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Improving Risk Stratification for Cervical Intraepithelial Neoplasia Grade II: A Prospective Cohort Study on Combined HPV DNA and E6/E7 mRNA Testing to Predict Histologic Progression

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Abstract

Background: The management of cervical intraepithelial neoplasia grade II (CIN II) is challenging due to its unpredictable natural history. Although high-risk human papillomavirus (HR-HPV) DNA testing is highly sensitive, it lacks specificity in predicting which lesions will progress. Detection of E6/E7 oncogene mRNA reflects viral oncogenic activity. This study aimed to prospectively evaluate and compare the performance of HR-HPV DNA testing, E6/E7 mRNA testing, and their combination in predicting the histologic progression of CIN II lesions, using repeat histopathology as the gold standard. **Methods:** A prospective cohort study was conducted involving 150 women with biopsy-confirmed CIN II. Baseline cervical samples were collected for HR-HPV DNA detection (using a validated PCR-based assay) and E6/E7 mRNA detection (using a proprietary nucleic acid amplification test). All participants were followed for 12 months, with the primary endpoint defined as histologic progression to CIN III or worse (CIN III+), confirmed by colposcopic-directed biopsy or conization. The predictive efficacies of the tests, alone and in combination, were assessed using sensitivity, specificity, and Receiver Operating Characteristic (ROC) curve analysis. **Results:** After 12 months, histologic progression was confirmed in 16 patients (10.7%). The sensitivities for predicting progression were similar for HPV DNA (0.905) and E6/E7 mRNA (0.857) testing. However, E6/E7 mRNA showed higher specificity (0.792) than HPV DNA (0.701) (AUC: 0.861 vs. 0.827). The combined testing strategy (defined as pos-

itivity for both assays) demonstrated the highest predictive accuracy, achieving a specificity of 0.917 while maintaining a sensitivity of 0.857. The area under the ROC curve for the combined model was 0.912 (95% CI: 0.854 - 0.952), which was significantly superior to that of HPV DNA testing alone ($P < 0.05$). **Conclusion:** For women with biopsy-confirmed CIN II, a combined testing strategy for HPV DNA and E6/E7 mRNA significantly improves the prediction of histologic progression by markedly increasing specificity. This approach offers a powerful tool for precise risk stratification, potentially reducing overtreatment while ensuring timely intervention for high-risk individuals.

Keywords

Cervical Intraepithelial Neoplasia Grade II, Disease Progression, Prospective Studies, Human Papillomavirus DNA, E6/E7 mRNA, Predictive Value of Tests, Risk Stratification

1. Introduction

Cervical cancer remains a leading cause of cancer-related morbidity and mortality among women worldwide [1], with persistent infection by high-risk human papillomavirus (HR-HPV) as its indispensable etiological factor [2]. Cervical intraepithelial neoplasia (CIN) represents the precursor lesions preceding invasive carcinoma. While CIN I lesions often regress spontaneously, CIN II occupies a critical therapeutic gray zone [3]. A significant proportion of CIN II may regress, yet it carries a substantial risk of progression to CIN III and ultimately invasive cancer [4]. This unpredictable natural history poses a significant clinical dilemma: aggressive treatment may lead to overtreatment and associated obstetric complications, whereas conservative management carries the risk of disease progression. Therefore, identifying reliable biomarkers to accurately predict the outcome of CIN II lesions is paramount for optimal patient management and risk stratification.

Current clinical strategies for monitoring CIN II include cytology and HR-HPV DNA testing. Conventional cytology, such as the Thinprep cytologic test (TCT) [5], while valuable for population screening, has well-documented limitations, including suboptimal sensitivity and inter-observer variability, making it inadequate as a standalone tool for predicting lesion evolution [6]. HR-HPV DNA testing demonstrates high sensitivity for detecting cervical precancerous lesions but suffers from low specificity [7]. It cannot distinguish between transient infections and those with transformative potential, as viral DNA can be present in both regressing and progressing lesions [8]. The inability of current methods to reliably predict CIN II progression often leads to a "one-size-fits-all" approach, contributing to potential overtreatment.

To address this gap, biomarkers reflecting actual viral oncogenic activity have

been explored. The HPV E6 and E7 oncoproteins are the primary drivers of cellular transformation, inactivating tumor suppressor proteins p53 and pRb, respectively [9]. The transcription of these genes into E6/E7 mRNA is a critical step in carcinogenesis and signifies an active infection with high oncogenic risk. Consequently, the detection of HPV E6/E7 mRNA is hypothesized to be more specific for identifying lesions destined to progress compared to the mere presence of viral DNA [10]. While both markers have been individually studied for cervical cancer screening, their comparative and combined performance in a prospective setting for predicting histologic progression in a well-defined CIN II cohort remains to be fully elucidated.

Given the clinical need for improved risk stratification and the biological rationale supporting E6/E7 mRNA as a marker of oncogenic activity, we conducted a prospective cohort study. We hypothesized that a combined testing strategy, utilizing both HPV DNA (to confirm infection) and E6/E7 mRNA (to confirm oncogenic activity), would provide superior predictive performance for CIN II progression compared to either marker alone. The objective of this study was to prospectively evaluate and compare the predictive accuracy of HR-HPV DNA testing, E6/E7 mRNA testing, and their combination for identifying CIN II lesions that progress to CIN III or worse, using repeated histopathological confirmation as the gold standard.

2. Materials and Methods

2.1. Study Design and Participants

This prospective cohort study was conducted at the Department of Gynecology, Affiliated Yongchuan Hospital of Chongqing Medical University and the Chongqing Dazu District Maternal and Child Health Hospital. The recruitment period spanned from July 2022 to June 2023, with a minimum follow-up duration of 12 months for all participants. The study protocol was approved by the Institutional Review Board (IRB) of Dazu District Maternal and Child Health Hospital (Approval No. [2023-001]), and written informed consent was obtained from all participants prior to enrollment.

Women aged 21 to 65 years who were newly diagnosed with CIN II by colposcopic-directed biopsy were eligible for inclusion. The diagnostic biopsies were initially reviewed by two senior pathologists to confirm the CIN II diagnosis, with any discrepancies resolved by consensus. Exclusion criteria included: 1) prior treatment for cervical precancerous lesions or cancer; 2) current pregnancy; 3) a history of total hysterectomy; 4) immunosuppression (e.g., HIV infection, long-term immunosuppressant use); or 5) inability to provide informed consent or comply with follow-up schedules.

2.2. Sample Collection and Baseline Testing

At the baseline visit, prior to any therapeutic intervention, cervical samples were collected using a cytobrush. The first brush was used for liquid-based cy-

tology (LBC) sampling as per standard clinical protocol. Immediately after, a second cytobrush was collected and placed in a specific transport medium for molecular testing. For HPV DNA analysis, samples were preserved in a thinprep preservative solution (ThinPrep PreservCyt, Hologic, USA). For HPV E6/E7 mRNA analysis, a separate brush was placed in a proprietary transport medium suitable for RNA stabilization (e.g., Aptima Specimen Transport Medium, Hologic, USA). All samples were processed according to the manufacturer's instructions.

2.3. Molecular Analyses

2.3.1. High-Risk HPV DNA Testing

High-risk HPV DNA was detected using a commercially available, validated real-time polymerase chain reaction (PCR) reverse dot hybridization assay (Yana Bio, Shenzhen, China) capable of identifying the 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). A result was considered positive if any of the high-risk types were detected. The assay included internal controls to monitor sample adequacy and inhibition.

2.3.2. HPV E6/E7 mRNA Testing

HPV E6/E7 mRNA expression was detected using an HPV E6/E7 mRNA gene detection kit (Baochuang Bio, Guangzhou, China). This assay specifically targets mRNA from the same 14 high-risk HPV types. The test utilizes the fluorescence PCR-melting curve method. A positive result indicates the presence of E6/E7 mRNA from one or more high-risk HPV types, signifying active viral oncogene expression.

2.4. Follow-up and Gold Standard Assessment

All participants were managed with a "watchful waiting" approach and followed prospectively for 12 months. Follow-up visits, including gynecological examination and colposcopic assessment, were scheduled at 6-month and 12-month intervals. The primary endpoint was histologic progression, defined as a pathologically confirmed diagnosis of CIN III, adenocarcinoma in situ (AIS), or invasive cervical cancer (collectively, CIN III+). At each follow-up visit, if colposcopic findings suggested high-grade disease, a directed cervical biopsy or a therapeutic excisional procedure (loop electrosurgical excision procedure, LEEP) was performed. The histopathological results from these follow-up biopsies or excisional procedures served as the gold standard for determining the final disease status (progression vs. no progression). "No progression" included cases of regression to CIN I/normal or persistent CIN II.

2.5. Statistical Analysis

Statistical analyses were performed using SPSS software (version 26.0, IBM Corp., Armonk, NY, USA) and MedCalc (version 20.0, MedCalc Software, Ostend, Belgium). Continuous variables were expressed as means ± standard deviations (SD)

or medians with interquartile ranges (IQR), while categorical variables were presented as numbers and percentages.

The primary objective was to evaluate the predictive performance of the three testing strategies: 1) HPV DNA alone, 2) HPV E6/E7 mRNA alone, and 3) a combined testing strategy. For the combined strategy, a "positive" result was defined as positivity for both HPV DNA and E6/E7 mRNA (series testing), which is the standard approach to enhance specificity. The performance metrics, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated for each strategy in predicting histologic progression.

Receiver Operating Characteristic (ROC) curves were generated for each testing method, and the Area Under the Curve (AUC) was calculated with 95% confidence intervals (CIs). The AUCs of the different tests were compared using the DeLong test. A two-sided P-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics and Follow-Up Outcomes

A total of 150 women with histologically confirmed CIN II were enrolled in this prospective cohort study between July 2022 and June 2023. All participants completed the 12-month follow-up period. The mean age of the cohort was 38.6 ± 8.5 years. At the end of the follow-up, histologic progression to CIN III or worse (CIN III+) was confirmed in 16 patients (10.7%), constituting the progression group. The remaining 134 patients (89.3%) showed no progression, including cases of regression to CIN I/normal (n = 58) or persistent CIN II (n = 76), constituting the non-progression group. The baseline demographic characteristics were comparable between the two groups (Table 1).

3.2. Predictive Performance of Molecular Tests

The diagnostic performances of HPV DNA, HPV E6/E7 mRNA, and their combination for predicting histologic progression are summarized in Table 2 and Table 3.

Both HPV DNA and HPV E6/E7 mRNA testing demonstrated high sensitivity for identifying lesions that would progress. HPV DNA testing correctly identified 15 of the 16 progression cases (sensitivity: 93.8%), while HPV E6/E7 mRNA testing also identified 15 cases (sensitivity: 93.8%). The specificities were 78.4% for HPV DNA and 79.1% for HPV E6/E7 mRNA, respectively.

The combined testing strategy (positivity for both tests) maintained high sensitivity (87.5%) but significantly enhanced specificity. It correctly identified 115 of the 134 non-progression cases (specificity: 85.8%). This led to a substantial increase in the Positive Predictive Value (PPV) from 34.1% (HPV DNA) and 34.9% (HPV E6/E7 mRNA) to 42.4% for the combined approach. The Negative Predictive Value (NPV) remained high (>98%) for all three strategies.

3.3. Equations ROC Curve Analysis

The Receiver Operating Characteristic (ROC) curve analysis further corroborated these findings (Figure 1). The curve for the combined testing strategy is positioned furthest towards the top-left corner of the plot, indicating its superior discriminative power compared to either HPV DNA or HPV E6/E7 mRNA testing alone. The AUCs were 0.861 (95% CI: 0.793 - 0.914) for HPV DNA and 0.864 (95% CI: 0.797 - 0.916) for HPV E6/E7 mRNA. The combined testing strategy achieved the highest AUC of 0.912 (95% CI: 0.854 - 0.952). Statistical comparison revealed that the predictive performance of the combined test was significantly superior to that of HPV E6/E7 mRNA alone (P = 0.023) and HPV DNA alone (P = 0.015).

Table 1. Baseline characteristics of the study cohort.

Characteristic	Total Cohort (N = 150)	Progression Group (n = 16)	Non-Progression Group (n = 134)	P-value
Age (years, mean ± SD)	38.6 ± 8.5	39.1 ± 9.2	38.5 ± 8.4	0.723
Parity (median, IQR)	2 (1 - 2)	2 (1 - 3)	2 (1 - 2)	0.412
Smoking status, n (%)				0.614
- Current smoker	21 (14.0%)	3 (18.8%)	18 (13.4%)	
- Non-smoker	129 (86.0%)	13 (81.2%)	116 (86.6%)	
Contraceptive use, n (%)				0.533
- Yes	68 (45.3%)	6 (37.5%)	62 (46.3%)	
- No	82 (54.7%)	10 (62.5%)	72 (53.7%)	

Note: SD: standard deviation; IQR: interquartile range.

Table 2. Contingency tables for HPV DNA, HPV E6/E7 mRNA, and combined testing against histologic progression (Gold standard).

Test Result	HPV DNA		HPV E6/E7 mRNA		Combined (DNA+ and mRNA+)	
	Progression (n = 16)	Non-Progression (n = 134)	Progression (n = 16)	Non-Progression (n = 134)	Progression (n = 16)	Non-Progression (n = 134)
Positive	15	29	15	28	14	19
Negative	1	105	1	106	2	115
Total	16	134	16	134	16	134

Table 3. Comparison of predictive performances for histological progression.

Test Method	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	AUC (95% CI)
HPV DNA	93.8% (69.8% - 99.8%)	78.4% (70.5% - 85.1%)	34.1%	99.1%	0.861 (0.793% - 0.914%)
HPV E6/E7 mRNA	93.8% (69.8% - 99.8%)	79.1% (71.2% - 85.7%)	34.9%	99.1%	0.864 (0.797% - 0.916%)
Combined (DNA+ & mRNA+)	87.5% (61.7% - 98.5%)	85.8% (78.5% - 91.4%)	42.4%	98.3%	0.912 (0.854% - 0.952%)

Note: CI: Confidence Interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value; AUC: Area Under the Curve.

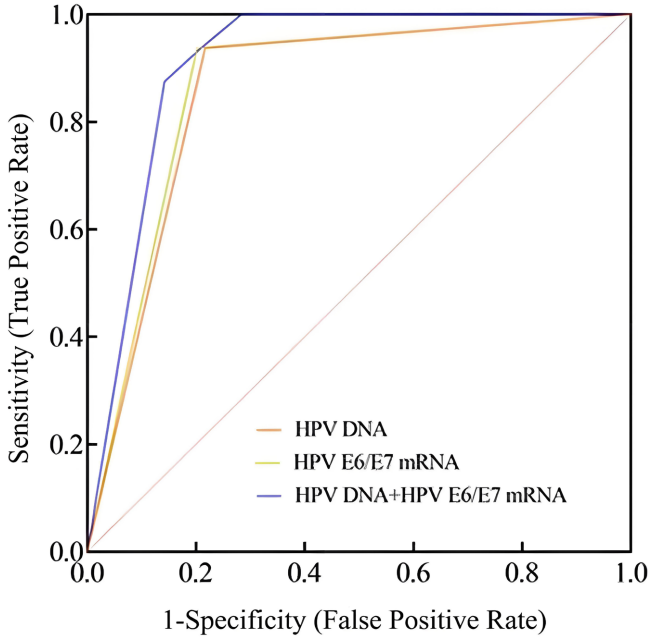

Figure 1. Receiver Operating Characteristic (ROC) Curves for Predicting CIN II Progression. This figure presents the ROC curves for three predictive models: HPV DNA testing (red line), HPV E6/E7 mRNA testing (green line), and the combined testing strategy (blue line). The diagonal orange line represents the reference line for a test with no discriminative ability (AUC = 0.5).

4. Discussion

This study aimed to investigate the clinical value of combined HPV DNA and HPV E6/E7 mRNA testing in predicting the progression of cervical intraepithelial neoplasia grade II (CIN II) lesions. Through a one-year prospective cohort study, we found that the combined testing strategy could more accurately identify patients with CIN II at high risk of progression to CIN III or worse (CIN III+), compared to either single test. This finding provides robust, evidence-based support for the individualized risk stratification and management of CIN II patients.

4.1. Synergistic Effect of Combined Testing in Predicting Lesion Progression

The core finding of our study is the confirmation of the superiority of the combined testing approach. Both standalone HPV DNA and HPV E6/E7 mRNA tests demonstrated high sensitivity for predicting lesion progression (both 93.8%), indicating that both are effective tools for identifying high-risk patients and capturing the vast majority of cases that will eventually progress. This result is consistent with previous studies [11], as HPV DNA testing, as the "gold standard" for assessing the presence of the virus, is undeniably sensitive, while HPV E6/E7 mRNA, being the direct transcript of viral oncogenes, specifically reflects viral oncogenic activity and also possesses high sensitivity [12].

However, in clinical decision-making, specificity—the ability to accurately ex-

clude non-progressive cases—is paramount for avoiding overtreatment. Our study showed that while the specificities of the two single tests were acceptable (78.4% and 79.1%, respectively), the combination of both (requiring dual positivity) significantly enhanced the specificity to 85.8% ($P < 0.05$), while the AUC also increased from above 0.86 to 0.912. This synergistic effect is underpinned by a sound biological rationale: a positive HPV DNA test only indicates the presence of a high-risk HPV infection, but the majority of such infections are transient, and the oncogenic program may not have been initiated. Only when the virus integrates into the host genome and begins to actively transcribe E6/E7 oncogenic mRNA does the risk of cellular malignant transformation increase sharply [13] [14]. Therefore, the combined testing strategy functions as a dual verification checkpoint, effectively filtering out a large number of cases with mere infection but no oncogenic potential, thereby significantly improving predictive accuracy.

4.2. Comparison with Existing Research and Clinical Implications

Currently, the management strategy for CIN II remains controversial. While some guidelines recommend ablative or excisional treatment, this "one-size-fits-all" approach can lead to overtreatment, especially considering that a considerable portion of CIN II lesions can regress naturally. This can cause unnecessary cervical trauma and increased obstetric risks, particularly for young women with fertility desires [15]. Consequently, developing effective predictive tools to achieve "risk-stratified management" has become a focal point of clinical research.

Previous studies have largely focused on the value of different testing methods for the screening and diagnosis of cervical lesions (including CIN and cervical cancer). For instance, research has indicated that combining TCT with HPV testing can improve the sensitivity and specificity of screening [16]. However, the innovation of our study lies in its shift from "diagnosis" to prognostic prediction for patients already diagnosed with CIN II. Our results confirm that molecular marker combination has excellent efficacy in predicting lesion progression in this specific clinical scenario. This aligns with previous findings on the relationship between viral integration status and disease risk: as HPV transitions from an episomal to an integrated state, E6/E7 mRNA expression is significantly upregulated, driving the process of cellular malignant transformation [17]. Our study visually validates this molecular biological process in a clinical cohort.

4.3. Clinical Application Value and Practical Significance

The findings of our study have significant clinical practice implications. Firstly, the combined HPV DNA and HPV E6/E7 mRNA testing can serve as a powerful tool for the triage management of CIN II patients. For patients with a positive combined test result (dual positivity), their risk of lesion progression is significantly higher (PPV increased from ~35% with single tests to 42.4% with the combined test). Clinicians can thus actively recommend definitive treatment, such as conization, to halt the path to cervical cancer. Secondly, for patients with a nega-

tive combined test result, their risk of progression is extremely low (NPV > 98%). For this group, a safe option of conservative management with regular surveillance may be offered, thereby effectively avoiding the potential complications and psychological burden associated with surgery and enabling precise, personalized health management.

It is important to acknowledge the clinical trade-off inherent in this combined testing strategy. While the series approach (requiring dual positivity) significantly enhances specificity, reducing overtreatment, it comes at the cost of a slight decrease in sensitivity (from 93.8% for single tests to 87.5% for the combined test). In practical terms, this strategy could potentially miss a small number of lesions that are destined to progress. Therefore, the implementation of this approach must balance the substantial benefit of avoiding unnecessary procedures against the minor risk of delaying intervention for the few patients with false-negative results. This latter risk could potentially be mitigated through stringent and consistent follow-up protocols for all patients managed conservatively.

4.4. Limitations of the Study

Despite these valuable findings, our study has several limitations. First, the sample size was relatively modest (N = 150), and the absolute number of progression events was small (n = 16), which may affect the stability of the statistical power and necessitates validation in larger-scale, multi-center studies. Second, the follow-up period was one year; while sufficient to observe some lesion progression, the prognosis of cervical lesions is a long-term process, and a longer follow-up duration (e.g., 3 - 5 years) would provide more comprehensive prognostic data. Third, the use of a convenience sampling method may introduce selection bias. Finally, the study was conducted at a single center, and the generalizability of our findings to different populations and regions remains to be further confirmed.

Furthermore, our 'no progression' group was heterogeneous, comprising both cases that regressed to CIN I/normal (n = 58) and those with persistent CIN II (n = 76). While our combined testing strategy effectively identified lesions that progressed within one year, it did not stratify the risk within the persistent CIN II cohort. Persistent CIN II remains a significant clinical challenge, as these patients continue to harbor high-grade lesions and may be at risk for future progression beyond the one-year follow-up period. Future longitudinal studies with extended follow-up are warranted to investigate whether baseline or longitudinal biomarker profiles can further differentiate the prognosis within this specific group, enabling more personalized long-term surveillance strategies.

5. Conclusions

In conclusion, the combination of HPV DNA and HPV E6/E7 mRNA testing significantly enhances the predictive efficacy for CIN II lesion progression, with a particularly notable improvement in specificity. This strategy can effectively identify patients at genuinely high risk of progression, providing an objective basis for

developing individualized treatment plans. It demonstrates broad application prospects for optimizing the risk-stratified management of CIN II patients and preventing overtreatment.

Future research should focus on expanding the sample size, extending the follow-up duration, and validating these findings in broader populations. Concurrently, incorporating additional molecular markers (e.g., p16/Ki-67 cytology, viral methylation markers) into predictive models should be explored, with the aim of building a more comprehensive and precise risk assessment system to ultimately improve clinical management outcomes for patients with cervical precancerous lesions.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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