Original Article

ThinPrep cytologic test combined with HPV typing to evaluate the degree of cervical diseases and the relationship between HPV typing and the pathological results of patients with atypical squamous cells of undetermined significance: a diagnostic test

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Background: Persistent infection with high-risk human papilloma virus (HPV) is the main cause of cervical cancer. Cervical precancerous lesions last for long and are reversible. Thus, the effective way to prevent cervical cancer is to make a timely diagnosis and administer treatment in the precancerous stage. This study sought to explore the evaluation of cervical cytology by a ThinPrep cytologic test (TCT) combined with HPV typing in patients with cervical diseases, and the relationship between HPV typing and the pathological results of patients with atypical squamous cells of undetermined significance (ASCUS).

Methods: The medical records of 414 patients who received outpatient treatment at the Suzhou Hospital of Traditional Chinese Medicine from February 2020 to February 2022. The pathological results of all cases were followed-up, and data on patients' age, menopause, pregnancy status, birth status, HPV typing, and HPV infection status were collected and statistically analyzed. The positive predictive value, negative predictive value, sensitivity, and specificity of the 2 detection methods were calculated. The factors associated with ASCUS pathological results were analyzed by logistic regression.

Results: Among the 414 patients, 230 had positive vaginal tissue biopsy results, taking this as the gold standard, the diagnostic value of TCT and HPV were examined and compared. HPV typing had a slightly higher sensitivity and positive predictive value than TCT; however, the 2 methods combined had the highest sensitivity and positive predictive value. The univariate analysis showed that the age, HPV infection, and HPV typing in the group of chronic cervicitis differed significantly from the group of cervical intraepithelial neoplasia (CIN) II+/cervical carcinoma ($P<0.05$). The logistic regression analysis showed that HPV infection, being HPV-16 positive, and being HPV-18 positive were risk factors of ASCUS disease ($P<0.05$).

Conclusions: Compared to individual detection methods, TCT combined with HPV typing had a higher detection rate and screening accuracy for cervical diseases, and had the highest sensitivity and positive predictive value. HPV infection, being HPV-16 positive, and being HPV-18 positive are risk factors for ASCUS lesions. HPV typing detection can improve the accuracy of ASCUS shunt diagnosis and provide a reliable basis for the establishment of ASCUS shunt management.

Keywords: ThinPrep cytologic test (TCT); human papilloma virus (HPV); cervical diseases; degree of lesion; atypical squamous cells of undetermined significance (ASCUS)

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Introduction

Cervical cancer is a major problem affecting women's health, and it was the 7th most common cancer in the world in 2020 (1). In 2018, there were about 560,000 new cases of cervical cancer worldwide and 340,000 cervical cancer-related deaths worldwide (2). In 2020, there were about 600,000 new cases of the disease and 340,000 cervical cancer-related deaths worldwide. Thus, the number of new cases of cervical cancer worldwide increased slightly from 2018 to 2020, but the number of cervical cancer-related deaths remained basically the same (2). China has 110,000 new cases of cervical cancer, which accounts for 18.33% of the cases worldwide, and 60,000 deaths, which accounts for 17.65% of the associated deaths worldwide. In developed countries, advances in science and technology, the wide popularization of cervical cancer screening technology, and vaccination have led to a decrease in the incidence of and death toll associated with cervical cancer year by year, but these are still increasing in relatively underdeveloped areas. The incidence and death toll of cervical cancer is 85% in low- and middle-income countries that lack active screening awareness and screening technology (3). However, the incidence shows younger trend what affect the quality of life of women around the world (1,4). It is now clear that persistent infection with high-risk human papilloma virus (HPV) is the main cause of cervical cancer. Cervical precancerous lesions last for a long time and are reversible. Thus, an effective way to prevent cervical cancer is to make a timely diagnosis and administer treatment in the precancerous stage, so screening during this period is very critical (5).

Atypical squamous cells of undetermined significance (ASCUS) is a vague category used in the classification of cervical cytology. It refers to a group of vaginal and cervical cytological lesions that have obvious morphological changes compared to benign lesions, but the number and degree are not enough to diagnose squamous intraepithelial lesions (6). ASCUS may be related to inflammation, pathogen infection, HPV stimulation, and other factors, including a few atypical squamous cell carcinoma (SCC) and adenocarcinoma cells. The thickness of the sections, the depth of the staining, and the number of inflammatory cells affect the diagnostic results. As there are individual differences in the diagnosis of ASCUS, it is difficult to make accurate clinical judgments (7). At present, the ThinPrep cytologic test (TCT) and the HPV typing test are used to screen cervical cancer and its precancerous lesions (3).

A consensus has been reached on the guiding principles of abnormal cervical cytology; however, there are still many problems in clinical practice. For example, the pathological examination results of ASCUS include inflammation, cervical intraepithelial neoplasia (CIN), and invasive cervical cancer. The questions of how to strengthen the management of ASCUS patients and provide individualized treatment are urgent problems that need to be solved (8). At present, the diagnosis of TCT is mainly based on the cervical cytology the Bethesda system (TBS). The results of the TCT and HPV typing affect clinical treatment (9). Cervical cancer is harmful, but it takes a long time (>10–20 years) for the cells to develop into cervical cancer from normal tissue after being infected with the HPV virus (1), which gives patients with cervical precancerous lesions a great deal of time for recovery. To achieve a comprehensive reduction in the incidence of cervical lesions and cervical cancer, we should combine the existing cervical cancer screening programs, to improve the sensitivity and specificity of the detection methods, and thus optimize the accuracy of the screening program, and implement targeted intervention programs in the early stage.

This study sought to explore the evaluation of cervical cytology by a TCT combined with HPV typing in patients with cervical diseases, and the relationship between HPV typing and the pathological results of patients with ASCUS to provide a certain reference basis for the clinical treatment of cervical diseases. We present the following article in accordance with the STARD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2026/rc).

Methods

Research participants

We conducted a retrospective analysis of patients who were hospitalized at the Suzhou Hospital of Traditional Chinese Medicine from February 2020 to February 2022 and screened for cervical precancerous lesions. To be eligible for inclusion in this study, patients had to meet the following inclusion criteria: (I) not be pregnant; (II) have undergone a TCT and HPV typing at the same time; (III) have undergone a colposcopy and histopathological biopsy within 2 months of the TCT; and (IV) have seen a doctor for reasons that included a gynecological physical examination, increased leucorrhea, irregular vaginal bleeding, menstrual disorders, and bleeding after having sex. Patients were

excluded from the study if they met any of the following exclusion criteria: (I) had missing or no TCT, HPV typing, or colposcopic biopsy data; (II) had acute genital tract inflammation, had engaged in sexual activity or vaginal flushing, or had been taking medication 3 days before the TCT; (III) had a history of cervical surgery; (IV) had other genital malignancies; and/or (V) had incomplete general information.

From February 2020 to February 2022, a total of 1,064 cases of HPV testing were performed, of which 701 underwent TCT testing at the same time, and among these, 414 cases of cervical biopsy pathological results were collected. The collected cases were followed-up. Data on patients' age, menopause, pregnancy status, parity, HPV typing, and HPV infection were collected and analyzed statistically. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Suzhou Hospital of Traditional Chinese Medicine (No. 2020-K32-11). All the patients gave informed consent to participate in this study.

Detection method

TCT

The TCT is administered 3 to 7 days after menstruation (and is not required for menopausal women). Patients were not allowed to engage in sexual activity 2 days before the sampling and were not allowed to engage vaginal douching or take vaginal drugs for 3 days before the examination. A special sampling brush for TCT was placed in the cervical canal, close to the cervix, rotated 3 times, left for 10 s, and then placed in the liquid-based cell preservation solution. Next, a special smear machine was used to process it into a thin-layer smear, and microscopy was then performed. The cytological diagnosis was divided into a normal or inflammatory response, ASCUS, low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), and SCC.

HPV typing test

For the TCT positive patients, an HPV nucleic acid typing test kit produced by Guangdong Kaipu Biotechnology Co., Ltd. (Guangdong, China) was used after sample labeling. HPV high-risk types include subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82, and 83, and HPV low-risk types include subtypes 6, 11, 42, 43, and 81. Detection principle: deoxyribonucleic acid (DNA) chip technology combining polymerase chain reaction *in-vitro* amplification and DNA reverse dot blot hybridization were used to design primers according to the genetic characteristics of HPV, and amplify the target fragments of the above different types of HPV genotypes. The amplified products were then hybridized with typing probes fixed on the membrane strip, including HPV high- and low-risk types. The existence of HPV genotypes was judged according to the existence of the hybridization signals.

Colposcopy cervical biopsy

Colposcopy was performed on those with positive or double positive results for the TCT and HPV typing test results. If no lesion was found by colposcopy, a biopsy was taken at 3, 6, 9 and 12 o'clock of the cervix. If the colposcopy image was abnormal, a biopsy was taken at the most serious or suspicious part of the lesion. According to the diagnostic criteria (10), the results were divided into chronic inflammation, CIN I, CIN II, CIN III, and cervical cancer. The pathological biopsy results were jointly diagnosed by 2 senior associate gynecologists.

Observation index

The results of the TCT and HPV typing were observed, a colposcopic biopsy was performed on any positive or double positive test results, the pathological results were diagnosed, and the sensitivity, specificity, positive predictive value, and negative predictive value of the 2 test methods were compared separately and jointly to analyze the relationship between HPV typing and the pathological results of the ASCUS patients.

Statistical analysis

After classifying and numbering the questionnaire, the Statistical Program of Social Science software version 23.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The diagnostic value of the 2 methods is compared. The following formulas were used: positive predictive value = number of true positive cases/(number of true positive cases + number of false positive cases); negative predictive value = number of true negative cases/(number of true negative cases + number of false negative cases); sensitivity = number of true positives/(number of true positives + number of false negatives); and specificity = true negative number/(true negative number + false positive number).

The *t*-test was used to compare the measurement data ($\bar{x}\pm s$). The χ^2 test and Fisher's exact probability method were used to compare the rates. The factors related to the ASCUS pathological results were analyzed by logistic regression. Two-sided test P<0.05 was considered statistically significant.

Results

Comparison between the TCT and pathological results

Among the 414 TCT results, 230 (55.56%) patients had a normal or inflammatory reaction, and 184 (44.44%) had abnormal TCT results, including 91 (49.46%) cases of ASCUS, 52 (28.26%) cases of LSIL, 38 (20.65%) cases of HSIL, and 3 (1.63%) cases of SCC. Compared to the pathological results, 81 (44.02%) of the 184 patients with abnormal TCT results had chronic cervicitis, 54 (29.35%) had CIN I, 27 (14.67%) had CIN II, 19 (10.33%) had CIN III, and 3 (1.63%) had cervical cancer (see *Table 1* and *Figure 1*).

Comparison between the HPV typing test and pathology test

Among the 414 patients, 206 (49.76%) were HPV positive, of whom 142 (68.93%) had high-risk HPV and 64 (31.07%) had low-risk HPV. Compared to the pathological results, 114 of the 206 HPV positive cases (55.34%) had chronic cervicitis, 46 (22.33%) had CIN I, 25 (12.14%) had CIN II, 12 (5.83%) had CIN III, and 9 (4.37%) had cervical cancer (see *Table 2*).

Comparison of the positive rates of the 2 detection methods

Among the 414 patients, the TCT results showed that 184 cases were cytologically positive, with a positive rate of 44.44%, the HPV typing results showed that 206 cases were HPV positive, with a positive rate of 49.76%, and the TCT and HPV typing results showed that 220 cases were positive, with a positive rate of 53.14%. The positive rate of HPV typing was slightly higher than that of TCT, but there was no significant difference between the 2 methods (P>0.05; see *Table 3*).

Comparison of diagnostic value of the 2 detection methods: Single detection and combined detection

Among the 414 patients, the vaginal tissue biopsy results showed that 230 cases were positive, including 120 cases of chronic cervicitis, 55 cases of CIN I, 30 cases of CIN II, 15 cases of CIN III, and 10 cases of cervical cancer. Taking this as the gold standard, the diagnostic value of the 2 detection methods was calculated and compared (see *Tables 4-6*). The sensitivity and positive predictive value of HPV typing were slightly higher than TCT, and the sensitivity and positive predictive value of the 2 methods combined were the highest (see *Table 7*).

Univariate analysis of ASCUS pathology

The univariate analysis showed that the age, HPV infection, and HPV typing in the group of chronic cervicitis differed significantly from the group of CIN II+/cervical carcinoma (P<0.05; see *Table 8*).

Multivariate logistic regression analysis of ASCUS pathology

A logistic regression analysis was conducted, under which the ASCUS pathological results were taken as the dependent variables (and defined as follows: "chronic cervicitis/CIN I" as 1, "CIN II+/cervical cancer" as 2), and the factors screened by univariate analysis were taken as the independent variables (and defined as follows: HPV infection "negative" =0, "positive" =1; HPV-16 "negative" =0, "positive" =1; HPV-18 "negative" =0, "positive" =1). The results showed that HPV infection, being HPV-16 positive, and being HPV-18 positive were risk factors for ASCUS disease (P<0.05; see *Table 9*).

Discussion

The occurrence and development of cervical cancer are part of a long process, and the early symptoms are not obvious. When contact bleeding or abnormal vaginal bleeding occur, most patients have reached the middle or late stage (4). Surgery or radiotherapy and chemotherapy cause great physical and mental damage to women. Thus, the timely screening of cervical precancerous lesions is key to the prevention and treatment of this disease and in improving the survival rate (11). Clinical studies have shown that it takes approximately 8–12 years for CIN to develop into invasive cancer. In untreated patients with CIN II and CIN III, about 5–30% develop into invasive cancer, but nearly 10–40% of the lesions can be reversed. HPV infection can lead to cancer after about 20 years (12). The results of this

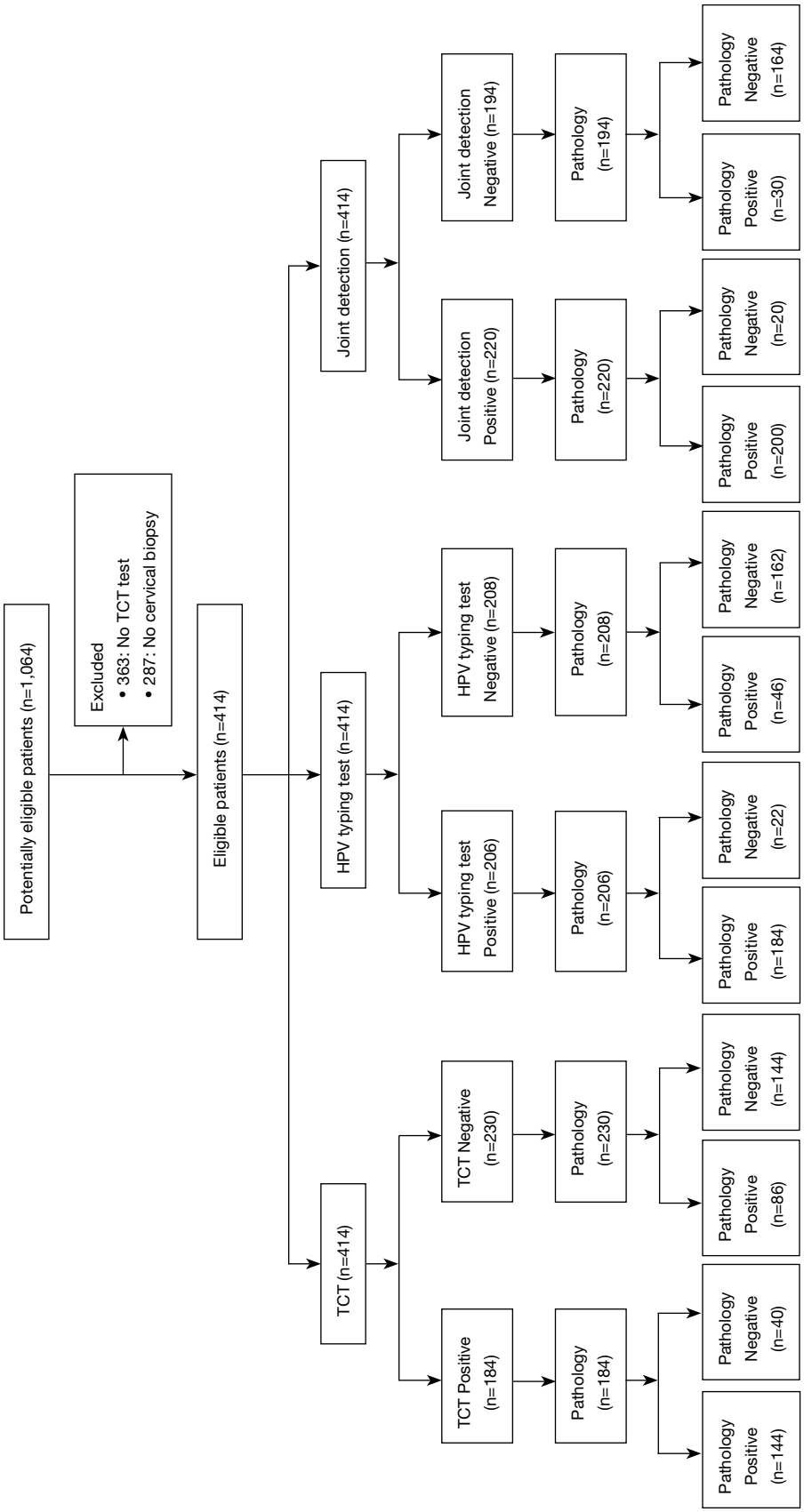

Figure 1 Study flowchart. TCT, ThinPrep cytologic test; HPV, human papilloma virus.

Table 1 Comparison of TCT and pathological results

TCT	N	Pathology, n (%)				
		Chronic cervicitis	CIN I	CIN II	CIN III	Cervical carcinoma
ASCUS	91	63 (69.23)	22 (24.18)	6 (6.59)	0 (0.00)	0 (0.00)
LSIL	52	18 (34.62)	27 (51.92)	5 (9.62)	2 (3.85)	0 (0.00)
HSIL	38	0 (0.00)	5 (13.16)	16 (42.11)	17 (44.74)	0 (0.00)
SCC	3	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (100.00)
Total	184	81 (44.02)	54 (29.35)	27 (14.67)	19 (10.33)	3 (1.63)

TCT, ThinPrep cytologic test; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous Intraepithelial Lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma; CIN, cervical intraepithelial neoplasia.

Table 2 Comparison of HPV typing test and pathology

HPV typing	N	Pathology, n (%)				
		Chronic cervicitis	CIN I	CIN II	CIN III	Cervical carcinoma
High-risk HPV	142	79 (55.63)	31 (21.83)	17 (11.97)	8 (5.63)	7 (4.93)
Low-risk HPV	64	35 (54.69)	15 (23.44)	8 (12.50)	4 (6.25)	2 (3.13)
Total	206	114 (55.34)	46 (22.33)	25 (12.14)	12 (5.83%)	9 (4.37)

HPV, human papilloma virus; CIN, cervical intraepithelial neoplasia.

Table 3 Comparison of the positive rate of two detection methods

Test method	Chronic cervicitis	CIN I	CIN II	CIN III	Cervical carcinoma	Positive rate
TCT (n=414), n (%)	81 (44.02)	54 (29.35)	27 (14.67)	19 (10.33)	3 (1.63)	184 (44.44)
HPV typing (n=414), n (%)	114 (55.34)	46 (22.33)	25 (12.14)	12 (5.83)	9 (4.37)	206 (49.76)
χ^2						2.350
P						0.126

CIN, cervical intraepithelial neoplasia; TCT, ThinPrep cytologic test; HPV, human papilloma virus.

Table 4 Comparison of gold-standard method and TCT

Pathology	TCT		Total
	+	–	
+	144	86	230
–	40	144	184
Total	184	230	

TCT, ThinPrep cytologic test.

Table 5 Comparison of gold-standard and HPV typing detection

Pathology	TCT		Total
	+	–	
+	184	46	230
–	22	162	184
Total	206	208	

HPV, human papilloma virus; TCT, ThinPrep cytologic test.

study showed that among the 414 patients, 230 (55.56%) had a normal or inflammatory reaction, and 184 (44.44%) had abnormal TCT results. The sensitivity and positive predictive value of TCT alone were 62.61% and 78.26%, respectively. TCT has been widely used in the diagnosis of cervical diseases, but if used alone, false positives or false negatives may occur due to factors, such as improper operation. Thus, TCT cannot be used as the only basis for the diagnosis of cervical cancer (13).

HPV refers to a group of DNA viruses. High-risk HPV mainly includes types 16 and 18, and the carcinogenic rates of different types also differ (14). HPV infection often occurs in young women, and most HPV infections are temporary; only about 3% of patients suffer from a continuous state of HPV infection (15). HPV infections that last for 1–2 years can cause mild cervical lesions, and high-risk HPV infections that last for 10–15 years can develop into cervical cancer. Thus, HPV screening is very important in the prevention of cervical cancer (16).

The results of this study showed that 206 of the 414 patients were HPV positive, with a positive rate of 49.76%, including 142 (68.93%) cases of high-risk HPV and 64 (31.07%) cases of low-risk HPV. High-risk HPV detection is highly valued by medical staff in the prevention of cervical cancer. In addition, HPV tests are easy to obtain and widely used in clinical practice. Studies have shown that the detection rates of HPV-16 and HPV-18 in cervical cancer patients are higher than those of other types (14). Thus, the detection of high-risk HPV typing has a certain

Table 6 Comparison of gold-standard method and joint detection

Pathology	Joint detection		Total
	+	–	
+	200	30	230
–	20	164	184
Total	220	194	

Table 7 Comparison of the diagnostic value of the 2 detection methods of single detection and combined detection

Test method	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
TCT	62.61	78.26	78.26	62.61
HPV typing test	80.00	88.04	89.32	77.88
Joint detection	86.96	89.13	90.91	84.54

TCT, ThinPrep cytologic test; HPV, human papilloma virus.

Table 8 Univariate analysis of ASCUS pathology ($\bar{x}$±s)

Factor	Category	n	Chronic cervicitis/CIN I (n=85)	CIN II+/cervical carcinoma (n=6)	χ^2/t	P
Age		91	40.22±10.03	36.18±10.23	0.952	0.340
Menopause	No	70	67	3	2.620	0.105
	Yes	21	18	3		
Gravidity		91	1.04±0.02	1.03±0.02	1.184	0.240
Parity		91	1.02±0.04	1.03±0.01	0.608	0.540
HPV infection	Negative	42	42	0	5.510	0.019
	Positive	49	43	6		
HPV-16	Negative	47	47	0	6.860	0.009
	Positive	44	38	6		
HPV-18	Negative	75	72	3	4.660	0.031
	Positive	16	13	3		

ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus.

Table 9 Multivariate logistic regression analysis of ASCUS pathology

Related factor	b	S.E	χ^2	P	OR	95% CI
Age	2.163	1.369	2.496	0.114	8.697	0.594–127.261
HPV infection	1.726	0.354	23.773	0.000	5.618	2.807–11.244
HPV-16	1.956	0.354	30.530	0.000	7.071	3.533–14.152
HPV-18	2.036	1.002	4.129	0.042	7.660	1.075–54.594

ASCUS, atypical squamous cells of undetermined significance; S.E, standard error; HPV, human papilloma virus.

guiding role in disease monitoring and evaluation. However, false positive or false negative results will occur if HPV typing is used alone, and it is impossible to know whether there is persistent infection, or whether there is cervical disease and its stage (17). One study found that the TCT or HPV typing alone have limitations in the diagnosis of cervical diseases, which may be affected by various factors, such as more keratinocytes, less living cells, bleeding, and vaginitis, in the sampled samples, and joint screening can effectively improve the detection level (18).

Ma *et al.* (19) evaluated the application value of TCT and HPV typing in women's cervical cancer screening and found that the combined use of the 2 tests improves the positive detection rate and sensitivity and reduces the missed diagnosis rate. Taking colposcopy biopsy as the gold standard, this article examined the value of the 2 detection methods used alone or in combination. The results showed that the sensitivity and positive predictive value of the 2 detection methods combined were the highest, which suggests that the combined screening of the TCT and HPV typing compensate for the defects of one another, improve the detection rate of cervical diseases, and reduce the missed diagnosis rate, which is worthy of extensive clinical promotion, ensure timely diagnosis and treatment, and thus prevent cervical cancer.

Studies have shown that among 18,574 women who underwent ASCUS HPV typing, the HPV positive rate was 10.9%, and the infection rate of women under 30 years old was the highest (20). Young women who have more sex may have more opportunities to cause cervical epithelial damage. If they have multiple sexual partners at the same time, they are more likely to be infected with a variety of HPVs. With the increase of age, acquired immunity improves, the risk of HPV infection decreases, and the infection rate decreases (21). These findings explain why the age of onset of CIN II+/cervical cancer lesions in 91 patients with ASCUS in this study was lower than that of those with chronic cervicitis/CIN I. At present, HPV typing has been recommended as the main means of ASCUS shunt diagnosis, but its specificity is not sufficiently high (22). This study found that being HPV-16 and HPV-18 positive were independent risk factors for high-grade cervical lesions. Thus, HPV-16 and HPV-18 positive patients should undergo a colposcopic biopsy to avoid missed diagnosis, and strict follow-up is required. In conclusion, HPV typing improves the diagnostic accuracy of ASCUS pathological results and provides a reliable basis for establishing ascus shunt management.

Conclusions

Compared to individual detection methods, TCT combined with HPV typing has a higher detection rate and screening accuracy for cervical diseases and has a higher sensitivity and positive predictive value. HPV infection, being HPV-16 positive, and being HPV-18 positive are risk factors for ASCUS lesions. HPV typing detection improves the diagnostic value of the ASCUS shunt and provides a reliable basis for the establishment of ASCUS shunt management. However, this study also had some limitations. This study was a retrospective, single-center study; thus, there may be some information bias. These findings need to be further confirmed in prospective and large sample size studies.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2026/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2026/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2026/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Suzhou Hospital of Traditional Chinese Medicine (No. 2020-K32-11). Informed consent was obtained from all patients.

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