HPV16 E7 Oncoprotein As a Predictor of Diagnosis and Prognosis in Patients with Cervical Lesions

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Research

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Abstract

Backgroud The early diagnosis and treatment of HSIL is a key measure to prevent the occurrence of cervical cancer. Although the methods of cervical cancer screening are becoming more and more abundant, some patients still have unnecessary colposcopy referrals. This study aim to explore the value of human papillomavirus 16 (HPV16) E7 oncoproteinin cervical lesion screening and risk assessment of the prognosis for more effective colposcopy.

Method: HPV16 E7 oncoprotein in cervical exfoliated cells was detected by using E7 Oncoprotein (HPV16) Diagnostic Kit (Magnetic Partical Chemiluminescence Method). In the first part, HPV16 E7 oncoprotein in different degrees of cervical lesions was retrospectively compared to find the best critical value; In the second part, the value of this test was verified ; In the third part, the women diagnosed as low-grade squamous intraepithelial lesions (LSIL) or normal were followed up for 3 years and the outcomes were compared.

Results: In the first part, the expression of HPV16 E7 oncoprotein was positively correlated with the degree of cervical lesion; The critical value determined by ROC curve is 8.68ng/ml, which is accurate in the diagnosis of high-grade squamous intraepithelial lesions (HSIL) and invasive carcinoma of cervix (CA); In the second part, there were higher sensitivity(87.1) and specificity(70) for E7 oncoprotein; HPV16 E7 oncoprotein has higher consistency with pathological examination in detection of HSIL or cervical cancer （0.573 vs 0.369) than TCT; In the third part，HPV16 E7 oncoprotein has a high positive predictive value (82.4%) and positive likelihood ratio (4.43) for the prognosis of patients with LSIL and below.

Conclusions: The status of HPV16E7 oncoprotein shows important clinical value for the detection and prediction of cervical lesions. Patients with positive HPV16 E7 oncoprotein are more likely to develop the disease and have a higher risk of disease progression.

Background

Cervical cancer is one of the most common malignant tumors among women. There are approximately 570,000 new cases of cervical cancer each year in the world, and 310,000 cases of cervical cancer deaths[1]. A large number of epidemiological and molecular biological studies have confirmed that persistent HPV infection is closely related to cervical precancerous lesions and cervical cancer [2, 3]. It takes about 10 years from cervical infection of HPV to cause precancerous lesions and to cervical cancer. Therefore, the early diagnosis and treatment of HSIL is a key measure to prevent the occurrence of cervical cancer. In 2014, the WHO used the HPV test as a primary screening method for cervical cancer screening [4]. However, 70%-80% of women will be infected with HPV during their lifetime. The vast majority of women only have a transient HPV infection. Only a small percentage of women with persistent HPV infection may develop cervical lesions and eventually develop cervical infiltration cancer [5]. In recent years, studies have confirmed that HPV E6, E7 oncoproteins play a key role in viral

proliferation and squamous intraepithelial lesions of the cervix until cervical invasive carcinoma [3, 6, 7]. Therefore, the detection of HPVE6 and E7 oncoproteins can help identify cervical precancerous lesions.

In this study, HPV16 E7 oncoprotein concentration in cervical exfoliated cells of normal cervix, LSIL, HSIL and cervical cancer was detected by using E7 Oncoprotein (HPV16) Diagnostic Kit (Magnetic Particle Chemiluminescence Method). Combined with colposcopy cervical biopsy and ThinPrep cytology test (TCT), HPV16 E7 oncoprotein was evaluated in cervical lesion screening for the application value, in order to explore the risk assessment of the prognosis of cervical lesions caused by HPV16 infection.

Materials And Methods

Subjects

The first part of the study selected 100 patients from December 2016 to March 2017 who were admitted to the Tianjin Central Hospital of Gynecology and Obstetrics with age ranging 20–72 years old with an average age at 42.18 years old. Inclusion criteria were (1) have sexual life history, all have TCT test and colposcopy, cervical histopathological results and HPV 16 positive from HPV DNA testing; (2) patients in non-pregnancy and non-pregnant period; (3) no recent vaginal infection and medication; (4) complete cervix; (5) no history of cervical cancer, no history of pelvic radiotherapy;(6) agree to participate in the study, sign an informed consent form. Patients who do not meet the above conditions will be excluded.

The second part is a prospective study of patients who were positive for HPV16 DNA, covering patients who were admitted to our hospital from April 2017. Assuming a power of 80% and a confidence level of 95%, a sample size of this part to be followed-up in the cohort with an estimated loss of 20% during the follow-up period was calculated. In view of experiences of past studies corresponding failure rates (e.g. the test for HPV16 E7 oncoprotein) must be taken into account with 10%. Thus, the total expected baseline sample size is 146. Inclusion criteria were (1) have sexual life history, all have HPV 16 positive from HPV DNA testing; (2) patients in non-pregnancy and non-pregnant period; (3) no recent vaginal infection and medication; (4) complete cervix; (5) no history of cervical cancer, no history of pelvic radiotherapy;(6) agree to participate in the study, sign an informed consent form and provide at least a telephone number to be contacted. Until March 2018, exfoliated cells from 152 patients were collected for the detection of HPV16 E7 oncoprotein and TCT, and then they would underwent colposcopy and cervical biopsy.12 patients were excluded because their E7 oncoprotein and TCT could not be tested because of poor sample quality and 30 patients were excluded because there were no pathological results. 10 patients decided to stop participating in the study. Finally, there were 100 patients who were admitted in this study with ages ranging 22–67 years old and an average age of 41.88, which is shown in **Fig. 1(**Figure 1: Flow diagram of the inclusion criteria for part 2 of study subjects.**)**.

The third part is the follow-up of 39 patients with normal cervix and below LSIL in the first part to analyze the effect of HPV16 E7 oncoprotein expression on the prognosis of LSIL and below. According to the results of E7 oncoprotein, the patients were divided into positive group and negative group. The end point

of follow-up was HPV negative or higher grade lesions. Follow-up events included negative HPV, persistent HPV infection, and disease progression. The follow-up period was 3 years.

Each patient provided a signed copy of informed consent. All procedures performed in studies involving human participants were approved by the Ethics Committee of the Tianjin Central Hospital of Gynecology and Obstetrics (2015KY031).

Research Design and Methodology

This study included three parts as shown in **Fig. 2(**Figure 2: Technology roadmap for this study**)**. In the first part, the concentration of HPV16 E7 oncoprotein in different degrees of cervical lesions was retrospectively compared to find the best critical value; In the second part, the value of this test was verified in HPV16-positive women; In the third part, patients diagnosed as low-grade squamous intraepithelial lesions (LSIL) or normal were followed up for 3 years and the outcomes of patients with different E7 oncoprotein were compared.

Specimen collection: use a special cervical brush to collect cervical exfoliated cells at the squamocolumnar junction of the cervix. After removing the cervix brush, store the brush head in the cell preservation solution and dry frozen tube, and perform TCT and HPV16 E7 oncoprotein detections.

TCT examination: According to the new Pfz standard, the bethesda system (TBS) classification diagnosis was made by our hospital's cytopathologist and divided into negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of unknown significance (ASC-US), ASC-H, LSIL, HSIL and squamous cell carcinoma. In this study,those diagnosed with ASC-US and above were positive and classified as a positive group.

E7 Oncoprotein (HPV16) Dignostic Kit (Magnetic Particle Chemiluminescence Method): centrifugation of the cell pellet was performed and the supernatant was assayed on a chemiluminometer. Strictly follow the operating instructions of E7 Oncoprotein (HPV16) Dignostic Kit (Magnetic Particle Chemiluminescence Method) and CIA 1200 Automatic Magnetic Particle Chemiluminescence Immunoassay Analyzer from FAMID Biomedical Technology (Tianjin) Co., Ltd.

Colposcopy and Cervical Histopathological Examination: A colposcopy specialist performed a colposcopy and biopsy. The cervical tissues were analyzed and diagnosed by at least two pathologists.

Statistical Analysis

Statistical analysis was performed using SPSS25.0 software. The measurement data of this study were tested to be not in line with the normal distribution, so they were expressed as the median (P25, P75). Wilcoxon rank sum test of two independent samples was used to compare differences between groups when type of data was quantitative variable. Chi-square tests were used to compare differences between groups when the type of data was qualitative variable. Spearman correlation analysis was used to analyze the correlation. Receiver operating characteristic (ROC) curve was used to assess the optimal diagnosis of E7 oncoprotein qualitative assay. In order to evaluate the accuracy, sensitivity(SEN),

specificity(SPE), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR) and negative likelihood ratio (- LR) were calculated. Kappa test was used to evaluate E7 oncoprotein and TCT. All tests were two-sided and p value < 0.05 was considered the cut-of level for statistical significance for all analysis.

Results

Detection of HPV16 E7 oncoprotein by using E7 Oncoprotein (HPV16) Dignostic Kit (Magnetic Particle Chemiluminescence Method) to assist in the diagnosis of cervical lesions

The results of 100 patients in the first part of the study were divided into 4 groups according to the gold standard for pathological diagnosis, including 30 normal cervix patients, 9 LSIL patients, 56 HSIL patients, and 5 cervix squamous cell carcinoma patients. General characteristics were shown in Table 1.

Table 1
The Result of Histological Diagnoses of Patients with HPV16(+) in the First Part

Characteristics	Number	Normal Cervix	LSIL	HSIL	CA
Age					
< 30	14	4	4	4	2
30–45	47	14	3	29	1
> 45	39	12	2	23	2
Marital Status					
Married	88	29	6	49	4
Unmarried	12	1	3	7	1
Smoking*					
No	90	29	8	51	2
Yes	10	1	1	5	3
TCT*					
NILM	24	17	1	4	2
ASC-US	32	9	4	18	1
ASCUS-H	14	0	1	12	1
LSIL	15	3	3	9	0
HSIL	15	1	0	13	1
Total		30	9	56	5
*p < 0.05					

Among the 100 cases,the results of spearman correlation analysis showed that the expression level of HPV16 E7 oncoprotein was positively correlated with the degree of cervical lesions. The more serious the degree of cervical lesions, the higher the expression level ($r = 0.589$, $P < 0.01$). The concentration of E7 oncoprotein in different degrees of cervical lesions was shown in Table 2. According to the principle of treatment, patients were divided into two groups. The normal cervix and LSIL (39 cases) were used as the control group, and the patients with HSIL and cervical cancer (61 cases) were in the observation group. The concentration of E7 oncoprotein in experimental group was higher than that in the control group ($P < 0.001$).

Table 2
Comparison of E7 Expression in Different Degrees of Cervical Lesions

Pathological Diagnosis of Cervical Lesions	Number of Patient	Expression of HPV16 E7 Oncoprotein*
normal cervix	30	4.34(0.5-17.81)
LSIL	9	5.67(2.46–25.25)
HSIL	56	43.05(17.09-170.02)
CA	5	25.9(17.36-399.43)
P Value		< 0.001
*Median of HPV 16 E7 oncoprotein concentration, with 25th–75th percentile in parentheses		

The ROC curve was used to evaluate the accuracy of the HPV16 E7 oncoprotein, detected HSIL and cervical cancer. The ROC curve obtained was shown in **Fig. 3**.(Figure 3: ROC Curve of Cervical Lesions Detected by HPV16 E7 Oncoprotein) The area under the ROC curve was AUC = 0.817, and the confidence interval was (0.729, 0.904), which was between 0.70 and 0.90. After calculating the Youden index, the critical value for grouping was determined to be 8.68 ng/ml. In another word, the HPV16 E7 oncoprotein concentration of 8.68 ng/ml can be used as a critical value to distinguish between LSIL and HSIL —– HPV16 E7 oncoprotein concentration ≥ 8.68 ng / ml was classified as positive result; <8.68 ng / ml was classified as negative.

Evaluation of the Accuracy of HPV16 E7 Oncoprotein in Detecting HSIL+

In the second part, 100 patients were included at last, as shown in Table 3. According to the results of HPV16 E7 oncoprotein detection, all patients were divided into E7 oncoprotein negative group and E7 oncoprotein positive group. In the E7 oncoprotein positive group, the number of patients with HSIL and CA was significantly higher than that in E7 oncoprotein negative group ($p < 0.05$). Taking pathological diagnosis as the gold standard, the SEN, SPE, PPV, NPV, LR and - LR of E7 oncoprotein concentration and TCT were shown in Table 4. TCT examination and HPV16 E7 oncoprotein detection were performed using consistent tests (Kappa test). The results showed that the Kappa value of HPV16 E7 oncoprotein was 0.571 compared with the pathological examination. The Kappa value of TCT was 0.369 compared with the pathological examination.

Table 3
General Characteristics of 100 Patients in the Second Part

Characteristics	Number	Normal Cervix	LSIL	HSIL	CA
Age					
< 30	9	3	2	3	1
30–45	54	16	2	35	1
> 45	37	8	0	25	4
TCT*					
NILM	36	18	1	15	2
ASC-US	23	7	0	15	1
ASCUS-H	12	1	0	11	0
LSIL	12	1	3	8	0
HSIL	17	0	0	14	3
E7 Oncoprotein*					
Positive	70	10	0	56	4
Negative	30	17	4	7	2
Total	100	27	4	63	6

Table 4
The Accuracy of HPV16 E7 Oncoprotein in Detecting HSIL+

Project	Pathological Diagnosis		SEN(%)	SPE(%)	PPV(%)	NPV(%)	LR	-LR
	Observation Group	Control Group						
E7								
+	61	9	87.1	70.0	87.1	70.0	2.9	0.184
-	9	21						
TCT								
+	53	11	75.7	63.3	82.8	52.8	2.062	0.384
-	17	19						

The predictive value of HPV16 E7 oncoprotein in prognosis of LSIL and below

39 patients with normal cervix and LSIL in the first part were followed up for 3 years. First of all, except that the age might have an effect on the outcome, Spearman correlation analysis showed that different outcomes were not related to age (r = 0.12). The proportion of disease progression/persistent infection was higher in E7 oncoprotein positive group (χ^2 = 14.899,P = 0.001) as shown in Table 5. After calculation, a higher PPV and positive likelihood ratio were obtained, which was shown in Table 6, suggesting that the detection of HPV16 E7 oncoprotein had a good predictive value for the prognosis of LSIL and below. Furthermore, the median (P25, P75) of E7 oncoprotein concentration of patients with HPV negative, persistent HPV infection and higher grade lesions was 2.32(0.5–5.67), 8.89 (4.36–35.1) and 78.43 (42.74-281.05)，P = 0.001). It is suggested that the concentration of E7 oncoprotein is positively correlated with the prognosis of patients with LSIL and below. The higher the concentration, the greater the possibility of higher grade lesions.

Table 5
Outcome of Different HPV16 E7 Oncoprotein in Normal Cervix and LSIL Patients

Group	Number (%)	HPV Negative (%)	HPV Persistent Infection (%)	Disease Progression (%)
HPV16 E7 Oncoprotein(+)	22(56.4)	16(72.7)	5(22.7)	1(4.5)
HPV16 E7 Oncoprotein(-)	17(43.6)	3(17.6)	5(29.5)	9(43.6)
Total	39	19(48.7)	10(25.6)	10(25.6)
P Value		0.001		

Table 6
The Value of HPV16 E7 Oncoprotein in Predicting the Outcome of Patients with LSIL and Below

Outcome of Patients	HPV 16 E7 Oncoprotein		SEN(%)	SPE(%)	PPV(%)	NPV(%)	LR	-LR
	+	-						
HPV Persistent Infection/Disease Progression	14	6	70	84.2	82.4	72.7	4.430	0.356
HPV Negative	3	16						

Discussions

HPV infection, especially high-risk HPV infection, is closely related to the occurrence of cervical precancerous lesions and cervical cancer and about 99.7% of cervical cancer patients have HPV infection[2]. The most common type of HPV infection is HPV16 infection[8–10]. At present, the detection methods of HPV are mostly at the level of RNA or DNA, and there are few detection methods of oncoprotein. Studies have confirmed that after cervical epithelial cells are infected with HPV, the expression of the E6, E7 oncoprotein co-action lead to the occurrence of cervical cancer [11, 12], and the

advanced stage of cervical cancer is mainly associated with E6 oncoprotein, early cancer stage is closely related to the E7 oncoprotein[13]. Therefore, the detection of HPV16 E7 oncoprotein in the cervix has important clinical value for the early detection and diagnosis of cervical precancerous lesions and cervical cancer.

At present, the methods used to detect HPV E6/E7 oncoprotein include: semi-quantitative detection of HPV E6/E7 oncoprotein in pathological tissues using immunohistochemistry, qualitative detection of HPV E6/E7 oncoprotein in cervical exfoliated cells using enzyme immunochromatography, and qualitative detection of HPV E6/E7 oncoprotein in cervical exfoliated cells using immunocytochemistry [14–16]. The above-mentioned methods have their own inadequacies. The enzymatic chemiluminescence method used in this study can semi-quantitatively detect the expression level of HPV16 E7 oncoprotein in exfoliated cells of the cervix, which is easy to obtain, and the detection method is simple and rapid. It has a great potential in the clinical application.

In the first part of the study, we performed a correlation analysis of the expression levels of HPV16 E7 oncoprotein in 100 cases of different degrees of cervical lesions. The results showed that the expression of HPV16 E7 oncoprotein was positively correlated with the degree of cervical lesions, which is consistent with past research results[15, 16]. It was shown that HPV16 E7 oncoprotein expression increased with the severity of cervical lesions, suggesting that HPV16 E7 oncoprotein detection can be used as a screening for cervical precancerous lesions and cervical cancer. A large number of clinical studies have shown that about 60% of LSIL patients will naturally subside, only need close observations of the follow-up patients. About 20% of HSIL will continue to develop, and 5% will develop to invasive cervical cancer[2]. Therefore, all patients with HSIL and higher degree of cervical lesions need to be treated [17]. So we divided the first part of the 100 women into two groups: (1) normal cervix and LSIL group as the control group; (2) HSIL and cervical cancer group as the observation group. We used the ROC curve to evaluate the diagnostic efficacy of the test method. After calculating the Youden index and determining its grouping threshold, it is HPV16 E7 oncoprotein concentration = 8.68 ng/ml, which can be used as a critical value to distinguish LSIL and HSIL. The results showed that the test method has good accuracy in distinguishing normal cervix, LSIL from HSIL and cervical cancer, suggesting that the method is reliable.

A large number of studies have confirmed that for the screening of high-grade cervical lesions, the sensitivity of HPV DNA detection is high and the specificity is insufficient while the specificity of TCT screening is high but the sensitivity is significantly reduced, resulting in partial missed diagnosis of HSIL[18, 19]. At the same time, studies have shown that the HPV E7 oncoprotein or mRNA assay has a higher specificity and positive predictive value than the HPV DNA assay and thus has a higher diagnostic value for the diagnosis of high-grade cervical lesions including HSIL and cervical cancer[20].

In the second part of the study, we used a prospective study to verify the value of HPV16 E7 oncoprotein in the diagnosis of cervical lesions. It showed that the positive result of E7 oncoprotein had a hint effect on HSIL. And the sensitivity, specificity, positive predictive value, and negative predictive value of HPV16 E7 oncoprotein detection for HSIL and cervical cancer were: 87.14%, 70.00%, 87.14%, and 70.00%. A

systematic review report by Burger et al. shows that the sensitivity of HPV DNA detection is 70%-100% and the specificity is only 28%-56%, while the Aptima mRNA detection approved by the FDA for clinical use in cytology is ASC-US population, the sensitivity is 91%-95% and the specificity is 42–61%[21]. Another research showed that the sensitivity is 91.4% and the specificity is 46.2% of Aptima mRNA [22]. The second-generation Hybrid Capture Technology (HC-2) specification showed that the sensitivity, specificity, positive predictive value, and negative predictive value of high-grade cervical intraepithelial lesions and cervical cancer were diagnosed in patients with Pap smear diagnosed as ASC-US were: 93.0%, 61.1%, 17.2%, 99.0%. Compared with HPV DNA and HPV mRNA detection methods, the HPV E7 oncoprotein assay used in this study has a higher specificity and positive predictive value. At the same time, its sensitivity and negative predictive value are not significantly reduced. This suggests that HPV E7 oncoprotein detection is a method with a higher diagnostic value, and it is expected to become a new indicator for cervical precancerous lesions and cervical cancer screening.

Previous studies have shown that HPV E6/E7 oncoprotein detection has better sensitivity than TCT detection, and has better specificity than HPV E6/E7 mRNA and HPV DNA detection[12]. Studies have also shown that HPV E6/E7 oncoprotein detection is more sensitive than HPV E6/E7 mRNA detection in HPV16 and HPV18 infected patients, 71.3% and 56.3%, respectively[23]. At the same time, studies have pointed out that in high-grade cervical intraepithelial lesions and cervical cancer, HPV E6/E7 oncoprotein detection compared to HPV E6/E7 mRNA detection, the difference in sensitivity between the two was not statistically significant, and HPV E6/ The E7 oncoprotein assay has high specificity and positive predictive value[24].

In our research, the sensitivity, specificity, positive predictive value, and negative predictive value of the HPV16 E7 oncoprotein assay were higher than those of the TCT assay, which is consistent with previous research results[25]. The consistency between HPV16 E7 oncoprotein examination and pathological examination was higher than that of TCT examination. It suggests that it has better diagnostic application value than TCT detection. The positive predictive value and negative predictive value of HPV16 E7 oncoprotein detection for high grade and above lesions as high as 87.14%, 70.00%, suggesting it can be used as a colposcope shunt method to reduce unnecessary colposcopy referral. In addition, due to the need for professional cytopathologists to determine the results of TCT testing, it caused high missed diagnosis and misdiagnosis in some underdeveloped areas. For these areas, it should consider the use of HPV E7 oncoprotein detection instead of TCT for cervical cancer screening.

Looking for potential biomarkers can help us identify patients with high risk of disease progression, and early intervention for these patients can effectively reduce the incidence of cervical cancer. The results suggest that the detection of E7 oncoprotein has a good diagnostic effect in predicting the progression of lesions, and the detection of E7 oncoprotein is helpful to predict the prognosis of patients with known HPV16 infection. For the patients with high detection level of E7 oncoprotein, it is necessary to strengthen the screening intensity or even give active treatment. Compared with known prognostic markers such as

p16, ki67, hTERC gene, E7 oncoprotein is more convenient and economical[26]. However, there are too few cases in the study and further studies are needed.

In summary, the HPV16 E7 oncoprotein detection method used in this study is accurate, reliable, and easy to obtain. The method is novel and can be semi-quantitatively tested. At the same time, HPV16 E7 oncoprotein concentration of 8.68 ng/ml can be used as a critical value to distinguish between HSIL and cervical cancer and there was high specificity and positive predictive value with no significant decrease in sensitivity and negative predictive value, suggesting that HPV E7 oncoprotein detection has more diagnostic values. It can be used as a colposcopy shunt method. And it also has a good predictive value for the prognosis of LSIL and below lesions. It is expected to be widely used for the clinical detection of cervical lesions and become a new indicator of precancerous cervical lesions and cervical cancer screening.

In addition, since this study only tested the E7 oncoprotein of HPV Type 16, a large-scale, multicenter study of the oncoproteins of all high-risk HPV types is still needed to evaluate the value of HPV E7 oncoprotein detection in cervical lesion screening.

Conclusion

The status of HPV16E7 oncoprotein shows important clinical value for the detection and prediction of cervical lesions. Patients with positive HPV16 E7 oncoprotein are more likely to develop the disease and have a higher risk of disease progression.The HPV16 E7 oncoprotein detection method used in this study is accurate, reliable, and easy to obtain. The method is novel and canbe semi-quantitatively tested. At the same time, there was high specificity and positive predictive value with no significant decrease in sensitivity and negative predictive value, suggesting that HPV E7 oncoprotein detection have more diagnostic value. It can be used as a colposcope shunt method. It is expected to be widely used for the clinical detection of cervical lesions and become a new indicator of precancerous cervical lesions and cervical cancer screening.Therefore, the detection of HPV16 E7 oncoprotein in the cervix has important clinical value for the early detection and diagnosis of cervical precancerous lesions and cervical cancer. Especially for poor countries and regions, it should consider the use of HPV E7 oncoprotein detection instead of TCT for cervical cancer screening.

Abbreviations

HPV	Human papilloma virus
DNA	Deoxyribonucleic acid
ASCUS	Atypical Squamous Cells of Undetermined Significance
HR-HPV	High Risk-Human papilloma virus
WHO	World Health Organization
RB	Retinoblastoma
TCT	ThinPrep cytological test
NILM	No intraepithelial lesion cells
ASC-H	and malignant cells
LSIL	Atypical squamous cells-cannot exclude HIS
HSIL	Low-grade squamous intraepithelial lesion
PPV	High-grade squamous intraepithelial lesion
NPV	Positive predictive value
	Negative predictive value

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Tianjin Central Hospital of Gynecology Obstetrics. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

No financial and non-financial competing interests exist in this study.

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coordinated the work of the laboratory, and did statistical processing. GS and JX participated in the experimental process, sorted out the data of all patients, did statistical processing, and wrote this article. ML, XZ and NZ participated in the patient sample and data collection of patient samples. LG participated in patient sample collection. AcknowledgementsThe authors would like to thank the patients, clinicians and laboratory personnel who participated in the project.Author InformationAffiliation

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27. *Declarations*.

Figures

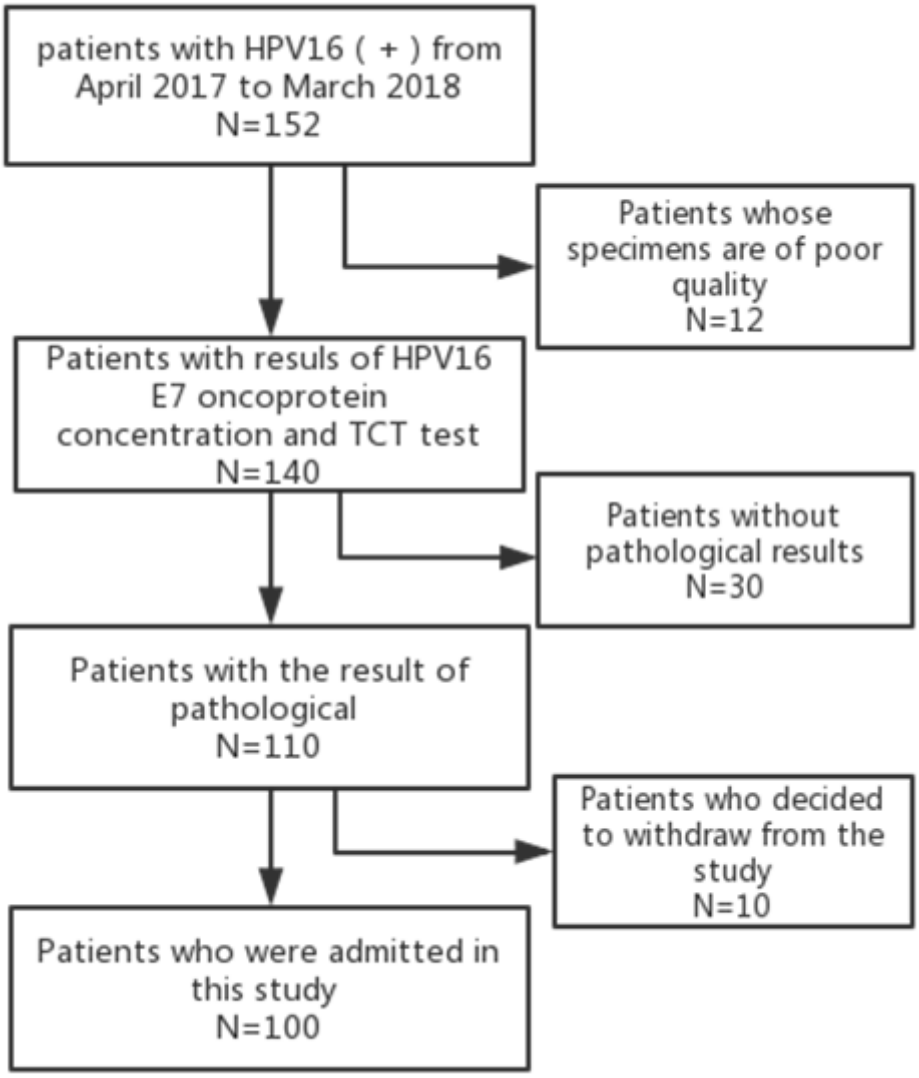

Figure 1

Flow diagram of the inclusion criteria for part 2 of study subjects.

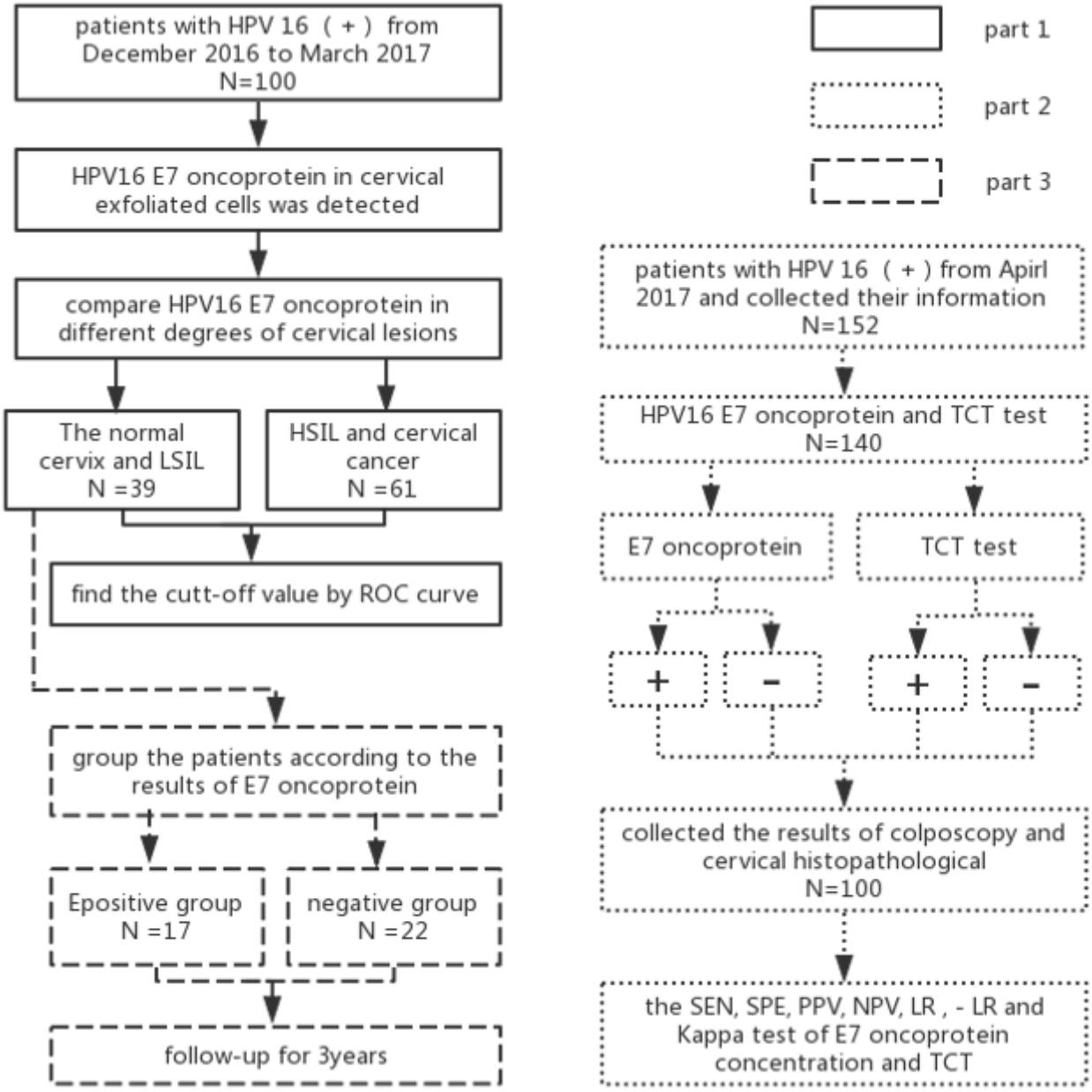

Figure 2

Technology roadmap for this study

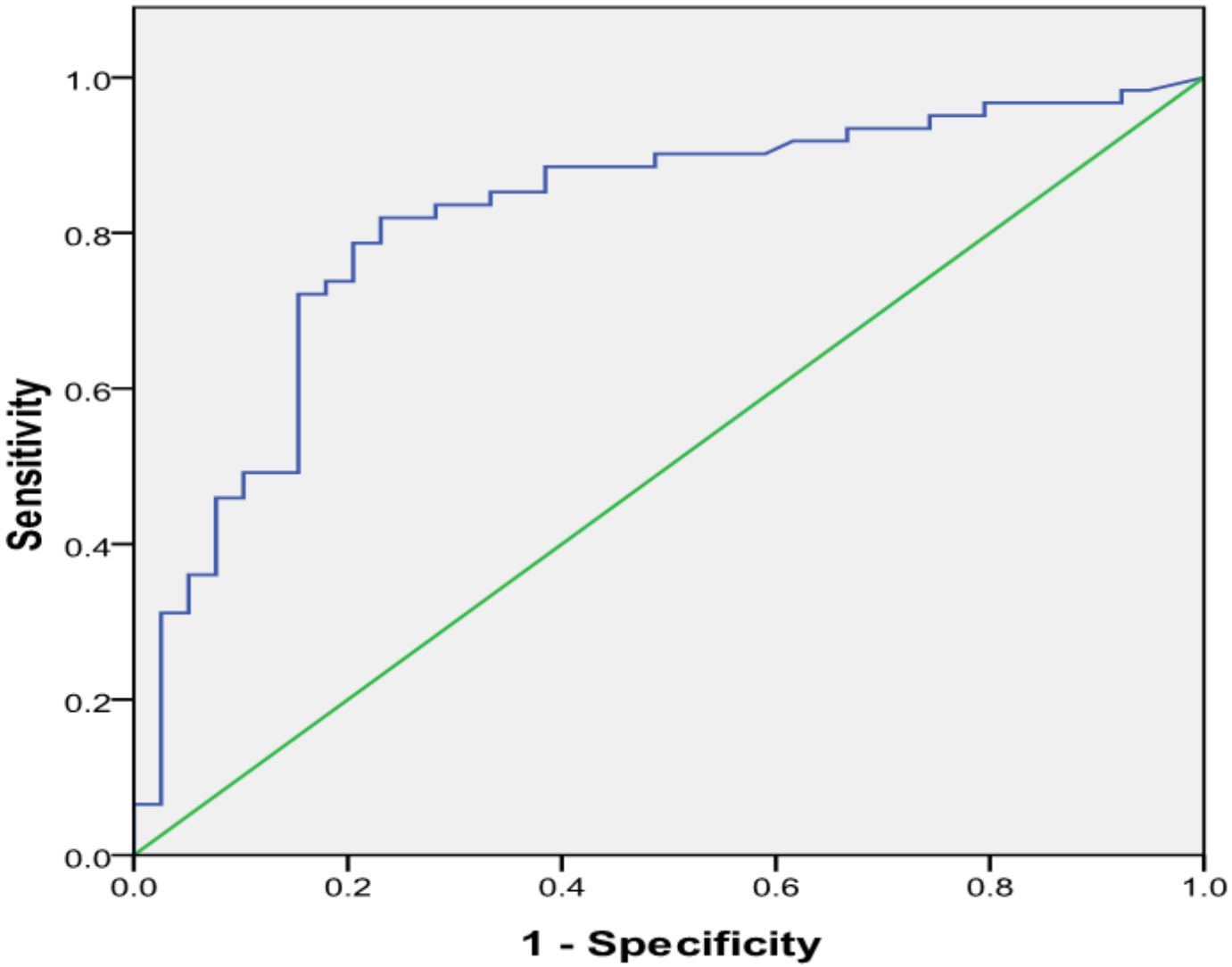

Figure 3

ROC Curve of Cervical Lesions Detected by HPV16 E7 Oncoprotein