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RESEARCH ARTICLE

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# Assessment of the effectiveness of HPV16/18 infection referred for colposcopy in cervical cancer screening in Northwest of China

Qian Zhang[1,2] | Minyi Zhao[1] | Di Cao[1] | Xing Wei[1] | Li Wang[3] | Yang Li[1] | Ting Yang[1] | Juan Zhao[1] | Meili Pei[1] | Hongran Jia[1,2] | Siyu Cao[1] | Shimin Quan[1] | Xiaofeng Yang[1]

[1] Department of Gynecology and Obstetrics, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China

[2] Department of Gynecology and Obstetrics, The Northwest Women and Children Hospital, Xi'an, Shaanxi, China

[3] Center of Maternal and Child Health Care, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China

**Correspondence**
Xiaofeng Yang, Department of Gynecological and Obstetric of the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China.
Email: yxf73@163.com

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To evaluate the effectiveness of Human papillomavirus16/18 infection referral to colposcopy in cervical cancer screening for women aged 25 years and older in Chinese northwest region Shaan'xi province. A total of 2224 women were diagnosed with primary high-risk HPV infection by HPV-DNA genotyping technology during August 2014 to August 2015. A total of 1916 cases referred for colposcopy with histological evidence were enrolled, including 1124 women with HPV16/18 genotype and 792 with other High-risk human papillomavirus genotypes. A total of 1916 women aged 25 years and older with HR-HPV positive were referred to colposcopy. The distribution of HPV16, HPV18, and other HR-HPVs infection were 49.22%, 9.45%, and 41.33%, respectively. 71.56% had normal cervical histology, 7.05% had Cervical Intraepithelial Neoplasia1, 8.82% had CIN2, 7.25% had CIN3, and 5.32% had cervical cancer. The percentage of positivity of HPV16 and HPV18 was highly associated with the relative risk of cervical lesion. The sensitivity and specificity of HPV16/18 for detection of CIN2+ (CIN3+) was 82.68% (92.12%) and 47.87% (46.15%), respectively. The positive predictive value and negative predictive value of HPV16/18 for detection of CIN2 + (CIN3+) was 30.16% (19.75%) and 91.03% (97.60%), respectively. HPV16 and HVP18 are the most common genotypes in high grade cervical lesions in Shaan'xi province. Meanwhile, these two types play predominant roles in the progression of high grade cervical lesion. Primary HPV16/18 detection has high sensitivity and negative predictive value in cervical cancer screening and the strategy for women with HPV16 and HPV18 infection referral to colposcopy is efficient and feasible in northwestern region of China.

**KEYWORDS**
cervical cancer screening, human papillomavirus, sensitivity, specificity

## 1 | INTRODUCTION

It is well known that persistent infection with high-risk human papillomavirus (HR-HPV) is critical for the development of cervical cancer (CC) and its precancerous lesion. Although HR-HPV infection is very common in sexual active young women, most infections were transient and could be cleared spontaneously within 2 years.[1,2] With more in-depth understanding of cervical carcinogenesis, cervical cancer screening strategy had been changed eventually. In addition to HPV testing combined with cytology as a routine co-testing screening procedure,[3,4] HR-HPV testing could be act as a primary screening strategy, suggesting that women with either HPV 16 or HPV 18 infection are referred to colposcopy immediately.[5,6] Given that the large population and uneven distribution of health resources in China, the second session of Chinese Society for Colposcopy and Cervical Pathology (CSCCP) advocated that doctors and healthcare workers should formulate the diversified cervical cancer screening strategy in 2016. In present study, we assessed the efficiency of HR-HPV testing as a primary strategy in Shaan'xi province to check the availability and feasibility as a preferred alternative program in cervical cancer screening

## 2 | OBJECTS

A total of 2264 women aged 25 years and older with primary HR-HPV infection who should undergo colposcope with multi-point biopsy for an abnormal cervix at visual inspection or risk factors for cervical lesions were recruited initially from the gynecology department of the First Affiliated Hospital of Xi'an Jiaotong University during August 2014 to August 2015. A total of 348 women were excluded because of incomplete result of colposcopy. Of the remaining 1916 women, 1124 women with HPV16 and or 18 infection while 792 women with other HR-HPV infecton.The median age of these patients was 39.00 years (range: 25-78 years). This study was approved by the Ethics Committee of the hospital. All subjects agreed to participate in the study and signed informed consent forms. The specific process as showed as follows (Figure 1).

## 3 | METHODS

### 3.1 | HPV genotyping detection

HPV genotyping was performed by using HPV GenoArray test (Hybribio Limited, HongKong), which made use of both DNA amplification and hybridization technique, thus allowing the simultaneous identification of a broad range of HPV genotype, including 14 high-risk genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, and 68). Specific steps were operated in accordance with the manufacturer's instructions.[7]

### 3.2 | Cervical histology detection

Women aged 25 years and older with a positive HR-HPV test were referred to colposcopy and performed multi-point cervical biopsy in the suspicious lesion if necessary. The histopathology was diagnosed by two senior pathologists according to cervical intraepithelial neoplasia (CIN) terminology.[8] Women with negative colposcopy results were deemed without cervical lesions.

### 3.3 | Diagnostic value of indicators

Based on the coincidence rate of HPV infection and pathological results, detection of CIN2+ was set up as the endpoints. Sensitivity is the ratio of the number of confirmed cervical lesions in the infected population of given HPV type and the overall number of confirmed cervical lesions. Specificity is the ratio of the number of diagnosed normal cervix in the non-infected population of given HPV type and the overall number of diagnosed normal cervix. Negative predictive value (NPV) is the ratio of the number of confirmed normal cervix in the non-infected population of given HPV type and the overall number of non-infected population of given type. Positive predictive value (PPV) is the ratio of the number of diagnosed cervical lesions in the infected population of given HPV type and the overall number of infected population of given type. All these indicators are only demonstrating the situation in women with the infection of HR-HPV since we did not perform colposcope on women without HR-HPV infection.

### 3.4 | Statistical analyses

HPV infection status was defined using two categories: (1) single infection, in which only a single HR-HPV genotype was present and (2) multiple infections, in which at least two different HR-HPV genotype were present. In this study, the multiple infections categorized into the type-specific HPV genotype infection according to the risk of specific HR-HPV genotypes by hierarchical ranking, which was calculated for the overall population and for each specific genotype as the proportion of women with valid results for high-grade cervical disease (≥CIN2).[9] The multiple infections were not discussed in this study. Data were analyzed using SPSS version 18.0. Kruskal-Wallis test was used to compare the relative risk of HPV16 and HPV18 versus Other HR-HPV with the progression of cervical lesions. A Chi-square test was used to compare the proportions among different groups. Logistic regression with odds ratio (OR) and 95% confidence interval (CI), which was adjusted for normal cervical histology, was used to estimate the risk of HR-HPV for cervical lesions. Significance tests were two-sided, with $P < 0.05$ as the level of statistical significance.

## 4 | RESULTS

### 4.1 | Distribution of HR-HPV genotypes in different cervical lesions

A total of 2264 women aged 25 years and older were detected with HR-HPV infection by primary genital tract HPV infection screening and 1916 of them referred to colposcopy. The distribution of HPV16, HPV18, and other HR-HPV infection was 49.22% (943), 9.45% (181), and 41.33% (792), respectively. The most common genotype was HPV-16, followed by HPV-58, HPV-52, HPV-18, and HPV-33 (Figure 2). The distribution of high-risk human papillomavirus infection in high grade cervical lesion was slightly different. Among these 410 women who had CIN2+, the most frequent

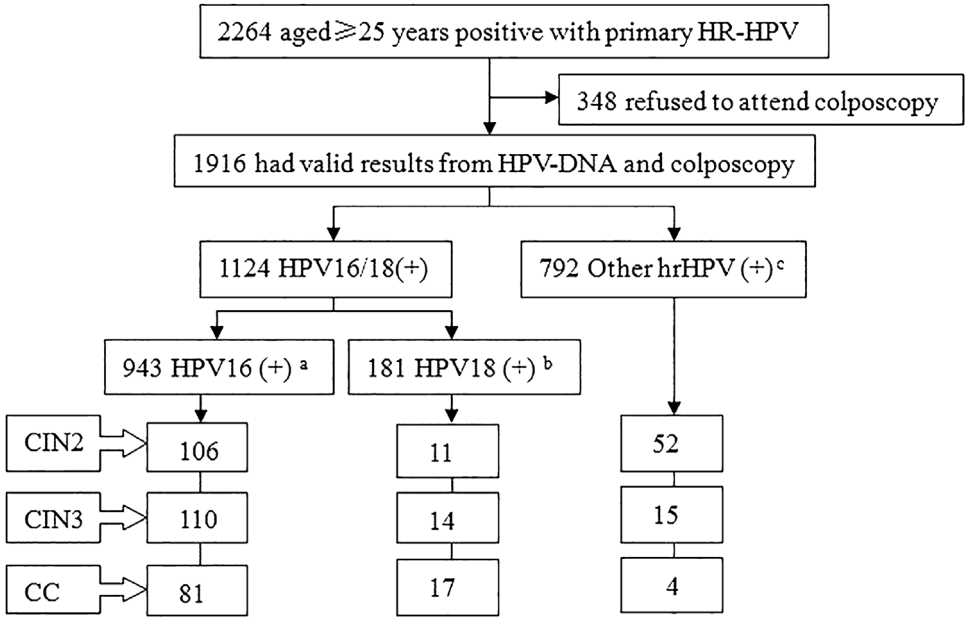


**FIGURE 1** Enrollment, screening results and outcomes of hrHPV positive in 1916 subjects. CIN, cervical intraepithelial neoplasia; CC, cervical cancer. a. HPV16+ includes HPV16+, with or without HPV18+, and with or without other HR-HPV+; b. HPV18+ includes HPV16−, HPV18+, and with or without other HR-HPV+; c. Other HR-HPV+ include HPV16−, and HPV18−, and other HR-HPV+

types were HPV16, HPV18, HPV58, HPV52, and HPV33, respectively. Yet the most common types for 241 CIN3+ were HPV16, HPV18, HPV58, HPV52, and HPV31, separately. Two common types including HPV16 and HPV18 comprised 82.68% (92.11%) of total CIN2+ (CIN3+) cases.

## 4.2 | Relationship between HPV infection and cervical lesions

Pathological results from 1916 women referred for colposcopy showed that 71.56% (1371) had normal cervical histology, 7.05% (135) had CIN1, 8.82% (169) had CIN2, 7.25% (139) had CIN3, and 5.32% (102) had cervical cancer (CC). The positive rate of HPV16 and HPV18 increased with the progression of cervical lesion. The estimated relative risk (RR) of CIN and CC associated with HR-HPV status was listed in Table 1. Compared with other HR-HPV types, the distribution of HPV 16 and HPV18 infection predominate in high grade cervical lesion. The RR was 8.71 (95% CI 5.02-15.11) of HPV16 and 5.10 (95%CI 2.40-10.82) of HPV18 for CIN3, the RR was even higher for CC, which was 24.05 (95% CI, 8.76-66.04) of HPV16 and 23.20 (95%CI, 5.94-70.12) of HPV18.

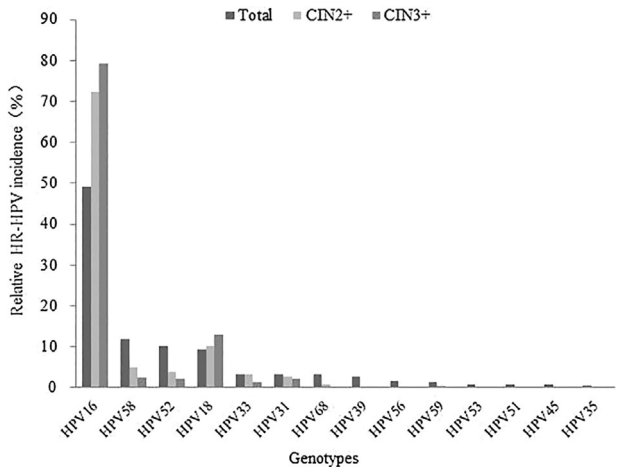


**FIGURE 2** Distribution of HR-HPV genotypes in high grade cervical lesions. HR-HPV, high-risk human papillomavirus; HR-HPV genotypes were detected using the HPV GenoArray test kit. CIN 2+, cervical intraepithelial neoplasia grade 2 or worse; CIN 3+, cervical intraepithelial neoplasia grade 3 or worse

## 4.3 | Distribution of HR-HPV infection in cervical lesions of different age groups

For women aged 30 years and younger, with the progress of cervical lesions, the distribution of HPV16 showed a ladder upward trend, appearing a rapid increase around CIN2, that of HPV18 suggests a peak around CIN1 and decline continue thereafter. For women aged 30-50 years old, the distribution of HPV16 increase continues until around CIN2, where it flatten out at a plateau level, that of HPV18 was lowest around CIN2 and then presented a linear upward trend. This phenomenon also appeared in the women aged 50 years and older. The distribution of HPV16 and HPV18 increased with the progression of the cervical lesion among almost all the age groups, for example, HPV16 was detected in 58.82% of CIN2, 90.91% of CIN3, and 100.00% of CC among women less than 30 years old. HPV18 was detected in 8.00% of CIN2, 10.53% of CIN3, and 17.24% of CC among women older than 50 years (Figure 3).

**TABLE 1** Estimated relative risk (RR) of cervical lesions according to the result of HR-HPV test

| | | HPV16+ VS Other HR-HPV | | | HPV18+ VS Other HR-HPV | | |
|---|---|---|---|---|---|---|---|
| Histology | Other HR-HPV | *n* (%) | OR(95%CI) | *P* | *n* (%) | OR(95%CI) | *P* |
| Normal | 677 (85.48) | 570 (60.45) | / | / | 124 (68.51) | / | / |
| CIN1 | 44 (5.56) | 76 (8.06) | 2.05 (1.39-3.02) | <0.05 | 15 (8.29) | 1.86 (1.01-3.44) | 0.06 |
| CIN2 | 52 (6.57) | 106 (11.25) | 2.42 (1.71-3.44) | <0.05 | 11 (6.08) | 1.15 (0.59-2.28) | 0.72 |
| CIN3 | 15 (1.89) | 110 (11.65) | 8.71 (5.02-15.11) | <0.05 | 14 (7.73) | 5.10 (2.40-10.82) | <0.05 |
| CC | 4 (0.50) | 81 (8.59) | 24.05 (8.76-66.04) | <0.05 | 17 (9.39) | 23.20 (7.68-70.12) | <0.05 |

HR-HPV, high-risk human papillomavirus; OR, odds ratio; 95%CI, 95% confidence interval.
HR-HPV+ includes HPV16+ and/or HPV18+ and/or other HR-HPV+ types; HPV16+ includes HPV16+, with or without HPV18+, and with or without other HR-HPV+ types; HPV18+ includes HPV16−, HPV18+, and with or without other HR-HPV+ types; Other HR-HPV+ include HPV16−,and HPV18−, and other HR-HPV+ types.

### 4.4 | Diagnostic value of HPV16/18 in detection of high grade cervical lesions

We set up CIN2+ as the endpoint to assess the efficiency of HR-HPV positive referred for colposcopy. A total of 410 (21.40%) were histologically diagnosed as CIN2+ and 241(12.58%) were CIN3+. For confirmed CIN2+ cases. For detection CIN2+, the sensitivity and specificity of HPV16/18 was 82.68% (95%CI, 80.99-84.37%) and 47.87% (95%CI, 45.63-50.11%), respectively. The PPV and NPV was 30.16% (95%CI, 28.10-32.22%) and 91.03% (95%CI, 89.74-92.32%), respectively. For detection CIN3+, the sensitivity and specificity of HPV16/18 was 92.12% (95%CI, 90.91-93.33%) and 46.15% (95%CI, (43.92-48.38%), respectively. The PPV and NPV was 19.75% (95%CI, 17.97-31.53%) and 97.60% (95%CI, 96.91-98.29%), respectively. Sensitivity of HPV16/18 was 92.12% for CIN3+ detection, which was higher than 82.68% for CIN2+ detection. The similar trend was observed for the NPV [Table 2, Figure 4].

## 5 | DISCUSSION

In 2012, American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology (ACS/ASCCP/ASCP) updated cervical cancer screening guideline and adopted the strategy of HPV and cytology co-testing for different age groups of women. They proposed that HPV16/18 positive referral directly to colposcopy in USA.[3] Before this, Eurogin roadmap on cervical cancer prevention in 2010 pointed out the superiority of HPV testing in primary screening for the first time.[10]

In 2014, the US Food and Drug Administration (FAD) approved primary HPV screening based of the results of the Addressing the Need for Advanced HPV Diagnostics (ATHENA) trials.[5] In 2015, ASCCP announced the latest cervical cancer screening interim clinical guidance, and advocated HPV primary screening as preferred alternative program.[6] In 2016, American College of Obstetricians

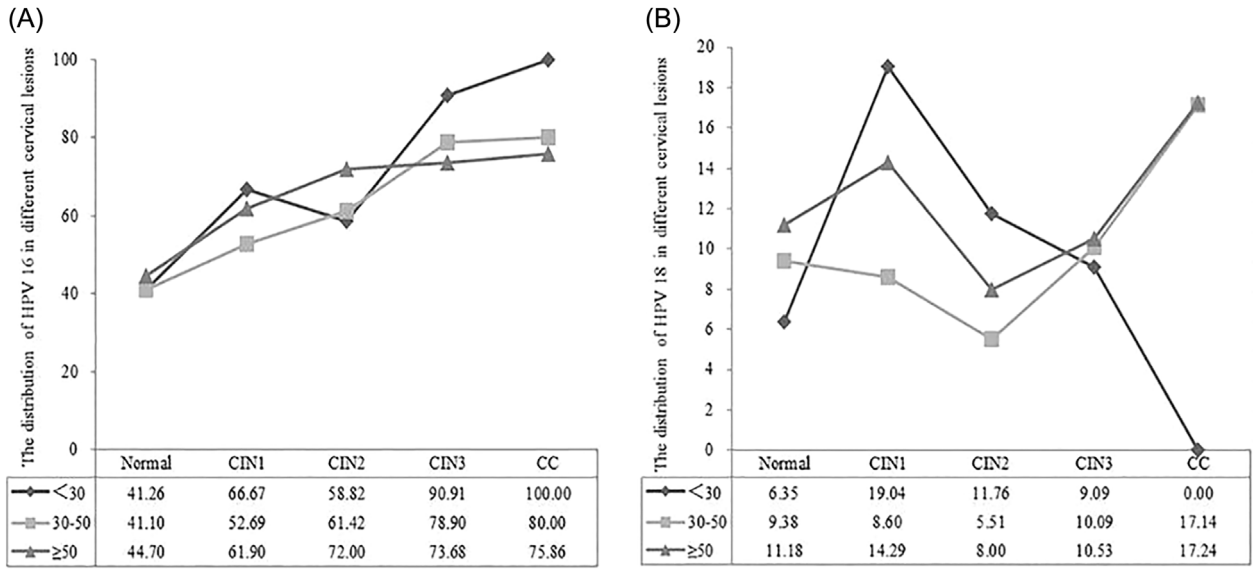


**FIGURE 3** Distribution of HPV16/HPV18 infection according to cervical lesions and different age groups. (A) The distribution of HPV16 infection; (B) The distribution of HPV18 infection. Figure 4 Receiver operating characteristic (ROC) curves. (A) Cut-off point for predicting CIN2+ is 34.80 (area under the ROC curve, 0.653); (B) Cut-off value of 46.00 predicts CIN3+ (area under the ROC curve, 0.691)

**TABLE 2** Diagnostic value of HR-HPV infection for screening high level cervical lesions

| | Sensitivity (95%CI) | Specificity (95%CI) | PPV (95%CI) | NPV (95%CI) |
|---|---|---|---|---|
| CIN2+ | | | | |
| HPV16/18 | 82.68 (80.99-84.37) | 47.87 (45.63-50.11) | 30.16 (28.10-32.22) | 91.03 (89.74-92.32) |
| Other HR-HPV | 17.32 (15.63-19.01) | 52.12 (49.88-54.36) | 8.96 (6.90-11.02) | 69.84 (68.55-71.13) |
| CIN3+ | | | | |
| HPV16/18 | 92.12 (90.91-93.33) | 46.15 (43.92-48.38) | 19.75 (17.97-21.53) | 97.60 (96.91-98.29) |
| Other HR-HPV | 7.88 (6.67-9.09) | 53.85 (51.62-56.08) | 2.40 (0.62-4.18) | 80.25 (79.56-80.94) |

CIN2+ cervical intraepithelial neoplasia grade 2 or worse; CIN3+ cervical intraepithelial neoplasia grade 3 or worse; PPV positive predictive value; NPV negative predictive value; HPV16/18 includes any type of infection with HPV16+ or HPV18+; Other hrHPV includes HPV16−, HPV18−, and other HR-HPV+ types.

and Gynecologists (ACOG) stated that the screening program by primary HPV testing is not recommended but can be considered.[11]

It is important to equilibrate the benefit of detecting high grade cervical lesion and the harm of overscreening, which results in patients' pain, anxiety and a risk of unnecessary colposcopies.[12] Since there was no perfect strategy for screening cervical cancer and based on the basic national conditions of China, Chinese Society for Colposcopy and Cervical Pathology (CSCCP) put forward that diversified schemes of cervical cancer screening should be adopt to make the screening system work more efficiently and feasibly.

Among women who had CIN2+ in our studied population, the most common genotypes were HPV16, HPV18, HPV58, HPV52, and HPV33, consecutively. Although the distribution of HPV 18 was much less common than HPV16 in all populations, the two common types (HPV16 and HPV18) played a dominant role in high-grade cervical lesions. They comprised 82.68% (92.11%) of total CIN2+ (CIN3+) cases. This was in coincidence with our prophase study, we found HPV16 was the most common genotype in CIN3+ cases, which accounting for 85.00%.[2] What is more, HPV16 and HPV18 were the most frequently genotypes in cervical carcinoma.[13] Similarly, a study focused on the distribution of HPV genotypes in New Mexico of United States found that HPV16 and 18 caused the majority of invasive cervical cancer.[14]

Compared with other HR-HPV types, HPV16/18 infection led to the increased possibility of CIN2 or higher grade lesion.[9,15,16] The ATHENA study found that for women aged ≧25 years of 23 states in the United States, HPV16 was detected by LINEAR ARRAY HPV Genotyping Test in CIN1, CIN2, CIN3, and CC was 9.8%, 18.7%, 42.6%, and 16.7%, respectively, and HPV18 was 4.5%, 2.2%, 9.3%, and 50%, respectively.[17] Our data illustrated that women aged 25 years and older in Shaan'xi province, the distribution of HPV16 was 8.06%, 11.25%, 11.65%, and 8.59% for CIN1, CIN2, CIN3, and CC, respectively, the distribution of HPV18 was 8.29%, 6.08%, 7.73%, and 9.39%, respectively. Unfortunately, our results did not exhibit the identical tendency probably for the insufficient sample. Generally speaking, the infection rate of HPV16 and HPV18 increased with the progression of cervical lesion and were highly associated with the relative risk of high grade cervical lesion. Compared with other HR-

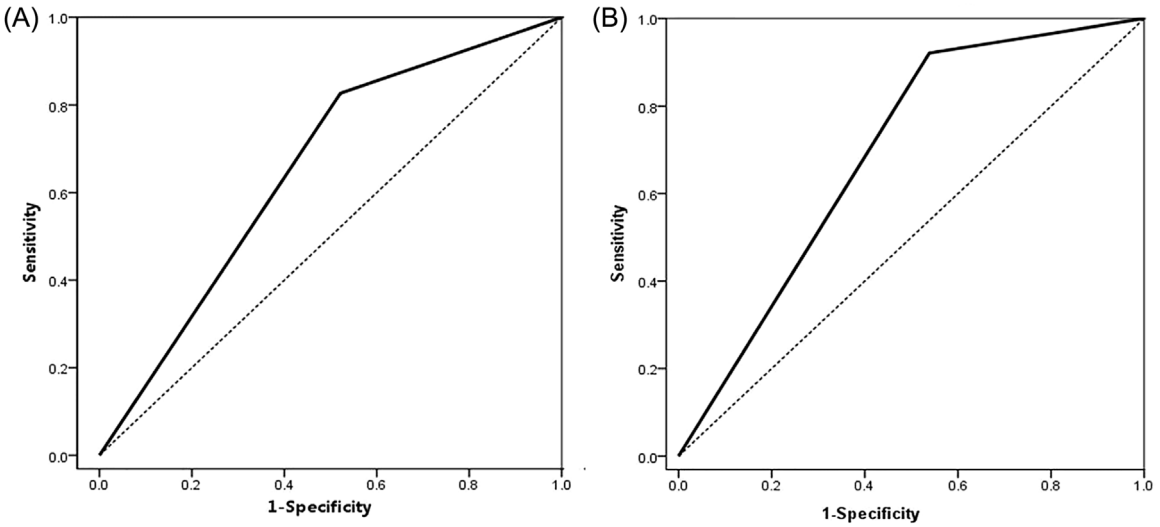


**FIGURE 4** Receiver operating characteristic (ROC) curves. (A) Cut-off point for predicting CIN2+ is 34.80 (area under the ROC curve, 0.653); (B) Cut-off value of 46.00 predicts CIN3+ (area under the ROC curve, 0.691)

HPV, the relative risk of HPV16 and HPV18 for CC was 24.05% and 23.20%, suggesting that HVP16 and HPV18 had significant contribution to cervical cancer.

There has not been detailed research focused on investigating the age-specific pattern of HPV16/18 related cervical lesions. In this study, for women aged under 30 years old, we found the proportion of HPV16 appeared more like a ladder rising trend with cervical lesion progression, while the rate of HPV18 showed a progressive downward trend. For women aged 30 years and older, the proportion of HPV16 showed a steady upward trend with the progress of cervical lesions, but for HPV18, there appeared a turning point around CIN2, we found the distribution of HPV18 was lowest in CIN2, subsequently, it showed a straight line rise trend with the progress of cervical lesions. On the whole, in addition to women aged under 30 years old, almost in all age groups, the positive rate of HPV16 and HPV18 showed an upward trend with the progress of cervical lesions, especially for the high-grade cervical lesions, which hinted that primary HPV test screening alone demonstrated a stable and reliable result in diagnosis of cervical lesions. In addition to this, our result showed that the three cases of biopsy-confirmed cervical cancer in women aged under 30 years old were all HPV 16 positive, which concurred with some evidence that HPV16/18-related cervical cancers occur on average at a younger age than cancers due to other HPV genotypes.[14,18] So we have a high intensity of support for the interim guidance of using primary high-risk HPV testing for cervical cancer screening for women aged 25 years and older could be applied to our population.[6]

It is unclear why this shift occurs at age 30 years old, which might be associated with the active sexually that lead to susceptibility to HPV, while the strong self-immunity system make HPV clear easily and difficult to cause cervical lesions among this age. This result was consistent with the cervical cancer screening that recommended women aged 30 years and older should preferably be screened with HPV testing every 3-5 years.[3]

In addition to this, we found the rate of cervical cancer was 0.99% in the women under 30 years old, which increased up to 18.52% in women 60 years and older, suggesting that a substantial cervical cancer risk occurred for older women. This was similar to the survey from Korea female, where the incidence of cervical cancer for women aged >65 years (13.0%) was significantly higher than that for women aged ≤65 years (6.6%).[19] While one major study observed a decreasing proportion of HPV16/18-positive cancers with increasing age in western countries.[20] This difference might be related to different races and crowds in the Eastern and Western.

Castle et al[12] found that the sensitivity of CIN2+ (CIN3+) was 88.20% (92.00%) and the specificity of CIN2+ (CIN3+) was 57.80% (56.90%). In present study, the sensitivity of HPV16/18 for CIN2+ (CIN3+) was 82.68% (92.12%) and the specificity for CIN2+ (CIN3+) was 47.87% (46.15%). The sensitivity of HPV16/18 for detection of CIN3+ was higher than that of CIN2+. So did the negative predictive value. Compared with other HR-HPV, HPV16/18 had higher sensitivity and negative predictive value in the diagnosis of high level cervical lesions, which agreed well with the findings of Zhou et al[21] and approved HPV16/18 genotyping detection as the primary screening.[6]

In recent years, a number of studies have supported the application of the interim clinical guidance. An overview of the European and North American studies on HPV testing in primary cervical cancer screening found HPV testing was substantially more sensitive than cytology, and support the use of HPV testing as the sole primary screening test.[22] A survey of Clinicians' attitude to Australian National Cervical Screening Program found that 60% of clinicians were willing to change practice if guidelines recommend cervical cancer screening using HPV testing, starting at 25 years of age, every 5 years.[23] Several countries were currently implementing a transition from cytology to primary HPV testing for cervical screening, including England,[24] Netherlands,[25,26] and Australia.[27] For example, in 2014, Australia announced a renewed cervical cancer screening strategy from conventional cytology to primary HPV screening with partial genotyping and direct referral for women testing HPV 16/18, and this strategy would be implemented at May 1, 2017.[26] More importantly, the National Cervical Screening Programme (NCSP) is planning to change the first step in the screening pathway from liquid-based cytology screening to primary HPV screening in 2018.[28]

As HPV-DNA testing has advantage of stability, automaticity, and high-throughput, the strategy of primary HR-HPV screening is feasible and should be recommended in the northwest China where has a large of population, less developed, and lack of resources and infrastructure. Although there are important discoveries revealed by this study, there are also limitations, for example, we did not know the status of cytology in this screened group, because all the subjects included in this study were performed HPV testing instead of cytology. In addition to that, as for other factors, such as cost, people's acceptability and so on will be included in subsequent experiments. Finally, the change in screening strategy HPV and cytology co-testing to HPV testing alone eventually depends on the support of a large number of scientific studies.

In summary, among the reproductive aged women in Shaan'xi province, HPV16 is the most common genotype inducing high grade cervical lesions and cervical cancer, followed by HPV 18. The positive rate of HPV16 and HPV18 was highly associated with the relative risk of cervical lesion. Using the automated and high throughput of HPV detection has a high sensitivity and negative predictive value in diagnosis of high level cervical lesion. We support the primary HPV16/18 infection referred to colposcopy as a credible and feasible strategy in the northwest of China.

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## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

## ORCID

*Qian Zhang* http://orcid.org/0000-0002-3784-3234

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