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The Diagnostic Significance of Combined Screening and Human Papillomavirus 16 and 18 Cycle Threshold Values for CIN2+ Cervical Lesions

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Background: Although both cervical intraepithelial neoplasia (CIN) II and CIN III carry the potential to progress into cervical cancer, to date, an optimal screening method for CIN2+ (CIN II, CIN III, and cervical cancer) cervical lesions is yet to be established.

Methods: In this retrospective study, data from 2035 patients treated at the Fourth Hospital of Hebei Medical University between 2019 and 2021 were analyzed. The screening efficacy of three methods—the ThinPrep cytologic test (TCT) alone, the high-risk-human papillomavirus (HR-HPV) test alone, and the combined TCT and HR-HPV screening for CIN2+ lesions—were assessed using cervical histopathology as the reference standard. Additionally, correlations between HPV16 cycle threshold (Ct) values, HPV18 Ct values, and the severity of cervical lesions were analyzed. Receiver operating characteristic (ROC) curves were plotted to evaluate the diagnostic utility of HPV16 Ct values for CIN2+ lesions.

Results: Compared with TCT or HR-HPV testing alone, the combined TCT and HR-HPV test had the highest sensitivity of 98.1% ($P < 0.0001$), the highest negative predictive value of 99.8% ($P = 0.0001$), and the lowest missed diagnosis rate of 1.9% ($P < 0.0001$) for screening CIN2+ lesions. Additionally, the combined test yielded the largest area under the ROC curve (AUC) value of 0.9480. There was a significant difference in HPV16 Ct values for various degrees of cervical lesions ($P < 0.001$), with the Spearman rank correlation test revealing a significant negative correlation ($rs = -0.447$, $P < 0.001$). The optimal HPV16 Ct value for diagnosing CIN2+ lesions was 29.995, with an AUC of 0.797 ($P < 0.0001$).

Conclusion: The combination of TCT and HR-HPV testing was the most effective method for screening CIN2+ lesions. Furthermore, HPV16 Ct values were negatively correlated with the severity of cervical lesions, with a threshold of 29.995 potentially indicating the presence of CIN2+ lesions.

Keywords: CIN2+ cervical lesions, cervical cancer, combined test, HPV16 Ct value, HR-HPV, TCT

Introduction

Cervical cancer, characterized by high incidence and mortality rates,[1–3] remains a significant global threat to women's health. According to the International Agency for Research on Cancer (IARC), China accounted for 109,000 new cervical cancer cases and 59,000 related deaths in 2020, representing 18.2% and 17.3% of global incidence and mortality, respectively.[3] The American Cancer Society (ACS) reported that the 5-year mortality rate for patients diagnosed with early (localized) cervical cancer is as low as 7%, but this rate escalates to 83% in cases where the cancer advances and metastasizes.[4] Therefore, effective screening and preventive measures for cervical cancer are essential to reduce its impact on women's health.

The human papillomavirus (HPV) is the most significant cause of cervical cancer, with persistent high-risk HPV (HR-HPV) infections playing a crucial role in the progression of cervical intraepithelial neoplasia (CIN) to cervical cancer.[5–7]

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CIN includes low-grade CIN (CIN I) and high-grade CIN (CIN II and CIN III), with the latter possessing a higher likelihood of progressing to cervical cancer. Consequently, early detection through screening of patients for CIN2+ (CIN II, CIN III, and cervical cancer) cervical lesions is crucial for timely intervention and prevention.

Screening for cervical cancer has progressed from traditional cytologic examinations to the inclusion of the HR-HPV test, with current guidelines recommending a combined use of the ThinPrep cytologic test (TCT) and HR-HPV testing.[8–12] However, the optimal screening method for CIN2+ cervical lesions remains inadequately defined.

In this study, the screening efficacies of TCT alone, HR-HPV alone, and TCT combined with HR-HPV testing for detecting CIN2+ cervical lesions in 2035 cases were assessed, using cervical histology as the reference standard. Additionally, the correlation between HPV16 cycle threshold (Ct) values, HPV18 Ct values, and the presence of CIN2+ cervical lesions was also explored.

Materials and Methods

Study Participants

In this retrospective study, data of 2035 patients with benign or malignant gynecological conditions who sought medical consultations at the Gynecology Department of the Fourth Hospital of Hebei Medical University between October 2019 and September 2021 were analyzed. All patients underwent preoperative cervical TCT and HPV examinations. Based on these results, colposcopy and cervical biopsy were performed to obtain cervical histologic results. For patients who did not require colposcopy or cervical biopsy, cervical histological data were obtained through necessary hysterectomy procedures.

The inclusion criteria for the study were as follows: (1) patients with a history of sexual activity; (2) those with no prior treatment for cervical atypical hyperplasia; (3) patients with no history of hysterectomy; and (4) patients who were not pregnant. Exclusion criteria included: (1) patients with history of malignant tumors outside the female reproductive system; (2) patients with a history of cervical cancer vaccination; and (3) those with severe disease affecting other tissues or organs.

The study protocol was approved by the Institutional Human Ethics Committee of the Fourth Hospital of Hebei Medical University (No. 2020KY266). All patients provided prior informed consent for participating in the study.

Methods

Cervical HPV-DNA Detection

Cervical HPV DNA was detected using fluorescent polymerase chain reaction (PCR) (Cobas HPV assay) as per the manufacturer's instructions (Hybribio Co. Ltd., Guangdong, China). This assay identified 14 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68),[13] six low-risk types (6, 11, 42, 43, 44, and 81), and three suspected high-risk types (53, 73, and 82).

Cycle threshold (Ct) values were used to determine positive results. A positive result was defined as a Ct value of $\leq$ 37.5 as per the manufacturer's guidelines. PCR-based Ct values were used to quantify viral load, where a high Ct value indicates a low viral load (requiring more amplification cycles for detection), while a low Ct value indicates a high viral load (requiring fewer cycles to yield a positive result).[14] For instance, a Ct value of 20 signifies a higher viral load than a Ct value of 25. The higher the viral load, the greater the likelihood of it causing cervical lesions.

All results were reviewed by two experts. If there were any discrepancies in opinions, a third expert was consulted to finalize the interpretation.

Cervical Cytology and Diagnostic Criteria

Cervical cytology was performed using liquid-based thin-layer cytology (TCT). The results were reported as per the 2001 Bethesda System,[15] in the following order of severity: no intraepithelial lesion or malignancy (NILM), which includes normal or inflamed tissue; atypical squamous cells of undetermined significance (ASC-US); low-grade squamous intraepithelial lesion (LSIL); atypical glandular cells of undetermined significance or not otherwise specified (AGUS/NOS); atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion (ASC-H); high-grade

squamous intraepithelial lesion (HSIL); adenocarcinoma in situ (AIS); squamous cell carcinoma (SCC); and adenocarcinoma. A positive TCT result was defined as the presence of ASC-US or any more severe cytologic abnormality.[16]

Histopathological Evaluation

Regardless of the HPV test outcome, patients with a TCT result indicating LSIL or more severe abnormalities, or those with a TCT result of ASC-US in combination with a positive HPV result, underwent pathological examination for a definitive diagnosis. Biopsy specimens were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin for histopathological evaluation.

The pathological assessment followed the fourth edition of the World Health Organization (WHO) classification criteria (2014). Inflammatory findings encompassed benign conditions such as chronic cervicitis, cervical hypertrophy, cervical naevus cysts, erosions, hemorrhage, and hyperplasia. CIN was categorized as CIN I (low-grade atypical hyperplasia), CIN II (moderate atypical hyperplasia), and CIN III (high-grade atypical hyperplasia). Cervical cancers were classified as AIS, SCC, adenocarcinoma, or other forms of cervical cancer.

Statistical Analysis

IBM SPSS Statistics 27 software was used for statistical analysis of data. The $\chi 2$ test was used to assess the significance of differences between groups and to compare positive detection rates across groups. The Mann–Whitney test was used to compare the HPV16 and HPV18 Ct values in patients with varying degrees of cervical lesions. The relationship between HPV16 Ct values and the severity of cervical lesions was further analyzed using Spearman's rank correlation.

A receiver operating characteristic (ROC) curve was constructed to determine the most effective diagnostic method for detecting CIN2+ cervical lesions from among TCT alone, HR-HPV alone, and the combined TCT and HR-HPV screening. Additionally, the ROC curve was used to identify the optimal HPV16 Ct threshold for diagnosing CIN2+ cervical lesions. All statistical tests were two-sided. A P value of < 0.05 was considered indicative of a statistically significant difference.

Results

Distribution of results for TCT, HPV, or Combined Screening in Cervical Lesions Based on Histopathology Standards

Out of the 2035 women, 1786 (87.8%) tested negative for TCT, while 249 (12.2%) tested positive. A total of 294 patients (14.5%) tested positive for HR-HPV. Cervical lesions less severe than CIN II (inflammation and CIN I) were observed in 1828 cases (89.8% of the total). CIN2+ cervical lesions (CIN II, CIN III, cervical cancer) were found in 207 cases (10.2%). The distribution is presented in Table 1.

As shown in Table 2, the HR-HPV infection rates in the CIN II, CIN III, and cervical cancer groups were 66.6%, 94.4%, and 85.2%, respectively. Among patients with positive results on the combined TCT and HR-HPV test, the detection rates in the CIN II, CIN III, and cervical cancer groups were 94.5%, 100%, and 97.8%, respectively. These rates were higher than the rates for TCT alone (83.3%, 87%, and 93.3%, respectively) or HR-HPV alone (66.6%, 94.4%, and 85.2%, respectively).

In addition, among the groups with varying degrees of cervical lesions, patients in the cervical cancer group had the highest positive rates of HPV16 and HPV18 at 63.0% and 8.9%, respectively. These differences were statistically significant compared to other lesion groups ($P < 0.0001$). The total proportion of patients with HPV16- and HPV18-positivity in the cervical cancer group was 71.9%, which was also statistically significant compared to other lesion groups ($P < 0.0001$).

Comparison of the Screening Effectiveness of TCT Alone, HR-HPV Alone, and Combined TCT and HR-HPV Testing for CIN2+ Cervical Lesions

The combined TCT and HR-HPV screening for CIN2+ cervical lesions had the highest sensitivity, reaching 98.1%, with statistically significant results ($P < 0.0001$), as shown in Table 3. The combined screening method also had the highest

Table 1 Distribution of TCT, HPV Test and Cervical Histopathological Results in Patients

Item	Classification	n	Percentage (%)
TCT	NILM	1786	87.8
	ASL-US	104	5.1
	LSIL	16	0.8
	AGUS/NOS	22	1.1
	ASC-H	23	1.1
	HSIL	80	3.9
	Squamous cell carcinoma	4	0.2
HR-HPV	–	1707	83.9
	HPV16+	164	8.1
	HPV18+	20	1.0
	Other high-risk types +	110	5.4
	Low-risk types +	21	1.0
	Suspected high-risk types+	13	0.6
Cervical histopathology	Inflammation	1791	88.0
	CINI	37	1.8
	CINII	18	0.9
	CINIII	54	2.7
	AIS	2	0.1
	Squamous cell carcinoma	112	5.5
	Adenocarcinoma	15	0.7
	Other types of cancer	6	0.3

Notes: (Other high-risk types: These refer to the other 12 hR-HPV subtypes except for the HPV-16 and HPV-18 subtypes).
Abbreviations: TCT, ThinPrep cytologic test; NILM, no intraepithelial lesion or malignancy; ASL-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; AGUS/NOS, atypical glandular cells of undetermined significance or not otherwise specified; ASC-H, atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; HR-HPV, high-risk-human papillomavirus, AIS, adenocarcinoma in situ.

Table 2 Results of TCT, HPV and Combined Testing in Patients and the Corresponding Results of Cervical Histopathology

Test	Classification	Cervical Histopathological Results (n/%)				
		Inflammation	CINI	CINII	CINIII	Cervical Cancer
TCT	–	1739 (97.1%)	28 (75.7%)	3 (16.7%)	7 (13.0%)	9 (6.7%)
	+	52 (2.9%)	9 (24.3%)	15 (83.3%)	47 (87.0%)	126 (93.3%)
HR-HPV	–	1688 (94.3%)	24 (64.9%)	6 (33.4%)	3 (5.6%)	20 (14.8%)
	HPV16+	38 (2.1%)	5 (13.5%)	4 (22.2%)	32 (59.2%)	85 (63.0%)
	HPV18+	4 (0.2%)	2 (5.4%)	0 (0%)	2 (3.7%)	12 (8.9%)
	Other HR-HPV+	61 (3.4%)	6 (16.2%)	8 (44.4%)	17 (31.5%)	18 (13.3%)
Combined	TCT-/HR-HPV-	1651 (92.2%)	21 (56.8%)	1 (5.5%)	0 (0%)	3 (2.2%)
	TCT+/HR-HPV-	37 (2.1%)	3 (8.1%)	5 (27.8%)	3 (5.6%)	17 (12.6%)
	TCT-/HPV16+	34 (1.9%)	4 (10.8%)	1 (5.5%)	6 (11.1%)	6 (4.5%)
	TCT-/HPV18+	4 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	TCT-/Other HR-HPV+	50 (2.8%)	3 (8.1%)	1 (5.5%)	1 (1.9%)	0 (0%)
	TCT+/HPV16+	4 (0.2%)	1 (2.7%)	3 (16.8%)	26 (48.1%)	79 (58.5%)
	TCT+/HPV18+	0 (0%)	2 (5.4%)	0 (0%)	2 (3.7%)	12 (8.9%)
	TCT+/other HR-HPV+	11 (0.6%)	3 (8.1%)	7 (38.9%)	16 (29.6%)	18 (13.3%)

Notes: (Cervical cancer includes AIS, SCC, adenocarcinoma and Other types of cancer. HR-HPV (-) includes low-risk HPV positive, suspected high-risk HPV positive, and no HPV of any type detected. The positive of combined detection refers to at least one positive in TCT and HR-HPV).
Abbreviations: TCT, ThinPrep cytologic test; HR-HPV, high-risk-human papillomavirus.

Table 3 The Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and 95% Confidence Intervals of TCT, HR-HPV and Combined Tests of TCT and HR-HPV for Screening Cervical Lesions (≥ CINII)

	TCT	HR-HPV	Combined	P Value
Sensitivity (95% CI)	90.8% (86.8~94.2)	85.9% (79.3~90.7)	98.1% (95.8~99.3)	P<0.0001
Specificity (95% CI)	96.7% (95.7~97.4)	93.7% (92.4~94.7)	91.5% (90.0~92.6)	P<0.0001
PPV (95% CI)	75.5% (69.5~80.6)	60.5% (53.1~64.8)	56.5% (51.2~61.7)	P<0.0001
NPV (95% CI)	98.9% (98.3~99.3)	98.3% (97.5~98.8)	99.8% (99.3~99.9)	P=0.0001

Notes: (A positive combined test indicates that the patient was TCT positive, HR-HPV positive or both were positive).
Abbreviations: TCT, ThinPrep cytologic test; HR-HPV, high-risk-human papillomavirus; PPV, positive predictive value, NPV, negative predictive value.

negative predictive value for CIN2+ cervical lesions (99.8%), and the difference was statistically significant (P = 0.0001). The specificity of the combined test for detecting CIN2+ cervical lesions was 91.5%.

An analysis of the diagnostic efficacy of TCT alone, HR-HPV alone, and combined TCT and HR-HPV screening for CIN2+ cervical lesions using ROC curves revealed that the combined screening had the largest area under the ROC curve (AUC) was for (0.9480), followed by TCT alone (0.9375) and HR-HPV testing alone (0.8980), as detailed in Figure 1.

When compared to TCT alone or HR-HPV alone, the combination of TCT with HR-HPV testing had the lowest rate of missed diagnoses for CIN2+ cervical lesions (1.9%), which was statistically significant ($P < 0.0001$), as presented in Table 4.

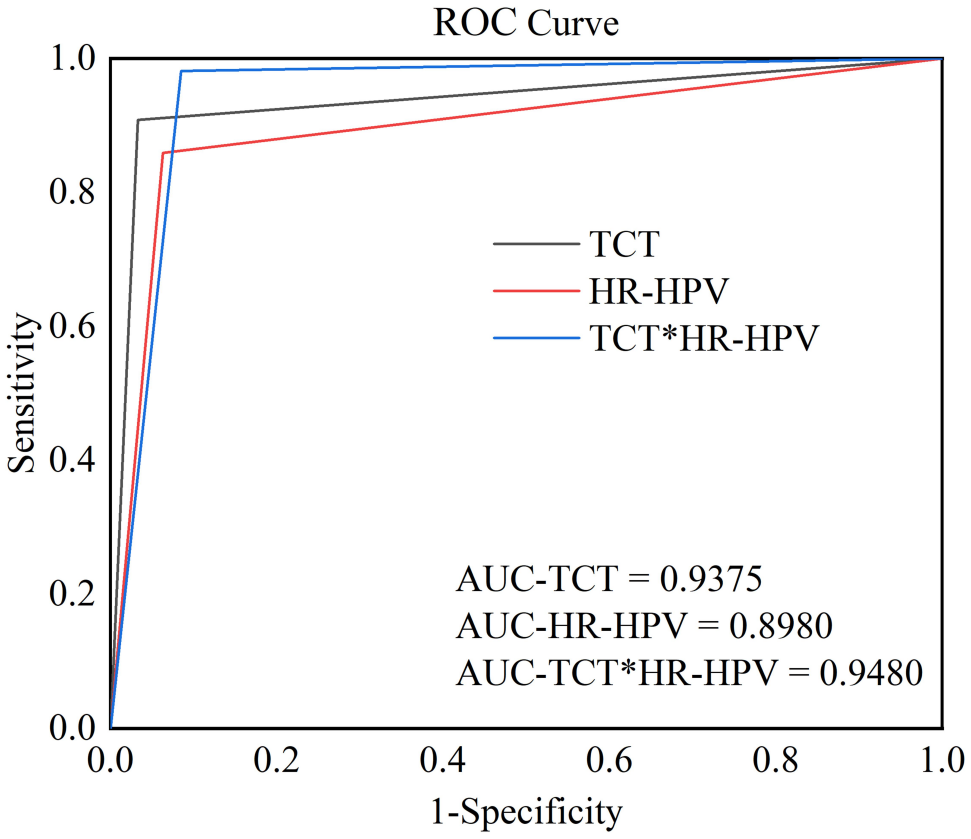

Figure 1 ROC curve of TCT, HR-HPV, and the combined screening of TCT and HR-HPV for the diagnosis of cervical lesions (≥ CIN II).
Notes: *means 'and'.
Abbreviations: TCT, ThinPrep cytologic test; HR-HPV, high-risk-human papillomavirus.

Table 4 The Missed Diagnosis Rate and Misdiagnosis Rate of TCT, HR-HPV Detection and Combined Detection of TCT and HR-HPV in Cervical Lesions (≥ CINII)

	TCT	HR-HPV	Combined	P Value
Missed diagnose rate (%)	9.2	14.0	1.9	P<0.0001
Misdiagnosis rate (%)	3.3	6.3	8.5	P<0.0001

Abbreviations: TCT, ThinPrep cytologic test; HR-HPV, high-risk-human papillomavirus.

Diagnostic Significance of HPV16 Ct Value and HPV18 Ct Value for CIN2+ Cervical Lesions

The HPV16 Ct values of infected patients varied significantly across all levels of cervical lesions ($P < 0.001$), as shown in Table 5. Patients in the CIN2+ cervical lesion group had the lowest median Ct value of HPV16 (26.00). There was no significant difference in the distribution of HPV18 Ct values among patients with varying degrees of cervical lesions. The Spearman's rank correlation test revealed a negative correlation between the Ct value of HPV16 and the severity of cervical lesions ($rs = -0.447$, $P < 0.001$).

An ROC curve was generated to quantitatively evaluate the diagnostic value of HPV16 Ct values for CIN2+ cervical lesions. As shown in Figure 2, the optimal threshold for HPV16 Ct values in diagnosing CIN2+ cervical lesions was 29.995. The AUC was 0.797 ($P < 0.0001$), with a sensitivity of 0.643 and a specificity of 0.817 at this threshold, indicating moderate diagnostic accuracy.

Discussion

Cervical cancer ranks as the most prevalent gynecological malignancy, with an age-standardized incidence of 13.35 cases per 100,000 individuals and a mortality rate of 6.51 cases per 100,000 individuals.[17] CIN is a spectrum of cervical lesions closely that serve as precursors to cervical cancer. While the majority of CIN I cases (approximately 60%) regress spontaneously, around 20% of CIN II lesions progress to CIN III, and about 5% of CIN III cases ultimately progress to invasive cervical cancer.[18] Therefore, prompt treatment is essential for all patients diagnosed with CIN II and CIN III. Early detection through effective screening of CIN II, CIN III, and cervical cancer is therefore crucial for reducing the incidence and mortality rates associated with cervical cancer.

HR-HPV (high-risk HPV) infection is a well-established driver of CIN and cervical cancer development.[11,19] Our study results corroborate this by showing that HR-HPV positivity rates in CIN II, CIN III, and cervical cancer were as high as 66.6%, 94.4%, and 85.2%, respectively. HR-HPV infection induces the production of viral oncoproteins, particularly E6 and E7, which disrupt host cell oncogenes P53 and Rb. This interference leads to their inactivation or degradation, initiating cellular abnormalities and triggering lesion formation in cervical tissues.[20,21] Current screening

Table 5 Relationships Between the Ct Values of HPV16 or HPV18 Infections and the Cervical Lesion Grade

HR-HPV type	Types of Cervical Lesions	n	Ct Value Median (Min–Max)	P Value
16(+)	Inflammation	38	31.90(22.00–37.47)	P<0.001
	CINI	5(1)	30.50(28.00–37.00)	
	≥ CINII	121(1)	26.00(14.00–36.00)	
18(+)	Inflammation	4	27.50(25.00–34.00)	P=0.440
	CINI	2	25.50(25.00–26.00)	
	≥ CINII	14(1)	30.38(17.00–34.00)	

Notes: (1) represents the number of missing Ct values.
Abbreviation: HR-HPV, high-risk-human papillomavirus.

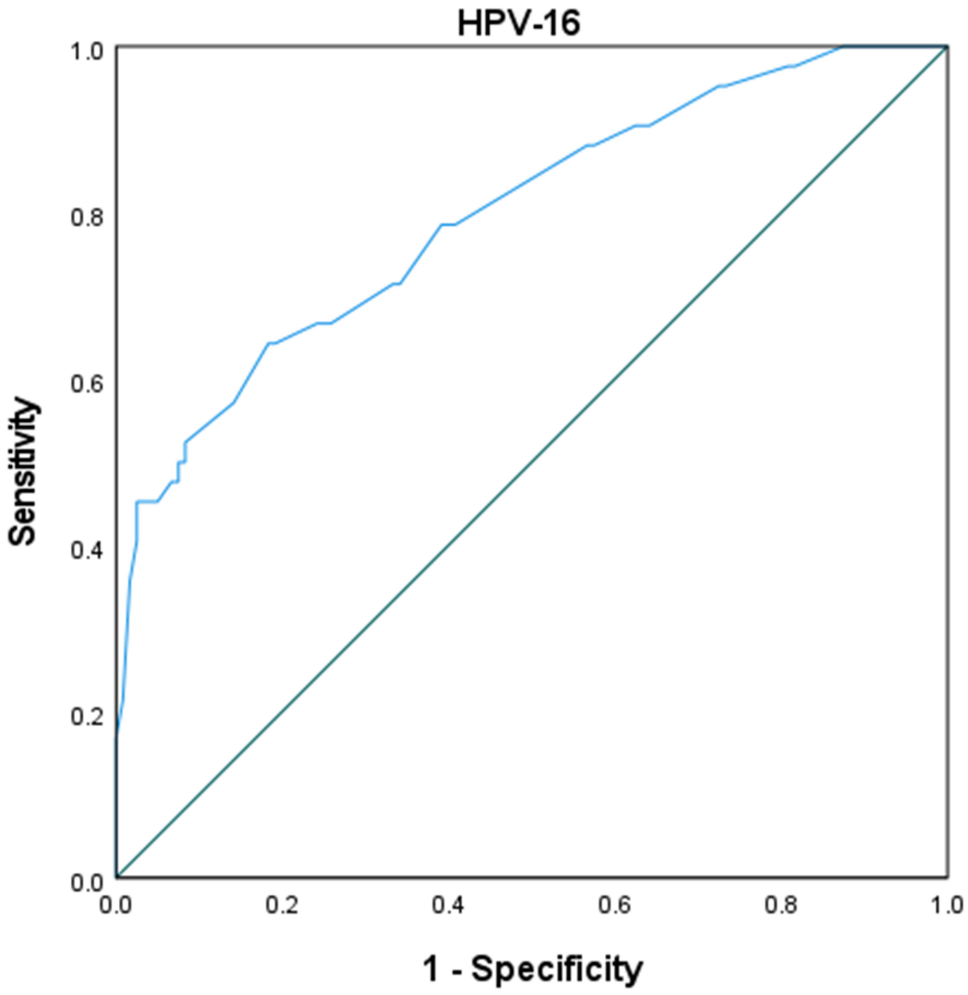

Figure 2 ROC curve of the diagnostic performance of HPV16 Ct values in identifying cervical intraepithelial lesions (≥ CIN II).

methods for CIN2+ cervical lesions (CIN II, CIN III, and cervical cancer) include TCT, HR-HPV, and a combination of both. However, there is no definitive evidence to establish the most effective screening approach for CIN2+ lesions.

TCT includes several steps in the screening process, such as sampling, cell section preparation, cell staining, and interpretation by a physician. Errors at any stage, as well as the physician's proficiency in interpreting the film, can directly impact the diagnostic accuracy of TCT, leading to a high false-negative rate.[22–24] Moreover, HR-HPV infection is often transient, with many infected individuals clearing the virus naturally over time. Only a small number of patients with persistent infections develop cervical lesions. Therefore, relying solely on HR-HPV testing as a screening method can result in a high false-positive rate. However, combined screening methods can compensate for the shortcomings of using either TCT or HR-HPV testing alone.

In our study, we found that the positivity rates of combined screening for the CIN II, CIN III, and cervical cancer groups were 94.5%, 100%, and 97.8%, respectively. These rates were significantly higher than the positivity rates in the CIN II, CIN III, and cervical cancer groups of TCT alone (83.3%, 87.0%, and 93.3%, respectively) or HR-HPV screening alone (66.6%, 94.4%, and 85.2%, respectively) for the same lesion groups. Moreover, combined screening had the highest sensitivity (98.1%) for detecting CIN2+ cervical lesions when compared with TCT alone or HR-HPV alone, and the difference was statistically significant, underscoring its superior diagnostic efficacy.

Additionally, the combined screening method also had the highest negative predictive value of 99.8% with a statistically significant difference and a specificity of 91.5%. A comparison of the missed diagnosis rates among the three approaches revealed that the combined screening for CIN2+ cervical lesions had the lowest rate (1.9%). The ROC

curve analysis used to evaluate the predictive performance of the three methods indicated that the combined detection had the largest AUC of 0.9480, reinforcing its superior predictive performance. These results suggest that the integration of TCT with HR-HPV testing may be the most effective strategy for screening CIN2+ cervical lesions.

HPV16 and HPV18 are recognized as the most carcinogenic high-risk HPV subtypes, comprising 50% of all detected subtypes in cervical cancer tissue, with HPV18 comprising about 14% of these cases.[25–28] Our study revealed that the combined positive rate for HPV16 and HPV18 among patients with cervical cancer was as high as 71.9%, with specific rates of 63.0% for HPV16 and 8.9% for HPV18. Previous studies have shown a correlation between specific HPV types and the pathological classifications of cervical cancer. For instance, the prevalence of HPV16 infection in cervical SCC is about 56%, while HPV18 infection rates in cervical adenocarcinoma are also around 56%.[29] In contrast, in our study, we observed that HPV16 accounted for 72.3% of cervical SCC cases, while HPV18 accounted for 41.2% of cervical adenocarcinoma cases. The discrepancy between these findings and previous studies can be attributed to potential sample bias in our study that included a small sample size (112 cases of cervical SCC and 17 cases of cervical adenocarcinoma out of 2035 patients).

A positive correlation between the viral loads of HPV16 and HPV18 and the severity of cervical lesions has been demonstrated in earlier research.[30] Our results that HPV16 was significantly associated with the severity of cervical lesions corroborate these findings, as evidenced by the lowest median Ct value of HPV16 observed in the CIN2+ cervical lesion group ($P < 0.001$). Spearman correlation analysis further confirmed a negative correlation between HPV16 Ct values and the grade of cervical lesions; specifically, lower Ct values indicate higher viral loads and more severe lesions. Additionally, ROC analysis established an optimal threshold of 29.995 for diagnosing CIN2+ cervical lesions based on HPV16 Ct values. Ct values below this threshold suggested a higher likelihood of CIN2+ cervical lesions.

However, we did not find a significant association between HPV18 Ct values and the severity of cervical lesions in this study. This may be attributed to the limited number of HPV18 infections (only 20 cases) that were included. Previous studies have similarly reported no significant correlation between HR-HPV viral load and cervical lesions, suggesting a complex interplay between these two aspects.[31,32] Some scholars have proposed that as cervical lesions progress in severity, the ability of diseased cells to replicate the virus may diminish, leading to the observed lack of correlation between HPV viral load and cervical lesions. In addition, the viral status—whether free, integrated, or in a mixed state—may affect this association; however, these viral status could not be clearly delineated in our study.

There are some limitations to our study. First, the retrospective nature of this study could have introduced potential selection bias, impacting the validity of the findings. Second, the sample size was relatively small, as it was drawn from a single center, and this may limit the generalizability of the results. Third, the study was restricted to data from a single institution. Consequently, these findings and conclusions are primarily applicable to women in northern China. To enhance the external validity and applicability of our results to diverse populations, future multicenter studies that are prospective in nature with large-sample studies are needed. Finally, the lack of repeated testing in our current analysis was another limitation. In future long-term follow-up studies, we aim to collect multiple HPV testing results from patients to determine whether HPV infections are transient or persistent, thereby improving the predictive value of our findings.

Conclusion

Our findings in this study showed that the combination of TCT and HR-HPV screening was the most effective screening method for detecting CIN2+ cervical lesions. The Ct value of HPV16 was negatively correlated with the severity of cervical lesions; that is, lower Ct values corresponded to higher viral loads and more severe lesions. Notably, when the Ct value of HPV16 was below 29.995, it indicated a greater likelihood of CIN2+ lesions.

Abbreviations

ACS, American Cancer Society; HPV, human papillomavirus; HR-HPV, high risk-human papillomavirus; CIN, cervical intraepithelial neoplasia; PCR, Polymerase Chain Reaction; Ct, Cycle threshold; TCT, ThinPrep cytologic test; NILM, no intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; AGUS/NOS, atypical glandular cells of undetermined significance or not otherwise

specified; ASC-H, atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AIS, adenocarcinoma in situ; SCC, squamous cell carcinoma; WHO, World Health Organization; ROC, receiver operating characteristic; AUC, area under the ROC curve.

Data Sharing Statement

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author (Nai-Yi Du) on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. The study was approved by the Institutional Human Ethics Committee of the Fourth Hospital of Hebei Medical University (No. 2020KY266). All patients provided prior informed consent for participating in the study.

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Disclosure

None of the authors have any financial disclosure or conflict of interest.

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