52+	253 (23.4)
HPV58+	132 (12.2)
HPV18+	88 (8.1)
HPV33+	61 (5.6)
HPV31+	60 (5.6)
HPV51+	59 (5.5)
HPV56+	52 (4.8)
HPV66+	51 (4.7)
HPV39+	50 (4.6)
HPV59+	36 (3.3)
HPV68+	34 (3.1)
HPV35+	24 (2.2)
HPV45+	19 (1.8)
Multiple types of HR-HPV	453 (41.9)

AGC, atypical glandular cell; AIS, adenocarcinoma in situ; ASC-H, atypical squamous cells cannot rule out high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus; HR-HPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesions and malignancy.

Among the 463 women with cytological NILM, 103 cases were diagnosed with histologic HSIL or worse, with more than 90% testing positive for HPV16, 18, 52 or 58, accounting for 36% of all histologic HSIL or worse. Within the NILM group, the incidence of histologic HSIL or worse for HPV16, 18, 52 and 58 positivity was 36.6%, 21.1%, 10.6% and 23.5%, respectively, while the incidence for the other 10 high-risk HPV genotypes was 9.0%. Compared to the other 10 high-risk HPV genotypes, the risk coefficients and 95% confidence intervals (CIs) for histologic HSIL or worse were 5.84 (2.86–11.92) for HPV16+, 2.69 (1.08–6.69) for HPV18+, and 3.11 (1.12–8.66) for HPV58+, with all $p < 0.05$. The risk coefficient for HPV52+ was 1.20 (0.46–3.09), $p > 0.05$ (results are not shown in the table).

Table 3 presents the univariate analysis of the 1081 study participants, identifying cytology results ≥ ASC-US, HPV16+, HPV18+ and HPV58+ as high-risk factors for histologic HSIL+, with risk coefficients of 1.47 (1.11–1.94), 5.24 (3.91–7.00), 2.00 (1.14–3.51) and 2.23 (1.37–3.62), respectively ($p < 0.05$). In contrast, the risk coefficient for HPV52+ was 1.13 (0.67–1.90), $p > 0.05$. Multivariate analysis revealed that the risk coefficient and 95% CI for histologic HSIL or worse at cytology ≥ ASC-US was 2.16 (1.59–2.94), $p < 0.05$. For HPV16/18/58+, the risk coefficient and 95% CI were 5.66 (4.12–7.77), $p < 0.05$. Cytology ≥ ASC-US and HPV16/18/58+ were identified as independent predictors of histologic HSIL or worse.

Table 4 shows the efficacy of detecting histologic cervical high-grade intraepithelial lesions or worse (HSIL+) using cytology ≥ ASC-US, HPV16/18/58+, and a combination of cytology ≥ ASC-US with HPV16/18/58+ as indications for histologic testing. When cytology or HPV genotyping alone was used as a predictor, sensitivity ranged from 64% to 75%, specificity from 45% to 61%, and the negative predictive value (NPV) was 77.8%. In contrast, when cytology ≥ ASC-US was combined with HPV16/18/58+, the sensitivity exceeded 90%, and the NPV reached 92.0% (95% CI: 88.1–95.9), although the specificity was reduced to 21–25%.

4. Discussion

In this study population, HPV16 was the most prevalent high-risk HPV genotype, followed by HPV52, HPV58, HPV18 and other types. Among cases with histologic HSIL or worse, HPV16 was the most frequently detected genotype (58.3%), followed by HPV18, HPV58 and other types. Previous studies have reported that in Asia, including China, HPV52 and HPV58 are common genotypes alongside HPV16 and HPV18 and are frequently associated with CIN2+ [5, 9–11]. A meta-analysis of HPV genotypes in cervical intraepithelial neoplasia in China similarly identified HPV16 as the most prevalent genotype (34.56–36.61%), followed by HPV58 (14.36–15.90%) and HPV52 (14.01–15.53%). In the CIN2/3 group, HPV16 was predominant, accounting for 45.69% of cases. The findings of our study align closely with those reported in the meta-analysis [9]. However, our study observed a higher incidence of HSIL or worse in HPV18-positive cases compared to HPV58-positive cases, a finding inconsistent with some reports. This discrepancy may be attributed to the study protocol, as cervical canal scraping was performed in most HPV18-positive subjects, potentially increasing the detection rate of histologic HSIL or worse in this subgroup.

The proportion of HPV52-positive women with high-grade

TABLE 2. Distribution of cytology, HPV genotyping, and histopathological outcomes in the 1081 study participants.

Genotype	NILM		ASC-US/LSIL		ASC-H/HSIL/AGC	
	No.	No. of histologic ≥ HSIL (%)	No.	No. of histologic ≥ HSIL (%)	No.	No. of histologic ≥ HSIL (%)
Any genetype+ (n = 1081)	463	103 (22.2)	542	125 (23.1)	76	58 (76.3)
HPV16+ (n = 335)	191	70 (36.6)	103	58 (56.3)	41	39 (95.1)
HPV18+ (n = 88)	57	12 (21.1)	25	9 (36.0)	6	6 (100.0)
HPV52+/16−/18−[a] (n = 211)	85	9 (10.6)	119	20 (16.8)	7	3 (42.9)
HPV58+/16−/18−[b] (n = 118)	34	8 (23.5)	77	15 (19.5)	7	6 (85.7)
10 other HR-HPV types+[c] (n = 368)	111	10 (9.0)	235	26 (11.1)	22	10 (45.5)
HPV16/18+ (n = 407)	241	80 (33.2)	123	65 (52.8)	43	41 (95.3)
HPV16/18/52/58+ (n = 713)	352	93 (26.4)	307	99 (32.2)	54	48 (88.9)

[a]*HPV 52 positive but not HPV52 co-infected with HPV16/18.*
[b]*HPV 58 positive but not HPV58 co-infected with HPV16/18.*
[c]*HPVs 31, 33, 35, 39, 45, 51, 56, 59, 66, 68.*
AGC, atypical glandular cell; ASC-H, atypical squamous cells cannot rule out high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus; HR-HPV, high-risk human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion and malignancy.

TABLE 3. Univariate and multivariate analysis of the correlation between HPV genotype, cytology and histology ≥ HSIL in the 1081 participants.

Variable	n (%)	Univariate Analysis	Multivariate Analysis
Cytology ≥ ASC-US[a]			
No (n = 463)	103 (22.2)	Ref	Ref
Yes (n = 618)	183 (29.6)	1.47 (1.11–1.94)*	2.16 (1.59–2.94)*
HPV16+			
No (n = 746)	119 (16.0)	Ref	
Yes (n = 335)	167 (49.9)	5.24 (3.91–7.00)*	
HPV18/HPV16−[b]			
No (n = 674)	101 (15.0)	Ref	
Yes (n = 73)	19 (26.0)	2.00 (1.14–3.51)*	
HPV58/HPV16−/18−[c]			
No (n = 556)	71 (12.8)	Ref	
Yes (n = 118)	29 (24.6)	2.23 (1.37–3.62)*	
HPV52/HPV16−/18−/58−[d]			
No (n = 366)	45 (12.3)	Ref	
Yes (n = 190)	26 (13.7)	1.13 (0.67–1.90)	
HPV16/18/58+			
No (n = 556)	71 (12.8)	Ref	Ref
Yes (n = 525)	215 (41.0)	4.74 (3.50–6.42)*	5.66 (4.12–7.77)*

[a]*Category Included cytology results were atypical squamous cells of undetermined significance (n = 421), low grade squamous intraepithelial lesion (n = 121), atypical squamous cells cannot rule out high-grade squamous intraepithelial lesion (n = 40), high grade squamous intraepithelial lesion (n = 28), atypical glandular cells (n = 8).*
[b]*HPV18 positive but not HPV18 co-infected with HPV16.*
[c]*HPV58 positive but not HPV58 co-infected with HPV16/18.*
[d]*HPV52 positive but not HPV52 co-infected with HPV16/18/58.*
**$p < 0.05$.*
ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; Ref, Reference.

TABLE 4. The efficiency of using cytology and partial HPV genotyping to predict the performance of histologic HSIL or worse.

Triage method	No. of HSIL+	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
Cytology ≥ ASC-US[a] (n = 618)	183	64.0 (58.4–69.6)	45.3 (41.8–48.8)	29.6 (26.0–33.2)	77.8 (74.0–81.6)
HPV16/18/58+ (n = 525)	215	75.2 (70.1–80.2)	61.0 (57.6–64.4)	41.0 (36.7–45.2)	87.2 (84.4–90.0)
Cytology ≥ ASC-US[a] & HPV 16/18/58+ (n = 893)	271	94.8 (92.2–97.4)	21.8 (18.9–24.6)	30.3 (27.3–33.4)	92.0 (88.1–95.9)

[a] *Cytology results ≥ ASC-US include atypical squamous cells of undetermined significance (n = 421), low-grade squamous intraepithelial lesion (n = 121), atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion (n = 40), high-grade squamous intraepithelial lesion (n = 28), and atypical glandular cells (n = 8).*
HPV, human papillomavirus; PPV, positive predictive value; NPV, negative predictive value; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; CI, confidence intervals.

intraepithelial lesions in this study was not statistically different from that observed in women with the other ten high-risk HPV genotypes, indicating that HPV52 may be more closely associated with low-grade cervical intraepithelial lesions. This observation is supported by findings from the previously mentioned meta-analysis, which identified HPV52 as the predominant cause of CIN1. In a study conducted in a rural area of northern China, Shuang Zhao *et al*. [10] reported that HPV52 was the most common HR-HPV genotype, followed by HPV58, HPV53 and HPV16. However, among CIN2+ cases, HPV16 (75.6%) was the most common genotype, followed by HPV52 (17.8%) and HPV58 (16.7%) [10]. These findings highlight regional variations in the distribution of high-risk HPV genotypes within China. A nationwide survey conducted in China in 2021 also demonstrated that the most common HR-HPV genotypes were HPV52, HPV58 and HPV16. Interestingly, in certain regions, the prevalence of HPV52 and HPV58 exceeded that of HPV16, further emphasizing the regional variability in genotype distribution [11, 12].

Our findings demonstrated that, even without cytological abnormalities, HPV16, 18 and 58 exhibited a significantly higher prevalence of histologic HSIL compared to other genotypes (36.6%, 21.1% and 26.5% *vs.* 9.0%). Many clinical guidelines recommend considering HPV16 and HPV18 positivity as high-risk factors warranting referral for colposcopy. In our study, among women without a standardized history of cervical cancer screening, 23.5% of those with NILM cytology and HPV58 positivity had histologic HSIL or worse, which represents a substantial population in regions with a high prevalence of HPV58. Thus, referring these women for colposcopy or histological testing may enhance the detection of high-grade cervical lesions. Our findings support the referral of HPV58-positive women in areas with a high prevalence of HPV58 for colposcopy or histological testing, particularly among women without a standardized cervical cancer screening history or regular follow-up opportunities. According to the ASCCP guidelines, women with HPV16 positivity and cytological findings of high-grade lesions are candidates for rapid treatment. However, HPV58, while associated with significant risk, is not classified at the same high-risk level as HPV16. Therefore, colposcopy or histological confirmation is recommended before initiating treatment for HPV58-positive cases. For women infected with HPV genotypes other than HPV16, 18, and 58, the incidence of histologic HSIL was 9.0% in those with NILM cytology and 11.1% in those with ASC-US or LSIL cytology. These findings support a triage strategy involving follow-up reviews for this population, which has the potential to reduce the burden of unnecessary colposcopy examinations.

The findings of this study indicate that combining HPV genotyping and cytological examination constitutes an effective protocol for guiding follow-up treatment in women without a history of cervical cancer screening who test positive for high-risk HPV. In this study, when cytology ≥ ASC-US or HPV16/18/58 positivity alone was used as an indication for histological testing, the sensitivity ranged from 64% to 75%. However, when cytology ≥ ASC-US was combined with HPV16/18/58 positivity, the sensitivity exceeded 90%, with a negative predictive value of 92.0% (95% CI: 88.1–95.9) and a specificity of 21–25%. This combination could serve as a useful approach for managing women who have never undergone cervical cancer screening. Nevertheless, the reduced specificity of this combined method may result in an increased number of unnecessary colposcopies or invasive cervical biopsies. In regions with a high prevalence of cervical cancer and low rates of standardized screening, physicians often prioritize confirming the presence of cervical precancerous lesions or cancer in large populations of unscreened women. To improve both sensitivity and specificity, novel screening stratification techniques should be explored. Emerging evidence suggests that p16/MKI67 (Ki-67) double-stained cytology and methylation testing offer superior sensitivity and specificity compared to conventional HPV testing. Additionally, extending screening intervals for low-risk populations and implementing cost-effective, easy-to-perform methods could enhance the feasibility and scalability of cervical cancer screening programs [13–20].

The quadrivalent HPV vaccine currently promoted in China does not include HPV58, whereas the nine-valent HPV vaccine does. However, access to the nine-valent HPV vaccine in China remains largely restricted to adolescents, presenting a significant challenge for middle-aged and older populations. Expanding vaccination coverage and developing appropriate screening technologies are essential measures to reduce the incidence of cervical cancer. In addition, it is important to establish a comprehensive public health database for cervical

cancer screening and enhancement of follow-up systems to ensure continuity of care.

This study was limited by its single-center design, although the relatively large study population partially mitigates this limitation. Further research across East Asia is necessary to better understand regional differences in the distribution of high-risk HPV genotypes, with the ultimate aim of improving cervical cancer screening and management programs.

5. Conclusions

In conclusion, our study suggests that active referral for colposcopy or biopsy in regions with a high prevalence of HPV58 infection may improve the detection of high-grade cervical lesions and even cervical cancer, as such an approach could be particularly beneficial for women who face barriers to standardized screening and follow-up procedures.

ABBREVIATIONS

HR-HPV: high-risk human papillomavirus; HSIL+: high-grade squamous intraepithelial lesions or worse; NILM: negative for intraepithelial lesion and malignancy; CIs: confidence intervals; ASC-US: atypical squamous cells of undetermined significance; WHO: World Health Organization; ASCCP: American Society of Colposcopy and Cervical Pathology; CIN: cervical intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion; AGC: atypical glandular cells; AIS: adenocarcinoma *in situ*; ORs: odds ratios; Ref: Reference; NPV: negative predictive value; PPV: positive predictive value; Ki-67: MKI67.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

SMZ and KHS—project development, data collection, manuscript writing. MMM—data Collection. BL—data analysis. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the institutional ethics committee, Drum Tower of Nanjing Hospital Group Suqian Hospital Ethics Committee, No. 2022048. Written informed consents were obtained from legally authorized representatives for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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