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## ORIGINAL ARTICLE

# Application Value of Detection of High-Risk HPV Infection in Early Cervical Cancer Patients in Disease Diagnosis and Prognosis Evaluation

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### SUMMARY

***Background:*** **To analyze the relationship between HPV infection and early cervical cancer and postoperative survival outcomes.**
***Methods:*** **A total of 556 women were recruited to receive TCT and HPV tests from October 2017 to October 2018. The type of disease was pathologically diagnosed. The HPV positive rate, HPV-DNA, and E6/E7 mRNA quantitative level were detected, and the diagnostic accuracy of the subjects was analyzed by the receiver operating characteristic (ROC). The cervical intraepithelial neoplasia (CIN) and early cervical cancer patients were radically cured and followed up for 12.0 months to analyze the recurrence rate.**
***Results:*** **Seventy-two cases of chronic cervicitis, 54 cases of CIN, and 51 cases of cervical cancer patients were pathologically diagnosed (32 cases in early stage and 19 cases in middle and late stage). HPV positive rate increased gradually in chronic cervicitis, CIN, and cervical cancer group ($p < 0.001$) and HPV 16 + 18 subtype. The positive rate was significantly different ($p = 0.009$). HPV-DNA and E6/E7 mRNA quantification also showed significant differences ($p < 0.001$). ROC analysis indicated that the accuracy of HPV-DNA and E6/E7 mRNA quantitative diagnosis of malignant lesions (CIN+ cervical cancer) were 0.865 and 0.879, respectively. There were 4 cases (7.41%) of recurrence in CIN group and 5 cases (15.63%) in early cervical cancer group. There was no difference ($p = 0.401$) among all of the patients. All patients with recurrence were HPV positive.**
***Conclusions:*** **HPV detection is an indispensable screening method for early cervical cancer and precancerous lesions, and comprehensive HPV 16 and 18 subtypes. DNA and E6/E7 mRNA quantification assay would further improve the accuracy of screening.**
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**KEY WORDS**

cervical cancer, precancerous lesions, high-risk human papillomavirus, liquid-based TLC cytology, colposcopy

### INTRODUCTION

Cervical cancer has become one of the major malignant tumors in women worldwide. The age of onset has shifted from post-menopausal to child-bearing age. Persistent human papillomavirus (HPV) infection is the most important risk factor for the occurrence and progression of cervical adenocarcinoma [1]. Research [2]

has indicated that the HPV 16 and 18 subtypes have a high positive rate in high-grade squamous intraepithelial lesions (HSIL) and more severe lesions (HSIL+) and are closely related to the occurrence of cervical cancer, but no further association has been observed with tumor TNM staging, differentiation grade, lymph node metastasis etc. HPV detection including HPV DNA qualitative and quantitative assays, E6/E7 mRNA quantitative assay, combined with thinprep cytologic test (TCT) in screening early cervical cancer patients at high risk, reasonable shunt and referral to receive colposcopy biopsy pathological diagnosis, cervical cancer screening, and primary prevention are the main measures to improve early cervical cancer diagnosis, improve postoperative survival outcome, which are of great importance [3,4]. Lei J et al. [5] evaluated the screening and risk of adeno-squamous carcinoma of endometrium (ASC) and rare invasive cervical cancer (RICC): A population - based nested case - control study found 4,254 cases of invasive cervical cancer in Sweden from 2002 to 2011 of which 338 were neither squamous cell carcinoma nor adenocarcinoma, 164 were ASC, and 174 were matched in 30 general Swedish population. Compared with non-screening groups, the screened women had lower risk of developing ASC (OR = 0.22, 95% CI = 0.14 ~ 0.34) and RICC (OR = 0.34, 95% CI = 0.21 - 0.55); high-risk human papillomavirus was detected in 148/211 (70%) tumor tissues, and women with virus positive (OR = 0.28,95% CI = 0.18 - 0.46) and negative (OR = 0.27, 95% CI = 0.13 - 0.59) were at lower risk compared with those without any test. Cervical screening was thought to be associated with reduced ASC and RICC risk, and most ASC and RICC were positive for high-risk human papillomavirus.

Zafari E et al. [6] compared low-risk and high-risk human papillomavirus E6 gene promoter methylation patterns and found that high-risk and low-risk HPV-E6 promoter methylation states are different. CpG dinucleotides are not methylated in both type 16 and type 18 target sequences, while in HPV-E6 type 11 target sequences all but one CpG dinucleotides are methylated. It is speculated that the methylation status is significantly correlated with the occurrence of HPV-induced cervical cancer, and the HPV 16 and 18E6 promoters have a low degree of methylation.

Based on the above-mentioned information, the study analyzed the association of high-risk HPV infection with early cervical cancer and evaluated the application value of postoperative survival outcomes by summarizing the strict implementation of the cervical cancer screening process in our center.

## MATERIALS AND METHODS

### Target information

A total of 556 women were selected for TCT and HPV testing in our hospital from October 2017 to October 2018, age from 23 to 65 with an average of 44.5 ± 12.3 years. Premenopausal 328, postmenopausal 228, pregnancy 0 to 3, average (1.1 ± 0.4), birth 0 to 1, average (0.5 ± 0.2), first sexual life age from 19 to 26, average was 23.3 ± 3.4 years.

Inclusion criteria: 1. Age 18 - 65; 2. Healthy, no history of reproductive urological surgery and no history of malignant tumors; 3. Acceptance of the complete screening process of this study, data completion.

Exclusion criteria: 1. Complicated infection, abnormal liver and kidney function; 2. Pregnancy or lactation; 3. Infertility; 4. Diseases of the genitourinary system, or being treated with corresponding drugs.

### Screening process

Before screening and signing the informed consent, we carefully explained the screening process. The tests were performed within a week after menstruation, with 10 experienced examiners completing the sample collections from 556 women. Three other experienced pathologists independently judged the results. Two other statisticians completed the data entry, comparison, and statistical analysis. From each subject cervical exfoliated cells were collected as specimens to complete the TCT and HPV tests. Every case with positive results was recommended for further pathological diagnosis via colposcopy biopsy.

### Sample collection

Fully expose the cervix, swab secretion with cotton swab, slowly insert the center of the brush into the cervix tube, turn the brush clockwise for 5 rounds, remove the brush head and place it in SurePath. Specimen requirements: Minimum cell volume of 5,000 well-preserved and well-formed squamous cells, at least 10 preserved cervical epithelial cells or metaplastic cells.

### TCT production and analysis

According to the Standard Commercialized Liquid Based Production System (Sigma, USA) and the International Cancer Society recommended TBS (The Bethesda system), the classification is divided into the groups including normal range, inflammation, atypical squamous cells of undetermined significance (ASC-US), of atypical squamous cells without excluding high-grade intraepithelial neoplasia (ASC-H), low-grade squamous intraepithelial lesion (SIL), high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma (SCC). ASC-US and more severe lesions were defined as TCT positive.

### HPV test

Aptima HPV 16/18 typing test used the human papillomavirus test kit provided by HOLOGIC, USA, using the capture hybridization method to detect the amplification products by target capture, transcription amplification, and hybridization protection reaction. According to the ratio of analyte signal to threshold (S/CO), 14 subtypes, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68, were positive for DNA quantifi-

cation > 1. HPV e6/e7mrna was tested using a kit provided by Guangzhou Anpiping Pharmaceutical Technology Co., Ltd. The PCR-reverse point hybridization method was used to design specific primers and type 28 probes in the L1 region of the late stage of human papillomavirus genome with mRNA quantification > 1 as positive.

**Colposcopy pathological examination**
Cervical biopsy tissues were processed by the steps including formalin fixation, gradient alcohol dehydration, xylene transparent, wax immersion, paraffin embedding, sections and hematoxylin-eosin (HE) staining, and optical microscope observation. The pathological results were divided into normal or inflammation, LSIL, HSIL, and SCC.

**Recurrence comparison**
CIN and early cervical cancer patients underwent radical surgery, intraoperative and postoperative pathological margin confirmed negative, no lymph node metastasis.

**Statistical methods**
SPSS20.0 software was applied for statistical analysis. The measurement data were expressed as mean ± standard deviation. Single factor ANOVA analysis was used for multi-group comparison. LSD-t method was used for comparison between the two groups, and the counting data were expressed as case number (%) and $\chi^2$ test. Colposcopy pathological results were used as diagnostic criteria to evaluate the accuracy, sensitivity, specificity, positive predictive value and negative predictive value of HPV positive for cervical malignant lesions (CIN plus cervical cancer). HPV-DNA quantification and e6/e7 mRNA quantification were used as diagnostic indicators. The receiver operating characteristic curve (ROC) analysis was used to determine the accuracy (area under the curve (AUC) value), sensitivity, and specificity of cervical malignant lesions. $p< 0.05$ showed a difference that was statistically significant.

## RESULTS

**Initial screening results**
Of the total 556 cases, 141 cases (25.36%) were TCT positive, 153 cases were HPV positive (27.52%), 89 cases were TCT plus HPV positive (16.01%), 72 cases were chronic cervicitis confirmed by colposcopy, 54 cases of CIN (24 cases of grade II, 30 cases of grade III), 51 cases of cervical cancer (32 cases in early stage and 19 cases in late stage). See Figure 1.

**HPV positive, DNA, and E6/E7 mRNA quantification in patients between groups**
The positive rate of HPV increased gradually between groups of chronic cervicitis, CIN, and cervical cancer ($\chi^2 = 25.069$, $p < 0.001$), HPV 16 and 18 subtypes. There was no significant difference in the positive rate ($\chi^2 = 3.626$, $p = 0.16$; $\chi^2 = 4.612$, $p = 0.100$), but 16 + 18 subtypes indicated significant difference in positive rate ($\chi^2 = 9.427$, $p = 0.009$). Quantitative comparison of HPV-DNA and E6/E7 mRNA showed significant difference ($F = 12.326$, $p < 0.001$; $F = 10.524$, $p < 0.001$). See Table 1.

**The value of 2.2 HPV positive predictive cervical malignant lesions**
CIN plus cervical cancer was classified as malignant lesions. Using colposcopy as the diagnostic criteria, the correct rate of HPV positive was 58.19% (103/177), sensitivity 87.62% (92/105), specificity 15.28% (11/72), positive predictive value 60.13% (92/153), and negative predictive value 45.83% (11/24). See Table 2.

**Value of HPV-DNA and E6/E7 mRNA in quantitative diagnosis of malignant cervical lesions**
The accuracy of inclusion of HPV-DNA in ROC analysis was as follows: accuracy 0.865, sensitivity 86.5, and specificity 82.4%. The accuracy of the diagnostic index using E6/E7 mRNA quantification is accuracy 0.879, sensitivity 90.3%, and specificity 86.5%. See Tables 3 and 2.

**Comparison of postoperative recurrence of CIN and early cervical cancer**
There were 4 cases of recurrence in the CIN group (7.41%, 4/54) and 5 cases in the early cervical cancer group (15.63%, 5/32) after 12.0 months of routine follow-up. $\chi^2 = 0.704$, $p = 0.401$), all patients with recurrence were HPV positive (Table 4).

## DISCUSSION

To date, HPV has been confirmed to have more than 180 antigenic types (i.e., subtypes) and 10 high-risk types, including 16, 18, 58, 52, 31, 33, and 45, among which HPV 16 and 18 are most closely related to cervical cancer [7]. The HPV genome consists of 7,900 bp, fully-enclosed, double-stranded, circular DNA molecules. The process by which a virus changes from a transient infection to a persistent infection in a host cell inducing cervical cancer may be caused by the integration of viral DNA into the host genome and the destruction of its own genome and host chromosome structure [8]. Ratshapeng P et al. [9] revealed that among the 185 cervical biopsy tissues collected, HSIL (n = 146) and squamous cell carcinoma (n = 39), from 2006 to 2008. Tissue DNA was extracted successfully from 162/185 (87.6%) tissues and 132/162 (82%) HR-HPV was tested positive. The HPV 16 positive rate was 50% (66/132), the HPV 18 positive rate was 15.2% (20/132), and the other group HR-HPV + 66 and 68 positive rates were 56.1% (74/132). Other HR-HPV types are more common in HSIL than in cancer, whereas HPV 16 is more prevalent in cancer than other HR-HPV genotypes.

**Table 1. Quantitative comparison of HPV positive, DNA, and E6/E7 mRNA between groups.**

| Group | Number of cases | HPV Total positive | 16 Positive | 18 Positive | 16 + 18 Positive | DNA | mRNA |
|---|---|---|---|---|---|---|---|
| Chronic cervicitis | 72 | 32 (44.44%) | 8 (11.11%) | 10 (13.89%) | 6 (8.33%) | 0.63 ± 0.22 | 0.52 ± 0.23 |
| CIN | 54 | 36 (66.67%) | 11 (20.37%) | 10 (18.52%) | 9 (16.67%) | 1.24 ± 0.36 | 1.19 ± 0.42 |
| Cervical cancer | 51 | 45 (88.24%) | 12 (23.53%) | 15 (29.41%) | 15 (29.41%) | 1.64 ± 0.52 | 1.43 ± 0.61 |
| $F/\chi^2$ | | 25.069 | 3.626 | 4.612 | 9.427 | 12.326 | 10.524 |
| p | | < 0.001 | 0.163 | 0.100 | 0.009 | < 0.001 | < 0.001 |

**Table 2. Value of HPV-positive predictive cervical malignant lesions [example (%)].**

| | | Colposcopy | | Total |
|---|---|---|---|---|
| | | + | - | |
| HPV positive | + | 92 (52.0%) | 61 (34.5%) | 153 |
| | - | 13 (7.3%) | 11 (6.2%) | 24 |
| | Total | 105 | 72 | 177 |

**Table 3. Value of quantitative diagnosis of cervical malignant lesions by HPV-DNA and E6/E7 mRNA.**

| Indicators | AUC | 95% CI | p | Sensitivity (%) | Specific (%) | Critical value |
|---|---|---|---|---|---|---|
| DNA | 0.865 | 0.816 - 0.945 | 0.012 | 86.5 | 82.4 | 0.83 |
| mRNA | 0.879 | 0.822 - 0.913 | 0.006 | 90.3 | 86.5 | 0.79 |

**Table 4. Comparison of postoperative recurrence of CIN and early cervical cancer [case (%)]].**

| Group | Number of cases | Recurrence | HPV positive |
|---|---|---|---|
| CIN | 54 | 4 (7.41%) | 4 (7.41%) |
| Early cervical cancer | 32 | 5 (15.63%) | 5 (15.63%) |
| $\chi^2$ | | 0.704 | 0.704 |
| p | | 0.401 | 0.401 |

Therefore, it is proposed that HPV 16 and other HR-HP genotypes are usually associated with HSIL, but HPV 18 is not common in the population of Botswana women, while emphasizing the need for other high-risk HPV cross-covered polyvalent HPV vaccines beyond HPV 16 and 18.

In the present study, the TCT positive rate was 25.36%, the HPV positive rate was 27.52%, and the TCT + HPV positive rate was 16.01% in 556 women screened by our center. TCT and HPV tests have become the important basis for cervical cancer screening, and as the important premise of colposcopy referral [10]. The HPV positive rate gradually increased between groups of chronic cervicitis, CIN, and cervical cancer ($p < 0.001$), suggesting that HPV positive was related to the progression of cervical malignancy. However, HPV 16 and 18

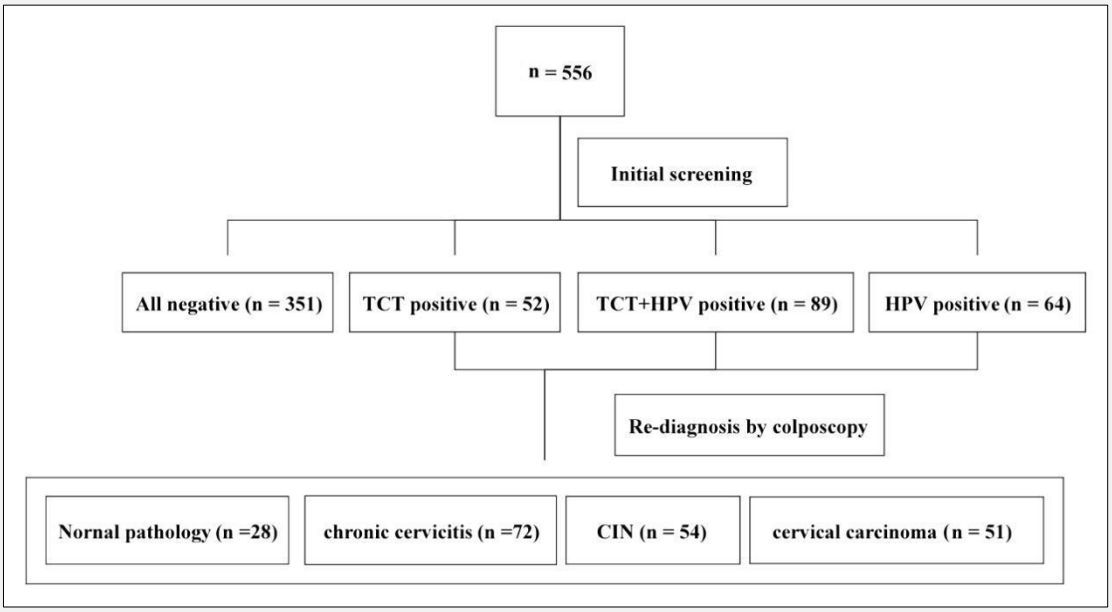


**Figure 1. Screening procedures and results of cervical diseases.**

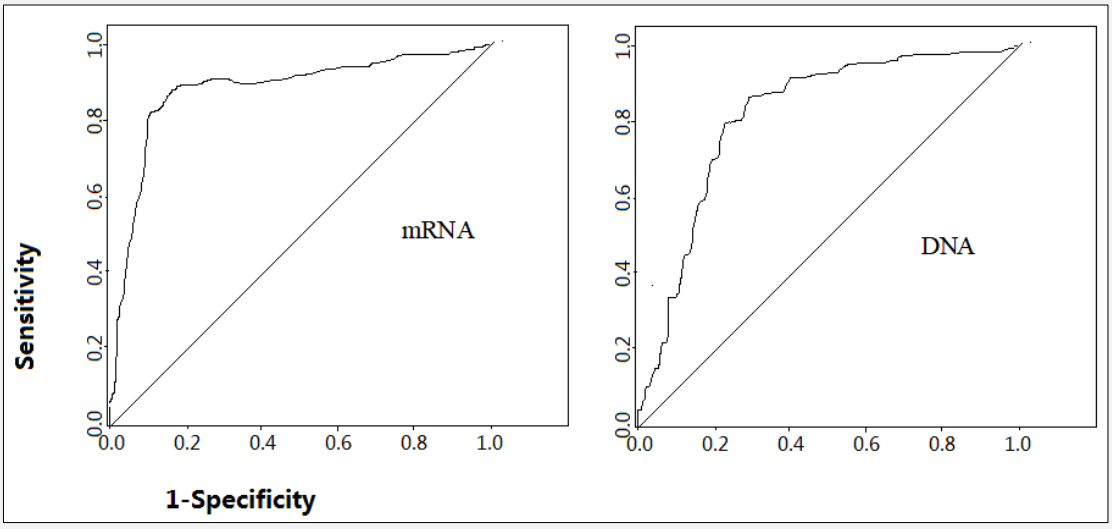


**Figure 2. ROC analysis of the value of HPV-DNA and E6/E7 mRNA in the quantitative diagnosis of cervical malignant lesions.**

subtypes further identified no significant difference in positive rates. In 16 + 18 subtypes, the positive rate was significantly different ($p = 0.009$). It was considered that HPV high-risk subtype 16 + 18 concurrent infection may have a strong predictive value for cervical malignancy [11]. Moreover, quantitative comparison of

HPV-DNA and E6/E7 mRNA showed significant differences ($p < 0.001$). The quantitative detection of HPV can reflect the viral load. The study found that the incidence of cervical cancer is not only related to HPV high-risk subtype infection, but also the higher the load, the greater the risk of malignant lesions [12,13]. The study used ROC analysis to find that the correct rate of HPV positive assessment of malignant lesions had an accuracy of 58.19%, sensitivity of 87.62%, specificity of 15.28%, positive predictive value of 60.13%, and negative predictive value of 45.83%. It thus suggested that single HPV detection is more sensitive to cervical malignancy. The accuracy of quantitative analysis of HPV-DNA for assessing malignant lesions had an accuracy of 0.865, sensitivity of 86.5%, and specificity of 82.4%. The accuracy of the quantification of E6/E7 mRNA is 0.879, sensitivity is 90.3%, and specificity is 86.5%, which suggested that HPV quantification is a good determination for evaluating cervical malignant lesions. Torres-Rojas FI et al. [14] revealed that the methylation of HPV 16 L 1 gene was increased with the increase of cervical lesion grade, low level of SIL compared with CC ($p < 0.0001$), and non-IL compared with CC ($p < 0.0001$). The degree of methylation of the HPV 18 L1 gene increased with the increase of histological grade, but there was no statistical difference ($p > 0.05$), methylation of HPV 16 L1 gene CpG at site 5608 was associated with all classifications of cervical lesions, and the methylation of CpG at site 5617 was most correlated with CC (OR 42.5, 95% CI 4.7 to 1861, $p <$ 00101). The coincidence rates of HPV 16 and 18 physiological status detection methods were 96.1% of quantitative polymerase chain reaction (qPCR) and in situ hybridization (ISH) was 76.7% of methylation of qPCR and L1 genes, and 84.8% of methylation of ISH and L1 genes, respectively. Therefore, it is considered that the methylation degree of HPV 16 L1 gene increases significantly with the degree of cervical lesions. The degree of methylation of its cPG at sites 5,608 and 5,617 can be used as biomarkers to predict cervical lesions. ISH and L1 gene methylation is in good agreement with qPCR in detecting HPV integration.

The study found no difference in recurrence rates between patients with CIN and early cervical cancer who underwent radical surgery and routine follow-up for 12.0 months ($p = 0.401$). All patients with recurrence were HPV positive, which suggested that HPV positive may also be associated with disease recurrence. Kang WD et al. [15] pointed out that HPV genotyping serves as a reliable prognostic indicator for recurrence after electrocyclic resection in CIN ii - iii patients, especially postmenopausal women. Okuma K et al. [16] studied 71 patients with radical radiation therapy (RT) and high-dose intracavitary proximity radiotherapy while receiving or not receiving chemotherapy and then took HPV-DNA samples before treatment. Each proximity radiotherapy and each follow-up examination explored the relationship between HPV clearance time and RT efficacy. Thirteen cases (18%) before radiotherapy failed to detect HPV-DNA, 58 cases were tested for HPV-DNA before treatment, 34% failed to detect HPV-DNA, and 66% failed to detect HPV-DNA after treatment. No HPV-DNA was detected in one patient within 6 months after RT, and a total of 20 patients were found to have relapse in 43 months (7 - 70 months) follow-up. Seventy-one patients had a 3-year cumulative disease-free survival rate (DFS) of 5.4. Multivariate analysis showed that DFS was significantly associated with HPV (detected and not detected) with a hazard ratio of 0.07 (95% CI = 0.008 - 0.6, $p = 0.009$).

To sum up, HPV detection is an important screening method for early cervical cancer and precancerous lesions. The combination of HPV 16 and 18 subtypes, DNA quantification, and e6/e7 mRNA quantification can further improve the accuracy of screening. A more sensitive data model of early cervical cancer assessment by establishing HPV detection is expected to reduce the rate of blind colposcopy referral and reduce the medical cost and burden. The current results suggest that HPV detection is important for assessing the risk of early cervical cancer and guiding colposcopy referral, but it is not considered to be instructive to evaluate postoperative recurrence. There is also a need to increase samples and extend follow-up observation time.

**Declaration of Interest:**

None.

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