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Risk stratification and conservative management of women aged 25–40 years with cervical intraepithelial neoplasia grade 2(CIN2)

Huanhua Wang[1*†] and Ping Jin[1†]

Abstract

Background Cervical intraepithelial neoplasia grade 2 (CIN2) can progress to CIN3 or worse (CIN3$^+$). Some patients diagnosed with CIN2 from a punch biopsy exhibit varied risks of occult CIN3$^+$ in the loop electrosurgical excision procedure (LEEP) specimens following treatment, underscoring the need for risk stratification.

Methods We conducted a retrospective observational study of 307 women aged ≤ 40 years, diagnosed with CIN2 via colposcopy-guided punch biopsy where the squamocolumnar junction was visible, and who underwent LEEP within three months. We compared the diagnoses from punch biopsies with the histology of the LEEP specimens and developed a stratified management algorithm based on identified risk factors.

Results The risk of CIN3$^+$ in the LEEP specimens for women aged 25–40 years was 24.9% (including one case of cervical microinvasive squamous cell carcinoma), significantly higher than in women under 25 years in univariate analysis (24.9% vs. 7.1%, $P < 0.05$). Multivariate analysis revealed HPV16/18 (OR 2.61, [95% CI 1.41–4.85]) and HSIL cytology (OR 4.14, [95% CI 2.03–8.47]) as independent risk factors.

Conclusion Patients aged 25–40 years with CIN2 diagnosed in punch biopsy exhibited a substantial risk of CIN3$^+$ in LEEP specimens, warranting consideration for surgical intervention, particularly in those with HPV16/18 and HSIL cytology. Approximately 30% of CIN2 patients with HPV16/18 and ASC-US/LSIL, or other high-risk HPV types and HSIL cytology, also showed CIN3$^+$, suggesting that treatment should be individualized considering the patient's preferences and adherence. Conversely, the risk was low for those with HPV16/18 and normal cytology or other high-risk HPV types and ASC-US/LSIL, making conservative management a viable option.

Keywords Cervical cancer prevention, Cervical intraepithelial neoplasia 2, Conservative treatment, Conization, HPV genotype, Cytology

Background

It is now well established that cervical intraepithelial neoplasia grade 2(CIN2) exhibits high rates (47% [1]—73.5% [2]) of spontaneous regression in young women within two years. Cervical dysplasia commonly occurs in women of reproductive age and excisional cervical treatment is associated with obstetric complications of mid-trimester loss and increased risk of preterm delivery [3, 4]. The 2019

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American Society for Colposcopy and Cervical Pathology (ASCCP) risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors state that "For young women with a diagnosis of histological cervical intraepithelial neoplasia 2 (CIN2) whose concern about the effects of treatment on a future pregnancy outweigh their concerns about cancer, either observation or treatment is acceptable provided the squamocolumnar junction is visible and $CIN2^+$ or ungraded CIN is not identified on endocervical sampling [5]. The primary concern associated with conservative management of CIN2 is the risk of progression to cervical cancer. Silver et al. [6] observed that among 2,417 patients aged 21–39 diagnosed with CIN2 and managed conservatively, with an average follow-up of 48 months, only 0.2% progressed to cervical cancer. Compared to the corresponding age-standardized rate of cervical cancer in 13.3 per 100,000 women worldwide [7], the incidence rate in women aged under 25 years is only 1 per 100,000 women [8]. Many studies focus on patients under 25 years [9–11], considering this age group more suitable for conservative management of CIN2 due to their very low cancer risk. However, with the average age of first childbirth rising, a significant number of live births now occur in women aged ≥25. In the UK in 2016, the average age at first delivery was 28.8 years and 54% of all live births occurred in mothers aged over 30 years [12]. In China between 2011 and 2019, the trend in advanced maternal age (≥ 35 years) increased by 75% [13]. This demographic shift underscores the importance of researching conservative treatment options for CIN2 in women aged ≥25 years. A study conducted on 13,120 Women aged 18–44 years diagnosed with CIN2 found that similar regression rates were seen in women younger and older than 30 years, suggesting that conservative management is justifiable for women of childbearing age [1]. A prospective observational study of 300 CIN2 patients (mean age 30 years) diagnosed by cervical biopsy showed that the regression rate of CIN2 lesions supported conservative management in selected patients regardless of their age after 2 years of follow-up [2].

However, 28% of women diagnosed with CIN2 by punch biopsy may receive a $CIN3^+$ diagnosis in the histology of the LEEP specimens [14], which suggests that approximately one-third of missed diagnosis for $CIN3^+$ lesions in patients diagnosed with CIN2 by punch biopsy. A landmark study reported about 31% cumulative incidence of invasive cervical cancer within 30 years among untreated CIN3 patients [15]. Given the significantly higher carcinogenic risk associated with CIN3, surgical intervention is required instead of conservative management. Conservative follow-up of untreated CIN2 typically relies on colposcopy and cervical cytology [1, 9–11], yet these methods may not always detect progression or persistent high-grade abnormalities in women undergoing observational management for CIN2 [16]. Not all patients diagnosed with CIN2 are suitable for conservative treatment, even if the squamocolumnar junction is visible. Therefore, for women aged ≥25 years, conservative treatment should be approached with caution, and stratified treatment should be considered. The main purpose of conservative treatment for CIN2 is to reduce the impact of surgical treatment on future fertility. However, It is well known that female reproduction ability decreases during the forth decade of life due to age-related changes in oocyte quality and quantity [17]. Based on National audit of British Society for Colposcopy and Cervical Pathology members' opinion: age >40 years is relative contraindication for conservative management of CIN2 [18]. So, participants in this study were limited to those aged ≤40 years. A comprehensive search of PubMed, Embase and Web of Science using the keywords "stratified management" or "risk stratification" and "CIN2" yielded no literature meeting the requirements. To our knowledge, this is the first study proposing stratified management for CIN2 in women aged 25 years and above who meet the conservative treatment criteria set by the ASCCP risk-based management consensus guidelines in 2019.

In this study, we included women aged ≤40 years who were diagnosed with CIN2 by colposcopy-guided punch biopsy and underwent LEEP treatment within three months. We compared the histology of the LEEP specimens with that of the punch biopsies and explored factors predicting the risk of $CIN3^+$ in the LEEP specimens. The risk of $CIN3^+$ in women aged 25–40 years diagnosed with CIN2 was assessed based on HPV status using partial genotyping and cervical cytology results obtained prior to the biopsy.

Materials and methods

Data sources and ethics statement

We included women aged ≤40 years, enrolled between January 2009 and December 2013, who were diagnosed with CIN2 via colposcopy-guided punch biopsy where the squamocolumnar junction was visible. These women underwent LEEP within three months of diagnosis. We conducted a retrospective observational study. Ethical approval for this non-interventional study was granted by the Ethical Committee of Shenzhen Maternity & Child Healthcare Hospital, Southern Medical University, Guangdong, China (SFY2019059). All procedures were carried out in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants.

All study data were retrieved from medical records and collected in a computerized database containing clinical data, colposcopic findings, Human papilloma virus (HPV) infection information, and Thin Prep cytology test (TCT) smear data. We collected cases with complete data and excluded those with missing data. All histopathology reports were reviewed by a team of experts and characterized by P16 expression (P16 positive individuals were diagnosed with CIN2, while P16 negative individuals were classified as CIN1). Women with type 1, 2 cervical transformation zone were treated with type 1, 2 conization, respectively [19]. To eliminate the histopathological degradation of conization due to non-resection of lesions, we chose women with no lesions (residual or recurrent) at 2-year follow-up. The exclusion criteria were as follows: age >40, CIN3$^+$, CIN2$^+$ or ungraded CIN identified on endocervical sampling, type 3 cervical transformation zone under colposcopy examination, pregnant, with a tumor, with immunological or infectious diseases, previous CIN or history of previous undergoing ablation surgery (e.g., electrocautery or laser), and residual or recurrent lesions noted during postoperative follow-up.

Eligibility criteria

Referral colposcopy indications include: 1) A positive HPV test for types 16/18, regardless of Pap smear results; 2) A positive test for other high-risk HPV types (excluding 16/18) accompanied by abnormal Pap smear results, including atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), and high-grade squamous intraepithelial lesion (HSIL); and 3) cervical bleeding post-contact. Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H), was grouped under HSIL cytology.

HPV genotyping test was performed by using HPV genotyping detection kit. This kit uses DNA chip technology that combines polymerase chain reaction (PCR) in vitro amplification and DNA reverse dot hybridization to detect 14 high-risk HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Patients with co-infection with 16 or 18 and another high-risk HPV were classified as HPV 16/18 infection.

All histopathological and cytological sample evaluations were based on the Bethesda terminology and the three-tiered CIN classification [20]. The colposcopic terminology used was from the revision of the international colposcopic terminology: Barcelona—2002 [21]. Experienced colposcopy doctors followed a standardized protocol while performing colposcopy examination and punch biopsy (at least 2 or more biopsy points) or endocervical curettage (ECC) examination of the cervix under colposcopic guidance. We regularly performed independent interpretations of patients' colposcopic images, assessing variability among colposcopy doctors and conducted physician training to reduce interobserver variability.

Statistical analyses

All statistical analyses were conducted using IBM SPSS Statistics version 26.0, with a significance level set at 5% ($P < 0.05$) for two-sided tests. Continuous variables were analyzed using the independent-samples T-test, while Pearson's chi-square test was employed for categorical variables where appropriate, and if necessary, Fisher's exact test was calculated the statistical significance (*P* value) of the difference between groups. Binary logistic regression analysis was utilized to examine the effects of various categorical risk factors on the diagnosis of CIN3$^+$ in the LEEP specimens, adjusting for all significant univariate predictors. The association between risk factors and CIN3$^+$ in the LEEP specimens was quantified using odds ratios (OR) with 95% confidence intervals (CI). The predictive value of risk factors for CIN3$^+$ in the LEEP specimens was assessed with ROC curve test.

Results

In total, 307 women aged 40 years and younger were included in the study, with 42 (13.7%) cases under 25 years and 265 (86.3%) cases 25–40 years old. The clinical data for patients aged 25–40 years were as follows: 127 cases (47.9%) tested positive for HPV16/18, and 138 cases (52.1%) for other high-risk HPV genotypes. Regarding HPV genotype distribution, 173 cases (65.3%) were infected with one type of HPV genotype, while 92 cases (34.7%) harbored two or more types. Cytological findings included: 38 cases (14.3%) were negative for intraepithelial lesion or malignancy (NILM), 182 cases (68.7%) showed ASC-US or LSIL, and 45 cases (17.0%) had ASC-H or HSIL.

Comparative analysis between preoperative colposcopy-guided punch biopsy histopathology and cone histopathology in 307 women aged 40 years and younger revealed: 113 cases (36.8%) were downgraded to Normal or CIN1, 125 cases (40.7%) showed agreement (CIN2), and 69 cases (22.5%) were upgraded to CIN3$^+$, including one case of cervical microinvasive squamous cell carcinoma in a 36-year-old woman with HPV16 infection and HSIL cytology. In univariate analysis, older age was significantly associated with a higher risk of CIN3$^+$ in the LEEP specimens ($P < 0.05$) as detailed in Table 1. Among 265 women aged 25–40 years, 66 cases of CIN2 exhibited CIN3$^+$ in the LEEP specimens, yielding a rate of 24.9%, markedly higher than the 7.1% observed in women younger than 25 years (24.9% vs

Table 1 Baseline characteristics of patients according to status of cone histopathology

Classification	Total (N)	Cone histopathology		*P* value
		≤ CIN2	≥ CIN3	
Compare with biopsy pathology	307	238(77.5%)	69(22.5%)	
Age (years)	307	31.1 ± 5.3	32.3 ± 3.8	0.03*
Smokers	265			0.59
Yes	58	42 (72.4%)	16 (27.6%)	
No	207	157 (75.8%)	50 (24.2%)	
Parity	265			0.16
Nulliparous	108	86 (79.6%)	22 (20.4%)	
Parous	157	113 (72.0%)	44 (28.0%)	
Contraceptive method	265			0.12
Condom	120	95 (79.2%)	25 (20.8%)	
Hormonal or IUD	145	104 (71.7%)	41 (28.3%)	

* $p < 0.05$. *IUD* intrauterine device

Table 2 Age ≥ 25 years old, cytological data and HPV data of patients according to the status of cone histopathology

Classification	Total (N)	Cone histopathology		*P* value
		≤ CIN2	≥ CIN3	
Age (years)	307			0.01*
< 25 years old	42	39(92.9%)	3 (7.1%)	
≥ 25 years old	265	199 (75.1%)	66(24.9%)	
Cytology	265			< 0.001*
≤ LSIL†	220	175 (79.5%)	45 (20.5%)	
HSIL‡	45	24(53.3%)	21 (46.7%)	
HPV genotype	265			0.02*
HPV16/18	127	87 (68.5%)	40(31.5%)	
Other HR-HPV	138	112(81.2%)	26 (18.8%)	
The number of HPV subtype	265			0.08
One HPV subtype	173	124 (71.7%)	49 (28.3%)	
Two HPV subtypes or more	92	75(81.5%)	17 (18.5%)	
HPV16 or 18 co-infection with another high-risk HPV	127			0.56
Yes	48	34(70.8%)	14(29.2%)	
No	79	52(65.8%)	27(34.2%)	

* $p < 0.05$. †including NILM, ASC-US and LSIL; ‡including ASC-H and HSIL. NILM: negative for intraepithelial lesion or malignancy; ASC-US: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; HR-HPV: high-risk human papillomavirus

7.1%, $P < 0.05$) (Table 2). However, in the multivariate analysis, after adjusting for potential confounding factors including HSIL cytology and HPV16/18 infections, the age of 25–40 years was no longer a significant predictor (OR 3.20, [95% CI: 0.93–10.97]) (Table 3). No significant differences were found in other baseline characteristics such as smoking, parity, contraceptive method, and cone histopathology status among women aged 25–40 years ($P > 0.05$) (Table 1).

Table 3 Multivariate analyses of risk factors for CIN3$^+$ in the LEEP specimens in women aged ≤ 40 years

Risk factor	OR	95% CI Lower bound	95% CI Upper bound	*P* value
Age25-40 years	3.20	0.93	10.97	0.07
HSIL cytology	3.53	1.74	7.13	< 0.001*
HPV16/18 infection	2.28	1.27	4.10	0.01*
One subtype HPV infection	0.60	0.33	1.11	0.11

HPV human papilloma virus; *HISL* high-grade squamous intraepithelial lesion; *OR* odds ratio; *CI* confidence intervals

* $p < 0.05$

Table 4 Multivariate analyses of risk factors for CIN3$^+$ in the LEEP specimens in women aged 25–40 years

Risk factor	OR	95% CI Lower bound	95% CI Upper bound	P value
HSIL cytology	4.14	2.03	8.47	< 0.001*
HPV16/18 infection	2.61	1.41	4.85	< 0.01*
One subtype HPV infection	0.559	0.29	1.07	0.08

HPV human papilloma virus; *HISL* high-grade squamous intraepithelial lesion; *OR* odds ratio; *CI* confidence intervals

* $p < 0.05$

The risk of CIN3$^+$ in the LEEP specimens was significantly higher in patients aged 25–40 years with HPV16/18 infection or HSIL cytology ($P < 0.05$). No correlation was found between the number of HPV subtypes and the risk of CIN3$^+$ in the LEEP specimens ($P > 0.05$). Co-infection with 16 or 18 and another high-risk HPV didn't increase the likelihood of CIN3$^+$ in the LEEP specimens ($P > 0.05$) (Table 2).

In multivariate analysis, HPV16/18 (OR 2.61, [95%CI 1.41–4.85]) and HSIL cytology (OR 4.14, [95%CI 2.03–8.47]) emerged as independent risk factors for the diagnosis of CIN3$^+$ in the LEEP specimens among patients aged 25–40 years (Table 4).

The distribution of CIN3$^+$ risk in the LEEP specimens, stratified by cervical cytology and HPV partial genotyping, showed that in patients with ASC-H/HSIL cytology, those infected with HPV16/18 had a significantly higher risk compared to those with other high-risk HPV infections (13/15 vs 26.7%, $P < 0.05$) (Table 5), and the same phenomenon showed in patients with ASC-US/LSIL cytology (32.4% vs 16.7%, $P < 0.05$) (Table 5). However, for patients with HPV16/18 infection and NILM cytology, the positive predictive value for detecting CIN3$^+$ in the LEEP specimens was only 7.9% (Table 5).

Table 5 Distribution of CIN3$^+$ in the LEEP specimens in patients aged 25–40 years stratified by risk factors

Classification	Total (N)	Cone histopathology		*P* value
		≤ CIN2	≥ CIN3	
Cytology: ASC-H/HSIL	45			< 0.001*
HPV16/18	15	2(2/15) †	13(13/15) †	
Other high-risk HPV	30	22(73.3%)	8(26.7%)	
Cytology: ASC-US/LSIL	182			0.01*
HPV16/18	74	50 (67.6%)	24 (32.4%)	
Other high-risk HPV	108	90 (83.3%)	18 (16.7%)	
Cytology: NILM + PV16/18	38	35(92.1%)	3(7.9%)	

* $p < 0.05$. †The denominator is less than 20, expressed as a fraction. NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; HR-HPV, high-risk human papillomavirus

We assessed the predictive value of HPV partial genotyping combined with cytological results for the CIN3$^+$ risk in the LEEP specimens in CIN2 patients aged 25–40 years by utilizing ROC curve test, and found the area under the curve (AUC) value was 0.70, the specific risk cut-off value was 25.2%, which predictive sensitivity and specificity were 0.68,0.63, respectively (Table 6).

A stratified management algorithm of CIN2 in patients aged 25–40 years based on varied risks of CIN3$^+$ in LEEP specimens utilizing HPV partial genotyping and cytological results in Fig. 1.

Discussion

Meta-analysis data suggest that age is inversely associated with the regression rate during conservative treatment of CIN2, with higher regression rates observed in studies that exclusively recruited patients with CIN2 as opposed to those including patients with mixed CIN2 and CIN3 diagnoses [22]. In our study, among women diagnosed with CIN2 in the punch biopsy, the risk of CIN3$^+$ in the LEEP specimens was significantly higher in patients aged 25–40 years (including one case of cervical microinvasive squamous cell carcinoma) compared to those under 25 years (24.9% vs 7.1%, $P < 0.05$), and older age was correlated with risk in univariate analysis. Our findings support the hypothesis that the lower regression rate of CIN2 in older women may be due to a higher proportion of undiagnosed CIN3$^+$ in the remaining cervix. Given that women aged 25–40 years comprised 86.3% of the CIN2 patients in our study, conservative management of CIN2 in this age group could potentially benefit a significant number of patients. However, careful patient selection and thorough risk stratification are crucial to optimizing outcomes.

Potential prognostic factors influencing the risk of progression of CIN2 lesions have been extensively studied. Varying opinions emerge among different studies regarding some risk factors. For example, in our study, age was a risk factor in univariate analysis but showed no statistically significant difference in multivariate analysis. Previous literature also exhibits inconsistent perspectives on the impact of age on the spontaneous regression of CIN2 lesions. A meta-analysis including patients not differing CIN2 or CIN3 suggests age is a negative factor affecting lesion regression [22]. However, two other studies found similar regression rates of CIN2 lesions in selected patients regardless of their age after 2 years of follow-up [1, 2]. Additionally, such as nulliparity and non-smoking, which have been linked to spontaneous regression in prior research [18, 23], did not emerge as significant factors in our analysis. Salvadó A et al.'s [2] prospective study also failed to identify an association between these two factors and the regression of CIN2 lesions. We conclude the reasons for these phenomena may be that age, parity, and smoking are non-independent risk factors, likely due to interaction effects of other risk factors in the enrolled data.

Currently well-established risk factors include HSIL cytology and HPV16/18 infections for the progression of CIN2 lesions during conservative management [2, 18, 24]. This is supported by HPV 16/18 and HSIL cytology being identified as independent risk factors for CIN3$^+$ in our multivariate analysis. In our study, the high detection rate of CIN3$^+$ in the LEEP specimens from patients with a CIN2 diagnosis on punch biopsy could be attributed to non-representative cervical biopsies where CIN3$^+$ was already present, which may be an objective issue that affects the progression of lesions in conservative treatment of CIN2. Additionally, another widely accepted view is that single HPV infection has a greater risk of developing SCC [25] and a greater histological persistence rate of CIN2 with respect to multiple infections [26]. A similar trend (although not statistically significant) was observed

Table 6 The predictive value of HPV partial genotyping combined with cytological results for the risk of CIN3$^+$ in the LEEP specimens utilizing the ROC curve test

Risk factor	AUC	*P* value	Cut-off value	Sensitivity	Specificity
Cytology combined with HPV partial genotyping	0.70	0.001*	25.2%	0.68	0.63

* $p < 0.05$. *HPV* human papilloma virus; *AUC* Area under the curve

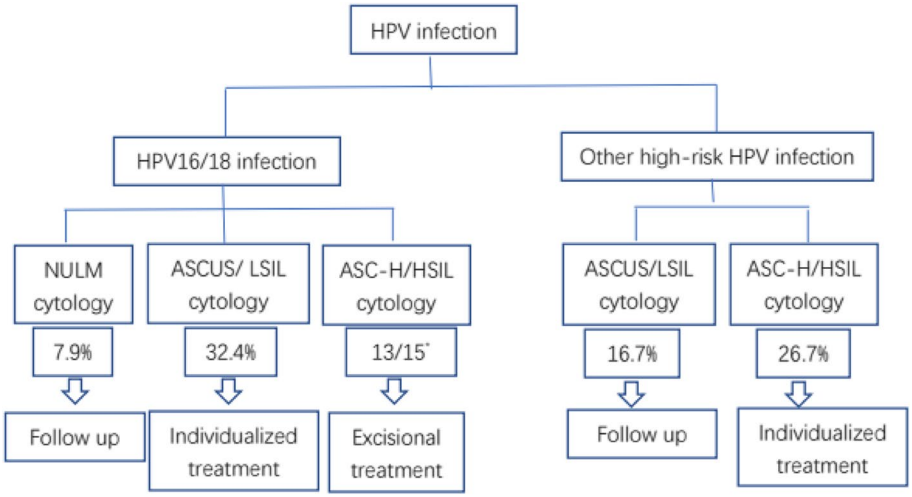

Fig. 1 A stratified management algorithm of CIN2 in patients aged 25–40 years based on varied risks of CIN3$^+$ in LEEP specimens utilizing HPV partial genotyping and cytological results. *The denominator is less than 20; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; HR-HPV, high-risk human papillomavirus

in this study: a greater risk of CIN3$^+$ in the LEEP specimens in patients with single HPV infection than those with multiple infections (28.3% vs18.5%, P = 0.08 in univariate analysis; OR 0.56, [95% CI 0.29–1.07], P = 0.08 in multivariate analysis), or enlarging the sample size may reveal statistically significant differences.

The literatures corroborate the role of HPV genotype as a differential marker in populations with cytological abnormalities during cervical cancer screening [27, 28]. An analysis included 2807 subjects with ASC-US or LSIL cytology from the baseline phase of the Onclarity HPV trial, and found that HPV 16 carried the highest risk for cervical intraepithelial neoplasia grade 2 or worse (≥ CIN2) in both the ASC-US and LSIL populations [27]. Another study was to determine the usefulness of HPV partial genotyping test in the triage of newly diagnosed LSILs during two-year following up, and concluded that the risk of HPV 16 for progression to CIN2$^+$ was 32.1%, 14.3% for HPV 18, and 5.8% for HPV (no16 no18) [28]. Furthermore, Karia N et al. [29] observed integrating HPV and cytological results significantly improved the positive predictive value for detecting higher-grade cervical lesions (CIN2$^+$). Our study also validated these phenomena that HPV genotype (specifically HPV16/18) is a significant risk factor for CIN3$^+$ in the LEEP specimens among women with CIN2 histology in punch biopsy and abnormal cytology (ASC-US/LSIL or HSIL). Different combinations of HPV genotypes and cytology results demonstrated varying positive predictive values for identifying CIN3$^+$ in the LEEP specimens in this study. In patients with ASC-H/HSIL cytology, those infected with HPV16/18 had a significantly higher risk compared to those with other high-risk HPV infections (13/15 vs 26.7%, $P < 0.05$), and the same phenomenon showed in patients with ASC-US/LSIL cytology (32.4% vs 16.7%, $P < 0.05$). However, for patients with HPV16/18 infection and NILM cytology, the positive predictive value for detecting CIN3 + in the LEEP specimens was only 7.9%.

We developed a flowchart for the stratified management of CIN2 for women aged 25–40 years based on the risk of CIN3$^+$ in the LEEP specimens, utilizing predictive factors such as HPV partial genotyping and cytological results. Salvadó A et al. [2] found that HPV 16 in combination with previous HSIL cytology, significantly increased the risk of CIN2 persistence or progression under conservative management. In our study, nearly all CIN2 patients (13/15) with HPV16/18 infection and HSIL cytology had CIN3$^+$ identified in their LEEP specimens, indicating that surgical rather than conservative treatment should be considered for this group. For patients with HPV16/18 infection and ASC-US/LSIL cytology, 32.4% had CIN3$^+$ in the LEEP specimens, and for those with other high-risk HPV infections and HSIL cytology, 26.7% had CIN3$^+$. The risk values of these latter two were slightly higher than the risk cut-off value (25.2%). For these two patient groups, conservative management under strict monitoring may be acceptable if patients agree to and adhere to follow-up instructions. However, if patients opt for surgery due to fear of risks or with poor compliance, surgical intervention should be recommended. For cases with HPV16/18 infection and normal cytology, the risk of CIN3$^+$ in the LEEP specimens was only 7.9%, and for those with other high-risk HPV types and ASC-US/LSIL cytology, it was 16.7%. Follow-up management appears to be a safe option for these groups.

This study has several limitations. Firstly, as a retrospective study, it lacks comprehensive behavioral and demographic data such as age of first sexual intercourse, number of sexual partners, education, occupation, and income, which may act as confounding factors influencing the results (e.g., socioeconomic status impacting access to healthcare or screening, sexual behavior affecting HPV exposure risk). Secondly, while persistent HPV infection is known to cause cervical cancer. Markedly reduced incidence rates of CIN3$^+$ followed consecutive negative HPV test results [30]. This study focused solely on the genotype of HPV without considering the duration of HPV infection, which is a critical factor in disease progression. Thirdly, HPV vaccines are poised to significantly reduce the risk of cervical cancer in the near future. Prevalence of different HPV genotypes is changing after HPV vaccination [31]. This manuscript did not address the impact of HPV vaccination and the analyzed HPV genotypes were limited to the traditional 14 high-risk types. Since HPV vaccines were gradually approved for marketing in China only after 2016, none of the patients in this study had received vaccines. Additionally, being based at a single site may limit the generalizability of the results. Some molecular signatures are identified as high biological risk for lesion progression. For example, gene methylation, an epigenetic marker, reflects stable alterations in gene regulation that precede morphological changes, making it a sensitive indicator of cellular dysplasia [32]. HPV gene integration into the host genome is a critical oncogenic step, as it disrupts cellular pathways (e.g., p53 and Rb tumor suppressor pathways) and correlates with increased malignancy potential [33]. Future multi-center clinical research could address these gaps and incorporate new predictive methods, such as gene methylation and HPV gene integration, for risk assessment of CIN2 disease progression. To our knowledge, this is the first study to explore stratified management for CIN2 in patients aged 25–40 years. All data included in the multivariate analysis are objective, supporting its applicability in a management algorithm.

Conclusions

Women aged 25–40 years with CIN2 diagnosed in punch biopsy exhibited varied risks of CIN3$^+$ in LEEP specimens, underscoring the need for risk stratification. Nearly all patients with CIN2, HPV16/18 infection, and HSIL cytology demonstrated CIN3$^+$ in their LEEP specimens, suggesting that surgical treatment should be recommended for this group. Approximately 30% of CIN2 patients with either HPV16/18 infection and ASC-US/LSIL cytology or other high-risk HPV infections and HSIL cytology had CIN3$^+$ in the LEEP specimens; treatment for these two could be individualized considering the patient's preferences and adherence. Conversely, patients with HPV16/18 infection and normal cytology or other high-risk HPV infections and ASC-US/LSIL cytology exhibited a low risk of CIN3$^+$, for whom conservative management and follow-up would be appropriate instead of immediate surgical intervention.

Abbreviations

ASCCP	American Society for Colposcopy and Cervical Pathology
CIN2	Cervical intraepithelial neoplasia grade 2
CIN	Cervical intraepithelial neoplasia
LEEP	Loop electrosurgical excision procedure
HPV	Human papilloma virus
TCT	ThinPrep cytology test
NILM	Negative for intraepithelial lesion or malignancy
ASC-US	Atypical squamous cells of undetermined significance
LSIL	Low-grade squamous intraepithelial lesion
ASC-H	Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion
HSIL	High-grade squamous intraepithelial lesion
ECC	Endocervical curettage
OR	Odds ratio
CI	Confidence intervals
AUC	Area under the curve
IUD	Intrauterine device

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Authors'contributions

HHW was responsible for the overall content as the guarantor who designed the research content, collected and vetted out the obtained clinical data, and wrote the manuscript. PJ played a guiding role with the overall content of the manuscript. All authors have read, reviewed, and approved the manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This non-interventional study was approved by the Ethical Committee of Shenzhen Maternity & Child Healthcare Hospital, Southern Medical University, Guangdong, China (SFY2019059), all methods were carried out in accordance with relevant guidelines and regulations. The written informed consent to participate was obtained from all the patients.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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